

ゾレア皮下注用75 mg, ゾレア皮下注用150 mg  
に関する資料

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## 1.5 起源又は発見の経緯及び開発の経緯

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## 略号一覧

| 略号                  | 省略していない表現（英）  | 省略していない表現（日）                |
|---------------------|---|-----------------------------|
| CSU                 | chronic spontaneous urticaria   | 慢性特発性蕁麻疹                    |
| CU                  | chronic urticaria   | 慢性蕁麻疹                       |
| DLQI                | Dermatology Life Quality Index  | —                           |
| EAACI               | the European Academy of Allergy and Clinical Immunology   | —                           |
| EDF                 | the European Dermatology Forum  | —                           |
| EU                  | European Union  | 欧州連合                        |
| FcεRI               | high affinity IgE receptor  | 高親和性 IgE 受容体                |
| GA <sup>2</sup> LEN | the Global Allergy and Asthma European Network  | —                           |
| H1AH                | H <sub>1</sub> antihistamine  | ヒスタミン H <sub>1</sub> 受容体拮抗薬 |
| H2AH                | H <sub>2</sub> antihistamine  | ヒスタミン H <sub>2</sub> 受容体拮抗薬 |
| ICH                 | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use | 日米 EU 医薬品規制調和国際会議           |
| IgE                 | immunoglobulin E  | 免疫グロブリン E                   |
| LTRA                | leukotriene receptor antagonist   | ロイコトリエン受容体拮抗薬               |
| MID                 | minimally important difference  | 意義のある最小の差                   |
| POC                 | proof of concept  | プルーフ・オブ・コンセプト               |
| QOL                 | quality of life   | 生活の質                        |
| UAS                 | urticaria activity score  | —                           |
| WAO                 | the World Allergy Organization  | —                           |

## 用語の定義一覧

| 用語                | 定義  |
|-------------------|---|
| 試験の表記方法           | 治験実施計画書番号は、試験番号で示した。<br>例)<br>CIGE025E2306→E2306 試験   |
| 投与群の記載方法          | オマリズマブ投与群の表記方法<br>用量にかかわらず、オマリズマブ投与群全体を総称する場合オマリズマブ投与群と表記した。<br>例)<br>オマリズマブ 300 mg, 150 mg, 75 mg 群を総称する場合→オマリズマブ投与群   |
| 慢性蕁麻疹と慢性特発性蕁麻疹の定義 | 日本皮膚科学会による蕁麻疹診療ガイドライン 2011（以下「日皮会ガイドライン 2011」）では、蕁麻疹は特発性蕁麻疹と刺激誘発性型の蕁麻疹に分類され、特発性蕁麻疹はさらに、発症後の期間によって急性蕁麻疹と慢性蕁麻疹（chronic urticaria, CU）に分けられる。日皮会ガイドライン 2011 によれば、CU は「直接的原因なく自発的に膨疹が出現するもののうち、発症後 1 ヶ月以上経過したもの」と定義される。CU はすべての蕁麻疹の約 5 割を占めるとされる（田中 他 2006）。一方、欧米の EAACI/GA <sup>2</sup> LEN/EDF/WAO ガイドライン 2013（以下 EAACI ガイドライン 2013）では、CU と同じ疾患概念は慢性特発性蕁麻疹（chronic spontaneous urticaria, CSU）と呼ばれ、その定義は「特定の原因なく自発的に出現する蕁麻疹が 6 週間以上持続するもの」とされている（Zuberbier et al. 2014）。このように、日本と欧米のガイドラインでは、症状の持続期間に関して若干の違いがあるが、これが診断上の問題となることは |

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| 用語  | 定義   |
|-----|--|
| 青少年 | なく、CUとCSUは同一の疾患であるとされる ( <a href="#">Hide and Hiragun 2012</a> )。<br>有効性及び安全性を評価した試験では、ICHの「Clinical Investigation of Medicinal Products in the Pediatric Population」(ICH-E11 ガイドライン)に基づき、青少年を「12歳以上18歳未満」と定義した。 |

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## 1 起原又は発見の経緯

オマリズマブ（遺伝子組換え，ゾレア®）（以下，オマリズマブ）は，チャイニーズハムスター卵巣細胞から産生される，マウス抗ヒト免疫グロブリン E（immunoglobulin E, IgE）モノクローナル抗体の相補性決定領域，並びにヒト IgG<sub>1</sub> に由来する定常部及びフレームワーク部からなるヒト化抗ヒト IgE モノクローナル抗体（分子量約 149,000，アミノ酸 1,338 残基からなる糖蛋白質）であり，ノバルティス社の共同開発会社である Genentech 社が作製した。

オマリズマブは，IgE の Cε3 部位に結合することで，IgE と高親和性 IgE 受容体（high affinity IgE receptor, FcεRI）との結合を競合的に阻害する。その結果，IgE の肥満細胞，好塩基球等の炎症細胞への結合が阻害されるため，これら炎症細胞の活性化が抑制され，アレルギー反応が抑制される。

オマリズマブはアレルギー性喘息の治療薬として開発され，国内では成人の気管支喘息治療剤として 2009 年 1 月（150 mg 製剤），2012 年 9 月（75 mg 製剤）に，小児の気管支喘息治療剤として 2013 年 8 月に承認を取得した。2017 年 2 月現在，世界 90 カ国以上でアレルギー性喘息の治療薬として，また，世界 85 カ国以上で慢性特発性蕁麻疹（chronic spontaneous urticaria, CSU）の治療薬として承認されている。

## 2 慢性蕁麻疹について

### 2.1 定義，診断基準及び患者数

蕁麻疹は最もよくみられる皮膚疾患のひとつで，平成 26 年（2014 年）の国内の患者数は約 23 万人と報告されている（厚生労働省 2014）。蕁麻疹の好発年齢は 20 歳～40 歳代であるが，患者は新生児から高齢者まで広い年齢層にみられる（田中 他 2006, Maurer et al. 2011）。

日本皮膚科学会による蕁麻疹診療ガイドライン 2011（以下「日皮会ガイドライン 2011」）では，蕁麻疹は特発性蕁麻疹と刺激誘発性型の蕁麻疹に分類され，特発性蕁麻疹はさらに，発症後の期間によって急性蕁麻疹と慢性蕁麻疹（chronic urticaria, CU）に分けられる。日皮会ガイドライン 2011 によれば，CU は「直接的原因なく自発的に膨疹が出現するもののうち，発症後 1 ヶ月以上経過したもの」と定義される。CU はすべての蕁麻疹の約 5 割を占めるとされる（田中 他 2006）。一方，欧米の EAACI/GA<sup>2</sup>LEN/EDF/WAO ガイドライン 2013（以下 EAACI ガイドライン 2013）では，CU と同じ疾患概念は CSU と呼ばれ，その定義は「特定の原因なく自発的に出現する蕁麻疹が 6 週間以上持続するもの」とされている（Zuberbier et al. 2014）。このように，日本と欧米のガイドラインでは，症状の持続期間に関して若干の違いがあるが，これが診断上の問題となることはなく，CU と CSU は同一の疾患であるとされる（Hide and Hiragun 2012）。

CU の最も大きな臨床上の問題は，ほぼ毎日みられるそう痒と膨疹である。これに加えて，CU 患者の約 20%に血管性浮腫が併発する（田中 他 2006）。そう痒及び膨疹は CU 患者にとって最

も辛い症状で、仕事や学業の能率を著しく低下させ、欠勤・欠席を余儀なくさせる等、日常・社会生活上の問題となって患者の生活の質（quality of life, QOL）を大きく損なう（Maurer et al. 2011）。また、CU 患者ではこれらの症状の発現を予測できないことからくる不安や抑うつ、あるいは睡眠障害等、心身に対する悪影響を訴える率が高くなる（O'Donnell et al. 1997）。血管性浮腫は身体のだどの部位にも起こり得るが、たとえば顔面（特に口唇や眼瞼）にみられると整容面での問題が大きく、気道粘膜に起こると呼吸困難や窒息等重篤な状況に陥る危険性もある（日皮会ガイドライン 2011）。このように、CU 患者では疾患による身体的・精神的な負荷が大きく、血管性浮腫を併発する場合はその負荷は一層大きくなる。

## 2.2 慢性蕁麻疹に対する治療の現状

蕁麻疹では、何らかの原因で活性化された肥満細胞が脱顆粒し、組織内に放出されたヒスタミン等の化学伝達物質が皮膚の微小血管に作用して血漿成分の漏出（膨疹）や血管拡張（紅斑）を生じ、また皮膚の神経に作用してそう痒を生じる。蕁麻疹の治療の目標は、治療により生活に支障のない程度まで症状を抑え、最終的には薬物治療を必要とすることなく症状の出現を完全に抑制することである（日皮会ガイドライン 2011）。

蕁麻疹に対する薬物治療の第一選択薬は、蕁麻疹の種類を問わず経口の抗ヒスタミン薬である。日皮会ガイドライン 2011 では、CU の薬物治療として段階的な手順を推奨しており、第一段階では第二世代ヒスタミン H<sub>1</sub> 受容体拮抗薬（H<sub>1</sub> antihistamine, H1AH）の通常用量（添付文書に記載されている用量）投与が推奨される。第二世代 H1AH は第一世代に比べて鎮静性が低いという利点があるが、通常用量の第二世代 H1AH では十分な効果が得られない患者も存在する。そのような患者には、同じ薬剤の倍量投与や他の第二世代 H1AH への変更が推奨されるが、全体として第二世代 H1AH に有効な患者はいまだ 50%未満と少ない（Maurer et al. 2011, Kaplan 2012, Sánchez-Borges et al. 2014）。

第二世代 H1AH で効果不十分の患者に対しては、次の段階として、ヒスタミン H<sub>2</sub> 受容体拮抗薬（H<sub>2</sub> antihistamine, H2AH）やロイコトリエン受容体拮抗薬（leukotriene receptor antagonist, LTRA）等の補助的治療薬との併用が推奨される。しかし、H2AH や LTRA を併用した場合の治療効果に関しては、複数のランダム化比較試験が行われているものの一貫した結果が得られておらず、有効性の科学的なエビデンスは不十分である（Khan 2013, Fedorowicz et al. 2012）。補助的治療薬を使用しても強い症状が続く場合は、副腎皮質ステロイド（プレドニゾン換算量で 15 mg/日まで）の使用が推奨される。ステロイドの内服で症状を抑制できる患者の割合は 70%～80%と高く（Kaplan 2012）、国内では重症例に限って承認が得られているが、長期的予後に対する治療効果のエビデンスはほとんどなく、逆に疾患を遷延化させやすいという専門家の意見もある（西岡 2006）。また、ステロイドは長期投与によって感染増悪、糖尿病・過血糖、副腎不全、骨折といった副作用が問題となることから（Manson et al. 2009）、原則として CU 患者にはステロイドの長期的使用は推奨されない（Zuberbier et al. 2014）。

これらの治療で効果不十分、あるいはこれらの治療に不耐容の場合は、試行的治療としてシクロスポリン、メトトレキサート等の免疫抑制薬が使用されている。たとえば、シクロスポリンは EAACI ガイドライン 2013 でその有効性が示されているが、高用量 (> 5 mg/kg/day) では悪性腫瘍、感染症、高血圧、腎障害といった重度の副作用がみられる。低用量でも腎障害や高血圧等が問題となるため、腎機能や血圧の頻回なモニタリングが必要となり (Khan 2013) , リスク・ベネフィットの観点からその使用は重症例に限定される (日皮会ガイドライン 2011) 。

また、上記に挙げられた薬剤の中で、蕁麻疹、又は蕁麻疹に伴うそう痒を効能・効果として承認されている薬剤は、H1AH 及び副腎皮質ステロイド (重症例に限る) のみである。H2AH, LTRA, 及びシクロスポリン等の免疫抑制薬は蕁麻疹、又は蕁麻疹に伴うそう痒を効能・効果として承認されておらず、蕁麻疹に対する適応を持つ薬剤は限られている。

以上のとおり、現在までのところ、「第二世代 H1AH で効果不十分な CU 患者」に対する治療薬として、安全に投与でき、かつ有効性が検証された薬剤はない。こうした背景から、既存治療に効果不十分な CU 患者に対する有効な治療薬が望まれてきた。

### 2.3 本剤の治療上の位置付け

CU の病態に関しては、その全容を説明できる背景・増悪因子はいまだ不明であるが、一部の患者では IgE 受容体あるいは IgE に対する自己抗体が認められることから、その病態に自己免疫性機序が関与すると考えられている (Sabroe and Greaves 2006) 。CU に対するオマリズマブの作用機序は一つの仮説として以下のように考えられ、オマリズマブは他の治療薬とは異なる作用機序を有することから (Kaplan and Greaves 2009, Saavedra and Sur 2011) , 既存治療で効果不十分な CU 患者への効果が期待できると考えた。

1. オマリズマブが遊離 IgE に結合して血中及び皮膚組織の遊離 IgE 濃度を低下させることにより、肥満細胞及び好塩基球表面の FcεRI の発現を低下させる。
2. その結果、FcεRI の下流シグナル経路が制御されて、肥満細胞及び好塩基球の活性化、並びにこれらの細胞からの脱顆粒が抑制され、膨疹・そう痒といった症状の発現抑制効果が期待できる。

また、後述する国内外の臨床試験の結果から、既存治療で効果不十分な CU 患者に対して、オマリズマブは蕁麻疹の臨床症状及び QOL をプラセボに比べて改善させ、また忍容性も良好であることが明らかとなった。そのことから、オマリズマブは既存治療に効果不十分な CU 患者に対する新規の有効な治療法となり得ると考える。EAACI ガイドライン 2013 では、オマリズマブは、第二世代 H1AH を増量しても効果不十分な場合に推奨される CU の治療薬として位置づけられている (Zuberbier et al. 2014) 。

なお、CU は症状の軽快・寛解と増悪を繰り返すため、オマリズマブで治療する際には、症状が改善・寛解した場合にはオマリズマブの継続投与の必要性を定期的に評価し、漫然と投与を継続すべきではないと考える。



## 3 開発の経緯

### 3.1 外国での開発経緯

2007 年の難治性の CU 患者に対するオマリズマブの効果を示した症例報告 (Spector and Tan 2007) , 及び 2008 年に報告された 2 つの医師主導試験成績 (Kaplan et al. 2008, Gober et al. 2008) を踏まえ、ノバルティス社による外国での CU に対するオマリズマブの臨床開発は、Proof of Concept (POC) 試験である ADE05 試験から始まった。その後、用量反応試験である Q4577g 試験を実施し、Q4577g 試験で確認された推定至適用量である 75~300 mg を用い、有効性を検証する目的で第 III 相検証試験 2 試験 (Q4881g 及び Q4882g 試験) を、安全性を確認する目的で Q4883g 試験を、それぞれ計画・実施した。その結果、既存治療で効果不十分な 12 歳以上の CU 患者に対するオマリズマブの臨床推奨用法・用量における有効性及び良好な忍容性が確認できた事から、欧州連合 (European Union, EU) 及び米国では CSU の効能・効果で 2013 年に承認申請し、それぞれ 2014 年 2 月及び 3 月に以下の効能・効果及び用法・用量にて承認を取得した。

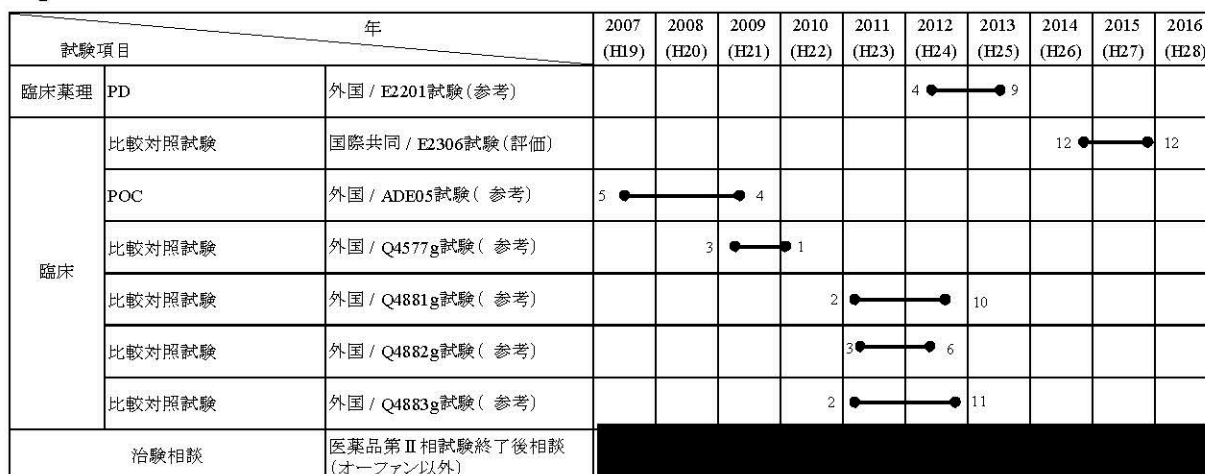
- EU :
  - 効能又は効果 : H1AH 治療で効果不十分な成人及び青少年 (12 歳以上) の CSU に対する併用療法
  - 用法及び用量 : 300 mg を 4 週間ごとに皮下投与する。
- 米国 :
  - 効能又は効果 : H1AH 治療にもかかわらず症状が持続的に認められる成人及び青少年 (12 歳以上) の CSU 患者
  - 用法及び用量 : 150 mg 又は 300 mg を 4 週間ごとに皮下投与する。

なお、CU に対するオマリズマブの作用機序を解明する目的で、オマリズマブ (300 mg を 12 週間投与) の皮内での FcεRI 陽性又は IgE 陽性細胞の変化をプラセボと比較する臨床薬理学的試験 (E2201 試験) も実施した。

### 3.2 国内での開発経緯

上述した外国でのオマリズマブの CU に対する開発経緯を踏まえ、日本での CU の適応に対する開発を計画・実施した。CU の適応追加に関わる開発の経緯図を Figure 3-1 に示す。

Figure 3-1 開発の経緯図



PD = pharmacodynamics, POC = proof of concept

CU の適応に対する日本での開発は、オマリズマブの既承認の適応症での国内データ及び海外の CU 患者の臨床試験データを以下の点で最大限に利用できると考え、オマリズマブ 2 用量 (150 mg, 300 mg) を用い、投与期間 12 週間の 12 歳以上 75 歳以下の CU 患者を対象とした第 III 相検証試験 (E2306 試験) のみを実施する計画とした (2.5-1.2.1.2 項)。

- E2306 試験ではオマリズマブの用量を 2 用量 (150 mg, 300 mg) と設定したが、日本人のオマリズマブの CU 患者での推定至適用法・用量の設定に、  
と考えたこと。
- E2306 試験では投与期間を 12 週間と設定したが、12 週を超えて投与した場合の日本人 CU 患者の有効性及び安全性の評価は、  
と考えたこと。
- E2306 試験では 12 歳以上 18 歳未満の青少年を含める計画としたが、  
と予想されたため、  
及び  
と考えたこと。

E2306 試験の試験デザイン及び臨床データパッケージの妥当性については、医薬品医療機器総合機構 (以下、機構と略す) と「医薬品第Ⅱ相試験終了後相談 (オープン以外)」で協議した。その際得られた助言の要約を以下に記載する (薬機審長発第 号, 平成 年 月 日)。

- である。

- [REDACTED] である。

以上を踏まえ、既存治療で効果不十分な日本人及び韓国人 CU 患者を対象とし、オマリズマブの有効性及び安全性を検証する第 III 相検証試験を計画・実施した。また、本申請では、E2306 試験成績を評価資料、外国試験成績を参考資料とする臨床データパッケージを構築した (Table 3-1)。なお、オマリズマブの品質、毒性の試験成績については、成人の気管支喘息申請時に提出済みである。

**Table 3-1 臨床データパッケージ**

| 試験の種類   |              | 試験対象                                     | 試験番号    | 実施地域 | 資料 |
|---------|--------------|--|---------|------|----|
| 臨床薬理    | PD           | H1AH に効果不十分な CU 患者                       | E2201   | 外国   | 参考 |
| 有効性・安全性 | POC          | H1AH に効果不十分な甲状腺ペルオキシダーゼに対する IgE 陽性 CU 患者 | ADE05   | 外国   | 参考 |
|         | 検証, プラセボ対照   | H1AH に効果不十分な CU 患者                       | E2306   | 日・韓  | 評価 |
|         | 用量設定, プラセボ対照 | H1AH に効果不十分な CU 患者                       | Q4577g  | 外国   | 参考 |
|         | 検証, プラセボ対照   | H1AH に効果不十分な CU 患者                       | Q4881g  | 外国   | 参考 |
|         | 検証, プラセボ対照   | H1AH に効果不十分な CU 患者                       | Q4882g  | 外国   | 参考 |
|         | 安全性, プラセボ対照  | H1AH+H2AH and/or LTRA に効果不十分な CU 患者      | Q4883g  | 外国   | 参考 |
| その他     | 長期投与時の安全性    | 小児アレルギー性喘息患者                             | B1301E1 | 日本   | 参考 |

PD=pharmacodynamics, POC=proof of concept, H1AH=ヒスタミン H<sub>1</sub> 受容体拮抗薬, H2AH=ヒスタミン H<sub>2</sub> 受容体拮抗薬, LTRA=ロイコトリエン受容体拮抗薬

### 3.2.1 既存治療で効果不十分な CU 患者を対象とした臨床試験 (E2306 試験)

E2306 試験は、H1AH 治療で効果不十分な CU 患者 (12 歳以上) を対象に、オマリズマブの有効性 (臨床症状改善効果) がプラセボに比べて優れることを検証することを目的とした、ランダム化、二重盲検、並行群間比較、国際共同試験 (日本及び韓国) である。本試験は、スクリーニング期 (2 週間)、投与期 (12 週間)、追跡調査期 (12 週間) で構成された。ランダム化された被験者は 218 名 (オマリズマブ 300 mg 群 73 名, 150 mg 群 71 名, プラセボ群 74 名, 以下同順) で、そのうち日本人被験者は 105 名 (35 名, 34 名, 36 名) であった。

主要評価項目である Week 12 の週間そう痒スコアのベースラインからの変化量の群間差 (オマリズマブ群-プラセボ群) は、オマリズマブ 300 mg 群で -3.70 (-5.310, -2.098) [最小二乗平均 (95%信頼区間)], 150 mg 群で -2.29 (-3.921, -0.654) であった。群間比較の結果、いずれの用量でも群間に有意な差が認められ、オマリズマブ 300 mg, 150 mg のそう痒改善効果はプラセボに比べて優れることが示された。週間そう痒スコアの変化量はいずれの群でも臨床的に意義のある最小差 (minimally important difference, MID=週間そう痒スコアの減少が 5 以上) を超えて

おり、300 mg 群では MID の約 2 倍に相当するスコアの大きな減少（改善）が認められた（2.5-4.3.4.1 項）。

そう痒と膨疹症状の包括的な評価項目である urticaria activity score 7 (UAS7) による評価では、Week 12 でレスポnder (UAS7 ≤ 6) となった被験者の割合は、プラセボ群 (19%) に比べてオマリズマブ群で有意に高く (300 mg 群 58%, 150 mg 群 43%)、オマリズマブは CU の臨床症状を良好にコントロールできることが示された。また、Week 12 で完全寛解 (UAS7 = 0) となった被験者の割合はプラセボ群 (4%) に比べてオマリズマブ群で高く (300 mg 群 36%, 150 mg 群 19%)、300 mg 群でのみプラセボ群に比べて有意な差が認められた (2.5-4.3.4.1 項)。

投与期 12 週間に認められたオマリズマブ投与群の有害事象発現率は、プラセボ群と同程度か、それより低く、高度の有害事象の発現はなかった (2.5-5.4.1 項)。また、本試験期間中に発現した重篤な有害事象は、すべて治験薬との関連を否定された。また、150 mg 群の 1 名が有害事象 (軽度の咽頭浮腫) により治験薬投与を中止した。本事象と治験薬との関連は否定できないと判断された (2.5-5.4.2 項)。

E2306 試験でのオマリズマブの忍容性は良好で、本試験の安全性プロファイルは CU 患者を対象とした外国臨床試験、並びに既承認の気管支喘息患者を対象とした国内外の臨床試験と同様であり、新たな安全性上の懸念は認められなかった。

以上の結果より、既存治療で効果不十分な CU 患者に対してオマリズマブの有効性及び安全性が確認された。

## 4 特徴及び有用性

現在までに実施された臨床薬理試験及び臨床試験成績に基づき、オマリズマブの特徴及び有用性を以下に示す。

### 1. 新規作用機序の CU 治療薬である

オマリズマブが遊離 IgE に結合して血中及び皮膚組織の遊離 IgE を低下させることにより、肥満細胞や好塩基球表面の FcεRI の発現が抑制される。その結果、CU の病態形成に関与する FcεRI の下流シグナル経路が制御され、炎症反応が抑制される。このように、オマリズマブは他の CU 治療薬とは異なる作用機序を有し、既存治療で効果不十分な CU 患者に対する新規の有効な治療法になり得ると期待される。

### 2. CU の主症状であるそう痒及び膨疹症状を速やかに改善・消失させる

E2306 試験では、オマリズマブ 300 mg, 150 mg の Week 12 の週間そう痒スコアのベースラインからの変化量はプラセボ群に比べて有意に大きく、オマリズマブ 300 mg, 150 mg 4 週間隔投与のそう痒改善効果はプラセボに比べて優れることが示された。そう痒・膨疹症状に対する改善効果は本剤投与開始後速やかに認められ (1~2 週間以内)、投与後 2 週間以内に約半数の被験者で週間そう痒スコア及び UAS7 のいずれも臨床的に意義のある程度まで改善した (週間そう痒ス

コア、UAS7 が MID に達するまでの期間の中央値は、いずれの項目に対してもオマリズマブ 300 mg 群 2.0 週、150 mg 群 2.0 週、プラセボ群 5.0 週)。したがって、オマリズマブの臨床的に意味のある症状改善効果は投与後早期より認められることが明らかとなった (2.5-4.3.4.1 項)。

また、Week 12 にレスポnder (UAS7 ≤ 6) となった被験者の割合はオマリズマブ 300 mg 群 (57.5%)、150 mg 群 (42.9%) がプラセボ群 (18.9%) より有意に高かった。完全寛解 (UAS7 = 0) に達した被験者の割合もオマリズマブ 300 mg 群 (35.6%)、150 mg 群 (18.6%) がプラセボ群 (4.1%) に比べて高かった。完全寛解に達した被験者の割合に関しては、300 mg 群でのみプラセボ群との比較で有意な差が認められた (2.5-4.3.4.1 項)。

以上より、オマリズマブ 300 mg は、CU の主症状であるそう痒及び膨疹症状を速やかに改善させ、また完全寛解も期待できた。

### 3. CU 罹患により大きく損なわれる QOL を改善する

皮膚疾患に特異的な健康関連 QOL の指標である Dermatology Life Quality Index (DLQI) 総合スコア (総合スコアの範囲: 0~30) は、スコアが大きいくほど QOL の障害度が高く (Finlay and Khan 1994)、スコアが 10 を超えると「疾患が患者の生活に非常に大きな影響を及ぼしている」とされる (Hongbo et al. 2005)。E2306 試験に参加した被験者の試験開始前の DLQI 総合スコアは 10.9~12.0 (各投与群の平均値) で、疾患による被験者の QOL の障害度が比較的高いことが示唆された。Week 12 の DLQI 総合スコアのベースラインからの変化量の投与群間差 (オマリズマブ群-プラセボ群) は、オマリズマブ 300 mg 群で-3.1 (-4.59, -1.69) [最小二乗平均 (95%信頼区間)]、150 mg 群で-1.9 (-3.36, -0.44) で、300 mg 群ではプラセボ群との比較で群間に有意な差が認められた。また、CU 患者での DLQI 総合スコアの変化量の MID は 2.2~3.1 とされていることから (Shikiar et al. 2005)、Week 12 の DLQI 総合スコアのベースラインからの変化量において、オマリズマブ 300 mg は臨床的に意義のある改善を示した (2.5-4.3.4.2 項)。

以上より、オマリズマブ 300 mg は CU 罹患により大きく損なわれる QOL を改善させることが期待できた。

### 4. CU 患者の予後を悪化させる血管性浮腫の改善が期待できる

血管性浮腫を合併する場合の予後はそうでない場合より不良とされ、患者の身体的・精神的負荷もより大きいとされる (日皮会ガイドライン 2011)。E2306 試験では、ベースラインで血管性浮腫ありの被験者はいずれの投与群も約 20%であった。E2306 試験の結果、ベースラインでの血管性浮腫の状態によらず、オマリズマブ投与群の被験者では 84 日間の投与期間中に「血管性浮腫あり」の報告はほとんどなかった。「血管性浮腫あり」の日数 (最小二乗平均) はオマリズマブ投与群 (300 mg 群 0.19 日、150 mg 群 0.51 日) のほうがプラセボ群 (1.57 日) より少なかった (2.5-4.3.4.3 項)。



Q4881g 及び Q4882g 試験では、ベースラインで血管性浮腫ありの被験者は全体の約半数 (47.5%) であった。Week 4 から Week 12 までの「血管性浮腫なし」の日の割合は、オマリズマブ 300 mg 群 (Q4881g 試験 96.1%, Q4882g 試験 95.5%) のほうがプラセボ群 (88.2%, 89.2%) より高く、いずれの試験でも群間に有意な差が認められた (2.5-4.3.4.3 項)。

以上より、オマリズマブ 300 mg は CU 患者の血管性浮腫を改善させることが期待できた。

## 5. 既存治療薬との併用時の CU 患者における忍容性は良好である

H1AH を併用した患者を対象とした E2306 試験で、投与期 12 週間の有害事象発現率は、オマリズマブ 300 mg 群 (35.6%) はプラセボ群 (41.9%) より低く、150 mg 群 (43.7%) はプラセボ群と同程度であった。副作用発現率 (オマリズマブ 300 mg 群 : 8.2%, オマリズマブ 150 mg 群 : 7.0%, プラセボ群 : 8.1%) は、オマリズマブ投与群とプラセボ群で同程度であった。投与期に発現した有害事象の重症度はすべて軽度又は中等度であり、高度の事象はなかった。また、用量の増加にともなって有害事象の発現率が高くなることはなく、有害事象の重症度が悪化することもなかった。さらに、本試験期間中に発現した重篤な有害事象は、すべて治験薬との関連を否定された。治験薬の投与中止に至った有害事象は、オマリズマブ 150 mg 群の 1 名にみられた軽度の咽頭浮腫だけであった (2.5-5.4 項)。

H1AH 等を併用した患者を対象とした外国の第 III 相試験 (Q4881g, Q4882g, Q4883g 試験) 併合データで多くみられた事象の内容及び頻度は、E2306 試験と同様であった。事象の多くは軽度又は中等度で、オマリズマブ投与群で発現した高度の事象の発現率は低く (1.7~5.3%)、プラセボ群 (6.2%) と同程度か、それより低かった (2.5-5.4 項)。

また、本剤の最新の Core Risk Management Plan (version 11) に基づき、「重要な特定されたりスク」及び「重要な潜在的リスク」の E2306 試験での発現状況を外国第 III 相試験 (Q4881g, Q4882g, Q4883g 試験) の結果と合せて評価した。その結果、CU 患者にオマリズマブを投与した際に予測される安全性プロファイルは既承認の適応に対するものと同様で、新たに追加すべきリスクはないことが確認できた (2.5-6.2 項)。

以上より、既存治療薬との併用時の CU 患者におけるオマリズマブの忍容性は良好であることが示された。

## 5 まとめ

CU ではほぼ毎日そう痒や膨疹があらわれるため、患者は正常な日常・社会生活をおくることができず、QOL が著しく低下する。また、CU の症状の発現は予測できないため、患者は強い不安感や抑うつ、睡眠障害等精神的な負荷を訴えることが多くなる。血管性浮腫を併発する場合には疾患の負荷は一層大きくなる (2.1 項)。

現在、国内外の治療ガイドラインで推奨される CU の第一選択薬は第二世代 H1AH である。しかし、第二世代 H1AH による治療を受けている患者でも、全体としておよそ半数はいまだ十分な

症状の改善が得られていない。さらに、現在までのところ、国内では、第二世代 H1AH に効果不十分な CU 患者に対し、安全に投与でき、かつ高い臨床効果が期待できる治療は存在しない (2.2 項)。

オマリズマブは、CU の既存治療薬のいずれとも異なる新規の薬理作用機序を有する。近年の知見により、既存治療で効果不十分な CU 患者に対するオマリズマブの有用性が示唆され、ノバルティス社は外国にて用量反応試験並びに複数の検証試験を実施した。その結果、オマリズマブの CU に対する有効性及び良好な忍容性を確認できたことから、EU 及び米国において CSU の効能・効果にて申請し、承認を取得した。

外国での良好な臨床試験成績を踏まえ、国内においても CU に対する臨床開発計画に着手した。そして、機構からの助言を踏まえ、日本・韓国の国際共同試験である第 III 相検証試験 (E2306 試験) を計画・実施した。E2306 試験の結果、既存治療で効果不十分な CU 患者に対し、オマリズマブ 300 mg はそう痒及び膨疹症状を速やかに改善・消失させることが確認できた。また、DLQI 総合スコアを指標とした評価にて、オマリズマブ 300 mg は CU 患者の QOL を改善させた。さらに、オマリズマブ 300 mg は CU 患者の血管性浮腫を改善させることが期待できた。

E2306 試験にて CU 患者にオマリズマブ 300 mg, 150 mg を投与した際の忍容性は良好であり、いずれの有害事象もオマリズマブの用量の増加にともなって発現率が高くなることはなかった。報告された有害事象は、外国の CU 患者での臨床試験やオマリズマブの既承認の適応症であるアレルギー性喘息患者でみられた事象と同様で、新たなリスクは特定されなかった。特に、抗体製剤で一般的にリスクとされる過敏症や即時型の事象の発現もほとんどみられず、重篤な有害事象や投与中止を要する事象の発現頻度は低く、多くはプラセボ群と同程度であった。

したがって、既存治療で効果不十分な CU 患者の薬物治療において、オマリズマブの期待されるベネフィットは予測されるリスクに比べて高く、オマリズマブは、現在の CU の薬物治療の医療ニーズに合致した、臨床上意義の高い薬剤であると考えられる。

以上を踏まえ、以下のとおり承認事項一部変更承認申請を行うこととした。

【申請品目】

ゾレア皮下注用 75 mg, ゾレア皮下注用 150 mg

【一般的名称】

オマリズマブ (遺伝子組換え)

【効能又は効果 (案)】

1. 気管支喘息 (既存治療によっても喘息症状をコントロールできない難治の患者に限る)
2. 慢性蕁麻疹 (既存治療で効果不十分な患者に限る)

(下線部：本申請に伴う変更箇所)

【用法及び用量 (案)】

1. 気管支喘息

通常、オマリズマブ (遺伝子組換え) として 1 回 75~600 mg を 2 又は 4 週間毎に皮下に注

射する。1 回あたりの投与量並びに投与間隔は、初回投与前の血清中総 IgE 濃度及び体重に基づき、下記の投与量換算表により設定する。

投与量換算表（1 回投与量）

（略）

## 2. 慢性蕁麻疹

通常、成人及び 12 歳以上の小児にはオマリズマブ（遺伝子組換え）として 1 回 300 mg を 4 週間毎に皮下に注射する。

（下線部：本申請に伴う変更箇所）

なお、審査中の独立行政法人医薬品医療機器総合機構との協議内容を踏まえ、本剤の投与対象をより明確にするため、効能又は効果（案）を以下のとおり変更した。

【効能又は効果（案）】

1. 気管支喘息（既存治療によっても喘息症状をコントロールできない難治の患者に限る）
2. 特発性の慢性蕁麻疹（既存治療で効果不十分な患者に限る）

（下線部：本申請に伴う変更箇所）

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## 1.6 外国における使用状況等に関する資料

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## 1 外国における使用状況等

2017年2月現在、本剤はアレルギー性喘息の適応としてEU、米国等世界90カ国以上で承認されている。また、慢性特発性蕁麻疹の適応としてEU、米国等世界85カ国以上で承認されている。主要国での承認状況をTable 1-1に示す。

**Table 1-1 主要国での承認状況**

| 国名 | 販売名  | 承認年月日  | 剤型・含量   | 効能・効果  |   |
|----|--|--|---|--|---|
| EU | Xolair<br>75 mg,<br>150 mg<br>powder and<br>solvent for<br>solution for<br>injection | 75 mg 及び 150 mg :<br>アレルギー性喘息 :<br>成人及び青少年 (12<br>歳以上) | 凍結乾燥注射剤及<br>び注射用溶解液<br>75 mg : 溶解後<br>0.6 mL 溶液中にオ<br>マリズマブ 75 mg<br>を含有          | 75 mg 及び 150 mg :<br><b>アレルギー性喘息</b><br>ゾレアは成人、青少年及び小児 (6 歳以上<br>12 歳未満) に適応である。<br><br>ゾレア投与は IgE (免疫グロブリン E) の<br>関与が確定した喘息患者に対してのみ考慮<br>すること。   |   |
|    |  | 2005年10月25日  | 150 mg : 溶解後<br>1.2 mL 溶液中にオ<br>マリズマブ<br>150 mg を含有                               | <u>成人及び青少年 (12 歳以上)</u><br>ゾレアは、通年性空中アレルギーに対して<br>皮膚試験陽性または <i>in vitro</i> 反応性であ<br>り、肺機能が低下し (FEV <sub>1</sub> <80%) かつ頻<br>回の日中の症状又は夜間覚醒があり、毎日<br>の高用量吸入ステロイド及び長時間作用性<br>吸入 β <sub>2</sub> 刺激薬併用にもかかわらず、重度<br>の喘息増悪が複数回証明されている重症の<br>持続性アレルギー性喘息の患者において、<br>喘息コントロールを改善するための併用療<br>法として適応がある。 |   |
|    |  | アレルギー性喘息 :<br>小児 (6 歳以上 12 歳<br>未満)<br>2009年7月27日      | 150 mg :<br>慢性特発性蕁麻疹<br>2014年2月28日  | <u>小児 (6 歳以上 12 歳未満)</u><br>ゾレアは、通年性空中アレルギーに対して<br>皮膚試験陽性または <i>in vitro</i> 反応性であ<br>り、頻回の日中の症状又は夜間覚醒があ<br>り、毎日の高用量吸入ステロイド及び長時<br>間作用性吸入 β <sub>2</sub> 刺激薬併用にもかかわら<br>ず重度の喘息増悪が複数回証明されている<br>重症の持続性アレルギー性喘息の患者にお<br>いて、喘息コントロールを改善するための<br>併用療法として適応がある。                                       |   |
|    | Xolair<br>75 mg,<br>150 mg<br>solution for<br>injection                              | 75 mg 及び 150 mg :<br>アレルギー性喘息 :<br>成人及び青少年 (12<br>歳以上) | シリンジ充填済み<br>注射剤<br>75 mg : 0.5 ml 溶<br>液のプレフィルド<br>シリンジ中にオマリ<br>ズマブ 75 mg を<br>含有 | 150 mg :<br>慢性特発性蕁麻疹<br>2014年2月28日   | 150 mg :<br><b>慢性特発性蕁麻疹</b><br>ゾレアは、ヒスタミン H1 受容体拮抗薬に<br>よる治療で効果不十分な成人及び青少年<br>(12 歳以上) 慢性特発性蕁麻疹患者の併<br>用療法として適応がある。 |
|    |  | 2009年2月10日   | 150 mg : 1 ml 溶液<br>のプレフィルドシ<br>リンジ中にオマリ<br>ズマブ 150 mg を<br>含有                    | 2009年7月27日   |   |
|    |  | アレルギー性喘息 :<br>小児 (6 歳以上 12 歳<br>未満)<br>2009年7月27日      | 150 mg :<br>慢性特発性蕁麻疹<br>2014年2月28日  |  |   |

|    |  |  |  |  |
|----|--|--|--|--|
| 米国 | XOLAIR<br>(omalizumab)<br>for<br>injection, for<br>subcutaneous<br>use | 喘息：成人及び青少年（12歳以上）<br>2003年6月20日<br><br>喘息：小児（6歳以上12歳未満）<br>2016年7月6日<br><br>慢性特発性蕁麻疹<br>2014年3月21日 | 凍結乾燥注射剤<br>150 mg：溶解後<br>1.2 mL 溶液中にオマリズマブ<br>150 mg を含有<br><br>75 mg 製剤は 2004年2月27日に承認されているが、添付文書は<br>150 mg 製剤のみ | <b>喘息</b><br><br>ゾレアは、通年性吸入抗原に対する皮膚テスト陽性又は <i>in vitro</i> 反応性を示し、吸入ステロイド薬で症状を十分にコントロールできない6歳以上の中等症～重症持続型喘息患者を適応とする。<br><br>これらの患者では、本剤投与により喘息増悪の発現率が低下することが示されている。<br><br><b>慢性特発性蕁麻疹</b><br><br>ゾレアは、ヒスタミン H1 受容体拮抗薬による治療にもかかわらず、症状が持続的に認められる成人及び12歳以上の青少年の慢性特発性蕁麻疹患者を適応とする治療薬である。 |
|----|--|--|--|--|

## 2 外国の添付文書等の概要

EU 共通の添付文書（2016年10月改訂）の概略を Table 2-1 に、米国の添付文書（2016年7月改訂）の概略を Table 2-2 に示す。

**Table 2-1 EU 共通の添付文書の概略**

|                     |   |
|---------------------|---|
| 販売名                 | Xolair 75 mg powder and solvent for solution for injection<br>Xolair 150 mg powder and solvent for solution for injection<br>Xolair 75 mg solution for injection<br>Xolair 150 mg solution for injection  |
| 剤型・含量               | <b>Xolair 75 mg powder and solvent for solution for injection</b><br>1 バイアル中にオマリズマブ 75 mg を含有する。溶解後は 1 バイアル中にオマリズマブ 125 mg/ml (0.6 ml 中に 75 mg) を含有する。<br><b>Xolair 150 mg powder and solvent for solution for injection</b><br>1 バイアル中にオマリズマブ 150 mg を含有する。溶解後は 1 バイアル中にオマリズマブ 125 mg/ml (1.2 ml 中に 150 mg) を含有する。<br><b>Xolair 75 mg solution for injection</b><br>0.5 ml 溶液のプレフィルドシリンジ中にオマリズマブ 75 mg を含有する。<br><b>Xolair 150 mg solution for injection</b><br>1 ml 溶液のプレフィルドシリンジ中にオマリズマブ 150 mg を含有する。 |
| 効能・効果 <sup>注)</sup> | <u>アレルギー性喘息</u><br>ゾレアは成人、青少年及び小児（6歳以上12歳未満）に適応である。<br><br>ゾレア投与は IgE（免疫グロブリン E）の関与が確定した喘息患者に対してのみ考慮すること。<br><br><u>成人及び青少年（12歳以上）</u><br>ゾレアは、通年性空中アレルギーに対して皮膚試験陽性または <i>in vitro</i> 反応性であり、肺機能が低下し（FEV <sub>1</sub> < 80%）かつ頻回に日中の症状又は夜間覚醒があり、毎日の高用量吸入ステロイド及び長時間作用性吸入 β <sub>2</sub> 刺激薬併用にもかかわらず、重度の喘息増悪が複数回証明され  |

|                     |   |
|---------------------|---|
| 販売名                 | <p>Xolair 75 mg powder and solvent for solution for injection<br/> Xolair 150 mg powder and solvent for solution for injection<br/> Xolair 75 mg solution for injection<br/> Xolair 150 mg solution for injection</p>   |
|                     | <p>ている重症の持続性アレルギー性喘息の患者において、喘息コントロールを改善するための併用療法として適応がある。</p> <p><u>小児（6歳以上12歳未満）</u><br/> ゾレアは、通年性空中アレルギーに対して皮膚試験陽性または <i>in vitro</i> 反応性であり、頻回に日中の症状又は夜間覚醒があり、毎日の高用量吸入ステロイド及び長時間作用性吸入 <math>\beta_2</math> 刺激薬併用にもかかわらず重度の喘息増悪が複数回証明されている重症の持続性アレルギー性喘息の患者において、喘息コントロールを改善するための併用療法として適応がある。</p> <p><u>慢性特発性蕁麻疹（CSU）</u><br/> ゾレアは、ヒスタミン H1 受容体拮抗薬による治療で効果不十分な成人及び青少年（12歳以上）慢性特発性蕁麻疹患者の併用療法として適応がある。</p>   |
| 用法・用量 <sup>注)</sup> | <p>ゾレア投与は、重症持続性喘息又は慢性特発性蕁麻疹の診断及び治療に熟練した医師が開始すること。</p> <p><u>アレルギー性喘息</u><br/> <u>用量</u><br/> ゾレアの適切な投与量及び投与頻度は、治療開始前に測定したベースライン IgE（IU/ml）及び体重によって決定する。患者の用量設定のため、初回投与の前に市販の血清中総 IgE 測定法により患者の IgE 濃度を測定すること。これらの測定値に基づき、各投与時にゾレア 75～600 mg を1～4回に分けて注射する必要がある。</p> <p>IgE が 76 IU/ml 未満の患者ではベネフィットが得られる可能性が低かった。処方医は、IgE が 76 IU/ml 未満の成人及び青少年患者、並びに IgE が 200 IU/ml 未満の小児患者（6歳以上12歳未満）について、治療開始前に通年性アレルギーに対する <i>in vitro</i> 反応性（RAST）が明らかに陽性であることを確認すること。</p> <p>換算表は表 1 を、成人、青少年及び小児（6歳以上12歳未満）の投与量設定は表 2 及び 3 を参照する。</p> <p>ベースラインの IgE 濃度又は体重（kg）が投与量設定表の範囲外となる患者にはゾレアを投与しないこと。</p> <p>最大推奨用量はオマリズマブ 600 mg を 2 週間ごとである。</p> |



| 販売名                | Xolair 75 mg powder and solvent for solution for injection<br>Xolair 150 mg powder and solvent for solution for injection<br>Xolair 75 mg solution for injection<br>Xolair 150 mg solution for injection  |                    |         |        |        |                               |        |        |         |          |  |  |        |        |        |        |        |        |        |        |         |          |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |     |          |  |  |  |  |  |  |  |  |     |     |          |  |  |  |  |  |  |     |     |     |     |          |  |  |  |  |  |     |     |     |     |  |          |  |     |  |  |     |     |     |     |  |  |          |     |     |     |     |     |     |     |     |  |  |          |     |     |     |     |     |     |     |  |  |  |           |     |     |     |     |     |     |  |  |  |  |            |     |     |     |     |     |  |  |  |  |  |            |     |     |     |     |     |                               |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |
|--------------------|---|--------------------|---------|--------|--------|-------------------------------|--------|--------|---------|----------|--|--|--------|--------|--------|--------|--------|--------|--------|--------|---------|----------|---------|--|--|--|--|--|--|--|--|--|--|----------|--|--|--|--|--|--|--|--|--|--|----------|--|--|--|--|--|--|--|--|--|-----|----------|--|--|--|--|--|--|--|--|-----|-----|----------|--|--|--|--|--|--|-----|-----|-----|-----|----------|--|--|--|--|--|-----|-----|-----|-----|--|----------|--|-----|--|--|-----|-----|-----|-----|--|--|----------|-----|-----|-----|-----|-----|-----|-----|-----|--|--|----------|-----|-----|-----|-----|-----|-----|-----|--|--|--|-----------|-----|-----|-----|-----|-----|-----|--|--|--|--|------------|-----|-----|-----|-----|-----|--|--|--|--|--|------------|-----|-----|-----|-----|-----|-------------------------------|--|--|--|--|------------|-----|-----|-----|-----|--|--|--|--|--|--|------------|-----|-----|-----|-----|--|--|--|--|--|--|
|                    | <p><b>表 3 : 2 週間ごとの投与。2 週間ごとに皮下注射で投与するゾレアの投与量 (mg/投与)</b></p> <table border="1" data-bbox="432 434 1382 1126"> <thead> <tr> <th rowspan="2">ベースライン IgE (IU/ml)</th> <th colspan="10">体重 (kg)</th> </tr> <tr> <th>≥20-25</th> <th>&gt;25-30</th> <th>&gt;30-40</th> <th>&gt;40-50</th> <th>&gt;50-60</th> <th>&gt;60-70</th> <th>&gt;70-80</th> <th>&gt;80-90</th> <th>&gt;90-125</th> <th>&gt;125-150</th> </tr> </thead> <tbody> <tr> <td>≥30-100</td> <td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td> </tr> <tr> <td>&gt;100-200</td> <td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td> </tr> <tr> <td>&gt;200-300</td> <td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>375</td> </tr> <tr> <td>&gt;300-400</td> <td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>450</td><td>525</td> </tr> <tr> <td>&gt;400-500</td> <td></td><td></td><td></td><td></td><td></td><td></td><td>375</td><td>375</td><td>525</td><td>600</td> </tr> <tr> <td>&gt;500-600</td> <td></td><td></td><td></td><td></td><td></td><td>375</td><td>450</td><td>450</td><td>600</td><td></td> </tr> <tr> <td>&gt;600-700</td> <td></td><td>225</td><td></td><td></td><td>375</td><td>450</td><td>450</td><td>525</td><td></td><td></td> </tr> <tr> <td>&gt;700-800</td> <td>225</td><td>225</td><td>300</td><td>375</td><td>450</td><td>450</td><td>525</td><td>600</td><td></td><td></td> </tr> <tr> <td>&gt;800-900</td> <td>225</td><td>225</td><td>300</td><td>375</td><td>450</td><td>525</td><td>600</td><td></td><td></td><td></td> </tr> <tr> <td>&gt;900-1000</td> <td>225</td><td>300</td><td>375</td><td>450</td><td>525</td><td>600</td><td></td><td></td><td></td><td></td> </tr> <tr> <td>&gt;1000-1100</td> <td>225</td><td>300</td><td>375</td><td>450</td><td>600</td><td></td><td></td><td></td><td></td><td></td> </tr> <tr> <td>&gt;1100-1200</td> <td>300</td><td>300</td><td>450</td><td>525</td><td>600</td><td colspan="5">投与しないこと。投与量推奨のためのデータが得られていない。</td> </tr> <tr> <td>&gt;1200-1300</td> <td>300</td><td>375</td><td>450</td><td>525</td><td></td><td colspan="5"></td> </tr> <tr> <td>&gt;1300-1500</td> <td>300</td><td>375</td><td>525</td><td>600</td><td colspan="6"></td> </tr> </tbody> </table> <p><u>投与期間, モニタリング及び用量調節</u></p> <p>ゾレアは長期投与用である。臨床試験ではゾレア治療の効果が現れるまでに 12~16 週間以上かかることが示されている。ゾレア治療開始から 16 週間後に主治医は、その後の注射を行う前に治療効果を評価すること。16 週以降にゾレアを継続するには、全般的な喘息コントロールに顕著な改善が認められたか否かに基づいて決定する。</p> <p>ゾレア投与の中止により、通常、遊離 IgE 濃度の上昇及び関連する症状が再現する。投与中は総 IgE 濃度が上昇し、投与中止後 1 年間は上昇が持続する。したがってゾレア投与中の IgE 濃度再測定は投与量設定の指針としては使用できない。投与中止後 1 年未満に投与量を設定する場合は、最初の用量設定時に得られた血清中 IgE 濃度に基づいて行うこと。ゾレアの投与中断が 1 年以上の場合は、用量設定のため血清中総 IgE 濃度を再測定してもよい。</p> <p>体重が大幅に変化した場合には投与量を調整すること (表 2 及び 3 参照)。</p> <p><u>慢性特発性蕁麻疹 (CSU)</u></p> <p><u>用量</u></p> <p>推奨用量は 300 mg であり、4 週間ごとに皮下投与する。</p> <p>処方医は治療継続の必要性を定期的に再評価すること。</p> <p>本適応症に対する 6 ヶ月を超える長期治療の臨床試験データは限られている。</p> <p><u>特別な集団</u></p> <p><u>高齢者 (65 歳以上)</u></p> | ベースライン IgE (IU/ml) | 体重 (kg) |        |        |                               |        |        |         |          |  |  | ≥20-25 | >25-30 | >30-40 | >40-50 | >50-60 | >60-70 | >70-80 | >80-90 | >90-125 | >125-150 | ≥30-100 |  |  |  |  |  |  |  |  |  |  | >100-200 |  |  |  |  |  |  |  |  |  |  | >200-300 |  |  |  |  |  |  |  |  |  | 375 | >300-400 |  |  |  |  |  |  |  |  | 450 | 525 | >400-500 |  |  |  |  |  |  | 375 | 375 | 525 | 600 | >500-600 |  |  |  |  |  | 375 | 450 | 450 | 600 |  | >600-700 |  | 225 |  |  | 375 | 450 | 450 | 525 |  |  | >700-800 | 225 | 225 | 300 | 375 | 450 | 450 | 525 | 600 |  |  | >800-900 | 225 | 225 | 300 | 375 | 450 | 525 | 600 |  |  |  | >900-1000 | 225 | 300 | 375 | 450 | 525 | 600 |  |  |  |  | >1000-1100 | 225 | 300 | 375 | 450 | 600 |  |  |  |  |  | >1100-1200 | 300 | 300 | 450 | 525 | 600 | 投与しないこと。投与量推奨のためのデータが得られていない。 |  |  |  |  | >1200-1300 | 300 | 375 | 450 | 525 |  |  |  |  |  |  | >1300-1500 | 300 | 375 | 525 | 600 |  |  |  |  |  |  |
| ベースライン IgE (IU/ml) | 体重 (kg)   |                    |         |        |        |                               |        |        |         |          |  |  |        |        |        |        |        |        |        |        |         |          |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |     |          |  |  |  |  |  |  |  |  |     |     |          |  |  |  |  |  |  |     |     |     |     |          |  |  |  |  |  |     |     |     |     |  |          |  |     |  |  |     |     |     |     |  |  |          |     |     |     |     |     |     |     |     |  |  |          |     |     |     |     |     |     |     |  |  |  |           |     |     |     |     |     |     |  |  |  |  |            |     |     |     |     |     |  |  |  |  |  |            |     |     |     |     |     |                               |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |
|                    | ≥20-25  | >25-30             | >30-40  | >40-50 | >50-60 | >60-70                        | >70-80 | >80-90 | >90-125 | >125-150 |  |  |        |        |        |        |        |        |        |        |         |          |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |     |          |  |  |  |  |  |  |  |  |     |     |          |  |  |  |  |  |  |     |     |     |     |          |  |  |  |  |  |     |     |     |     |  |          |  |     |  |  |     |     |     |     |  |  |          |     |     |     |     |     |     |     |     |  |  |          |     |     |     |     |     |     |     |  |  |  |           |     |     |     |     |     |     |  |  |  |  |            |     |     |     |     |     |  |  |  |  |  |            |     |     |     |     |     |                               |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |
| ≥30-100            |   |                    |         |        |        |                               |        |        |         |          |  |  |        |        |        |        |        |        |        |        |         |          |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |     |          |  |  |  |  |  |  |  |  |     |     |          |  |  |  |  |  |  |     |     |     |     |          |  |  |  |  |  |     |     |     |     |  |          |  |     |  |  |     |     |     |     |  |  |          |     |     |     |     |     |     |     |     |  |  |          |     |     |     |     |     |     |     |  |  |  |           |     |     |     |     |     |     |  |  |  |  |            |     |     |     |     |     |  |  |  |  |  |            |     |     |     |     |     |                               |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |
| >100-200           |   |                    |         |        |        |                               |        |        |         |          |  |  |        |        |        |        |        |        |        |        |         |          |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |     |          |  |  |  |  |  |  |  |  |     |     |          |  |  |  |  |  |  |     |     |     |     |          |  |  |  |  |  |     |     |     |     |  |          |  |     |  |  |     |     |     |     |  |  |          |     |     |     |     |     |     |     |     |  |  |          |     |     |     |     |     |     |     |  |  |  |           |     |     |     |     |     |     |  |  |  |  |            |     |     |     |     |     |  |  |  |  |  |            |     |     |     |     |     |                               |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |
| >200-300           |   |                    |         |        |        |                               |        |        |         | 375      |  |  |        |        |        |        |        |        |        |        |         |          |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |     |          |  |  |  |  |  |  |  |  |     |     |          |  |  |  |  |  |  |     |     |     |     |          |  |  |  |  |  |     |     |     |     |  |          |  |     |  |  |     |     |     |     |  |  |          |     |     |     |     |     |     |     |     |  |  |          |     |     |     |     |     |     |     |  |  |  |           |     |     |     |     |     |     |  |  |  |  |            |     |     |     |     |     |  |  |  |  |  |            |     |     |     |     |     |                               |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |
| >300-400           |   |                    |         |        |        |                               |        |        | 450     | 525      |  |  |        |        |        |        |        |        |        |        |         |          |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |     |          |  |  |  |  |  |  |  |  |     |     |          |  |  |  |  |  |  |     |     |     |     |          |  |  |  |  |  |     |     |     |     |  |          |  |     |  |  |     |     |     |     |  |  |          |     |     |     |     |     |     |     |     |  |  |          |     |     |     |     |     |     |     |  |  |  |           |     |     |     |     |     |     |  |  |  |  |            |     |     |     |     |     |  |  |  |  |  |            |     |     |     |     |     |                               |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |
| >400-500           |   |                    |         |        |        |                               | 375    | 375    | 525     | 600      |  |  |        |        |        |        |        |        |        |        |         |          |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |     |          |  |  |  |  |  |  |  |  |     |     |          |  |  |  |  |  |  |     |     |     |     |          |  |  |  |  |  |     |     |     |     |  |          |  |     |  |  |     |     |     |     |  |  |          |     |     |     |     |     |     |     |     |  |  |          |     |     |     |     |     |     |     |  |  |  |           |     |     |     |     |     |     |  |  |  |  |            |     |     |     |     |     |  |  |  |  |  |            |     |     |     |     |     |                               |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |
| >500-600           |   |                    |         |        |        | 375                           | 450    | 450    | 600     |          |  |  |        |        |        |        |        |        |        |        |         |          |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |     |          |  |  |  |  |  |  |  |  |     |     |          |  |  |  |  |  |  |     |     |     |     |          |  |  |  |  |  |     |     |     |     |  |          |  |     |  |  |     |     |     |     |  |  |          |     |     |     |     |     |     |     |     |  |  |          |     |     |     |     |     |     |     |  |  |  |           |     |     |     |     |     |     |  |  |  |  |            |     |     |     |     |     |  |  |  |  |  |            |     |     |     |     |     |                               |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |
| >600-700           |   | 225                |         |        | 375    | 450                           | 450    | 525    |         |          |  |  |        |        |        |        |        |        |        |        |         |          |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |     |          |  |  |  |  |  |  |  |  |     |     |          |  |  |  |  |  |  |     |     |     |     |          |  |  |  |  |  |     |     |     |     |  |          |  |     |  |  |     |     |     |     |  |  |          |     |     |     |     |     |     |     |     |  |  |          |     |     |     |     |     |     |     |  |  |  |           |     |     |     |     |     |     |  |  |  |  |            |     |     |     |     |     |  |  |  |  |  |            |     |     |     |     |     |                               |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |
| >700-800           | 225   | 225                | 300     | 375    | 450    | 450                           | 525    | 600    |         |          |  |  |        |        |        |        |        |        |        |        |         |          |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |     |          |  |  |  |  |  |  |  |  |     |     |          |  |  |  |  |  |  |     |     |     |     |          |  |  |  |  |  |     |     |     |     |  |          |  |     |  |  |     |     |     |     |  |  |          |     |     |     |     |     |     |     |     |  |  |          |     |     |     |     |     |     |     |  |  |  |           |     |     |     |     |     |     |  |  |  |  |            |     |     |     |     |     |  |  |  |  |  |            |     |     |     |     |     |                               |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |
| >800-900           | 225   | 225                | 300     | 375    | 450    | 525                           | 600    |        |         |          |  |  |        |        |        |        |        |        |        |        |         |          |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |     |          |  |  |  |  |  |  |  |  |     |     |          |  |  |  |  |  |  |     |     |     |     |          |  |  |  |  |  |     |     |     |     |  |          |  |     |  |  |     |     |     |     |  |  |          |     |     |     |     |     |     |     |     |  |  |          |     |     |     |     |     |     |     |  |  |  |           |     |     |     |     |     |     |  |  |  |  |            |     |     |     |     |     |  |  |  |  |  |            |     |     |     |     |     |                               |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |
| >900-1000          | 225   | 300                | 375     | 450    | 525    | 600                           |        |        |         |          |  |  |        |        |        |        |        |        |        |        |         |          |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |     |          |  |  |  |  |  |  |  |  |     |     |          |  |  |  |  |  |  |     |     |     |     |          |  |  |  |  |  |     |     |     |     |  |          |  |     |  |  |     |     |     |     |  |  |          |     |     |     |     |     |     |     |     |  |  |          |     |     |     |     |     |     |     |  |  |  |           |     |     |     |     |     |     |  |  |  |  |            |     |     |     |     |     |  |  |  |  |  |            |     |     |     |     |     |                               |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |
| >1000-1100         | 225   | 300                | 375     | 450    | 600    |                               |        |        |         |          |  |  |        |        |        |        |        |        |        |        |         |          |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |     |          |  |  |  |  |  |  |  |  |     |     |          |  |  |  |  |  |  |     |     |     |     |          |  |  |  |  |  |     |     |     |     |  |          |  |     |  |  |     |     |     |     |  |  |          |     |     |     |     |     |     |     |     |  |  |          |     |     |     |     |     |     |     |  |  |  |           |     |     |     |     |     |     |  |  |  |  |            |     |     |     |     |     |  |  |  |  |  |            |     |     |     |     |     |                               |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |
| >1100-1200         | 300   | 300                | 450     | 525    | 600    | 投与しないこと。投与量推奨のためのデータが得られていない。 |        |        |         |          |  |  |        |        |        |        |        |        |        |        |         |          |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |     |          |  |  |  |  |  |  |  |  |     |     |          |  |  |  |  |  |  |     |     |     |     |          |  |  |  |  |  |     |     |     |     |  |          |  |     |  |  |     |     |     |     |  |  |          |     |     |     |     |     |     |     |     |  |  |          |     |     |     |     |     |     |     |  |  |  |           |     |     |     |     |     |     |  |  |  |  |            |     |     |     |     |     |  |  |  |  |  |            |     |     |     |     |     |                               |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |
| >1200-1300         | 300   | 375                | 450     | 525    |        |                               |        |        |         |          |  |  |        |        |        |        |        |        |        |        |         |          |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |     |          |  |  |  |  |  |  |  |  |     |     |          |  |  |  |  |  |  |     |     |     |     |          |  |  |  |  |  |     |     |     |     |  |          |  |     |  |  |     |     |     |     |  |  |          |     |     |     |     |     |     |     |     |  |  |          |     |     |     |     |     |     |     |  |  |  |           |     |     |     |     |     |     |  |  |  |  |            |     |     |     |     |     |  |  |  |  |  |            |     |     |     |     |     |                               |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |
| >1300-1500         | 300   | 375                | 525     | 600    |        |                               |        |        |         |          |  |  |        |        |        |        |        |        |        |        |         |          |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |     |          |  |  |  |  |  |  |  |  |     |     |          |  |  |  |  |  |  |     |     |     |     |          |  |  |  |  |  |     |     |     |     |  |          |  |     |  |  |     |     |     |     |  |  |          |     |     |     |     |     |     |     |     |  |  |          |     |     |     |     |     |     |     |  |  |  |           |     |     |     |     |     |     |  |  |  |  |            |     |     |     |     |     |  |  |  |  |  |            |     |     |     |     |     |                               |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |            |     |     |     |     |  |  |  |  |  |  |



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| 販売名                  | <p>Xolair 75 mg powder and solvent for solution for injection<br/> Xolair 150 mg powder and solvent for solution for injection<br/> Xolair 75 mg solution for injection<br/> Xolair 150 mg solution for injection</p>   |
|                      | <p>65歳を超える患者においてゾレアの使用に関して得られたデータは限られているが、高齢者が非高齢成人と異なる用量を要するという根拠はない。</p> <p><u>腎機能障害又は肝機能障害</u><br/> 腎又は肝機能障害がゾレアの薬物動態に及ぼす影響に関する試験は行われていない。臨床用量では主に細網内皮系（RES）がオマリズマブのクリアランスを担うため、腎又は肝機能障害によってクリアランスが変化する可能性は低い。これらの患者では特別な用量調節は推奨されないが、注意して投与すること。</p> <p><u>小児患者集団</u><br/> 6歳未満の小児アレルギー性喘息患者におけるゾレアの安全性及び有効性は確立していない。データが得られていない。</p> <p>12歳未満の小児CSU患者におけるゾレアの安全性及び有効性は確立していない。</p> <p><u>用法</u><br/> 皮下投与にのみ使用する。静脈内又は筋肉内に投与しないこと。</p> <p>皮下注射は上肢の三角筋領域に行う。または、三角筋領域に投与できない理由がある場合は、代わりに大腿部に注射してもよい。</p> <p>ゾレアの自己注射の経験は限られている。したがって医療関係者による投与に限定する。</p> <p>投与前の製剤の溶解法は本剤の使用法の項、及び添付文書の医療従事者向け情報を参照する。</p> |
| 使用上の注意 <sup>注)</sup> | <p><b>禁忌</b><br/> 有効成分又は添加物に対する過敏症。</p> <p><b>警告及び使用上の注意</b><br/> <u>全般</u><br/> ゾレアは喘息の急性増悪、急性気管支痙攣又は喘息発作重積には適応がない。</p> <p>ゾレアは、高IgE症候群又はアレルギー性気管支肺アスペルギルス症の患者において、若しくは食物アレルギー、アトピー性皮膚炎、又はアレルギー性鼻炎に誘発されるものを含むアナフィラキシー反応の予防に関して試験されていない。ゾレアはこれらの疾患には適応がない。</p> <p>ゾレア治療は、自己免疫疾患、免疫複合体介在疾患、若しくは既存の腎又は肝機能障害がある患者において試験されていない。これらの疾患集団にゾレアを投与する場合は注意すること。</p> <p>ゾレア治療の開始後に全身性又は吸入ステロイドを急に中止することは推奨されない。ステロイドの減量は医師が直接監督して徐々に行うこと。</p> <p><u>免疫系異常</u><br/> <u>I型アレルギー反応</u></p>   |

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|     | <p>アナフィラキシー及びアナフィラキシーショックを含む局所又は全身の I 型アレルギー反応が、ゾレア投与時、又は長期間の投与後に発現することがある。これらの反応の大部分はゾレアの初回注射時及びそれ以降の注射時に 2 時間以内に発現したが、注射から 2 時間超が経過してから発現した反応があり、24 時間超が経過してから発現した反応さえもあった。したがってゾレア投与後にはアナフィラキシー反応の治療薬が速やかに使用できるよう常備すること。このような反応の可能性があること、及びアレルギー反応が発現した場合は速やかに医療機関を受診することを患者に説明すること。オマリズマブ投与と関連のないアナフィラキシーの既往歴がある場合、ゾレア投与後のアナフィラキシーの危険因子となる可能性がある。</p> <p>臨床試験において少数の患者に抗オマリズマブ抗体が検出されている。抗ゾレア抗体の臨床的意義はよくわかっていない。</p> <p><u>血清病</u><br/> オマリズマブを含めヒトモノクローナル抗体を投与した患者で、遅延型の III 型アレルギー反応である血清病及び血清病様反応が認められている。病態生理学的な機序として、抗オマリズマブ抗体の発現による免疫複合体の形成及び沈着等が示唆される。発症は通常、初回又は以降の注射から 1～5 日後であったが、長期間の投与後の場合もあった。血清病を示唆する症状には、関節炎／関節痛、発疹（蕁麻疹又は他の形態）、発熱及びリンパ節症がある。本疾患の予防又は治療に抗ヒスタミン薬及びコルチコステロイドが有用なことがあり、患者には疑わしい症状があった場合は報告するよう指導すること。</p> <p><u>Churg-Strauss 症候群及び好酸球増加症候群</u><br/> 重症喘息患者はまれに全身性の好酸球増加症候群又はアレルギー性好酸球性肉芽腫性血管炎（Churg-Strauss 症候群）を呈することがあり、いずれも通常はステロイドの全身投与で治療する。</p> <p>オマリズマブを含め抗喘息薬で治療中の患者は、まれに全身性好酸球増加症及び血管炎を呈する、又は発現することがある。これらの事象は通常、経口ステロイド治療の減量と関連する。</p> <p>これらの患者においては、医師は著明な好酸球増加症、血管炎性皮疹、発疹、肺症状の悪化、副鼻腔の異常、心臓合併症、又はニューロパチーの発現に注意すること。</p> <p>上記の免疫異常があるすべての重症例で、オマリズマブの中止を考慮すること。</p> <p><u>寄生虫（蠕虫）感染症</u><br/> IgE は一部の寄生虫感染症に対する免疫反応に関与している可能性がある。寄生虫感染症のリスクが慢性的に高い患者において、プラセボ対照試験でオマリズマブ投与により感染率がわずかに上昇したが、感染症の経過、重症度、及び治療反応性は変化しなかった。寄生虫感染症を検出するデザインではなかったが、臨床プログラム全体における寄生虫感染症の発現率は 1000 分の 1 名未満であった。しかし、寄生虫感染症のリスクが高い患者では、特に寄生虫感染症が流行している地域に旅行するときには、注意が必要である。推奨される寄生虫治療に反応しない患者では、ゾレアの中止を考慮すること。</p> <p><u>ラテックス過敏症者（Xolair 75 mg, 150 mg solution for injection のみ該当）</u><br/> 本薬剤充填済み注射器の着脱式の針キャップには天然ゴムラテックスの誘導体が含まれる。現</p> |

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|     | <p>時点までに、脱着式の針キャップに天然ゴムラテックスは検出されていない。しかし、ラテックス過敏症の患者を対象に、薬剤充填済み注射器で投与するゾレア溶剤の試験は行われていないため、過敏症反応の潜在的リスクは否定できない。</p> <p><b>薬物相互作用及びその他の形の相互作用</b></p> <p>IgE は一部の寄生虫感染症に対する免疫反応に関与している可能性があるため、ゾレアは蠕虫又は他の寄生虫感染症に対する医薬品の効果を間接的に減弱する可能性がある。</p> <p>チトクローム P450 酵素、排出ポンプ及びタンパク結合機構はオマリズマブのクリアランスに関与しないため、薬物-薬物相互作用の可能性は低い。ゾレアの薬物又はワクチン相互作用試験は実施していない。喘息又は CSU の治療に使用される一般的な処方医薬品が、オマリズマブと相互作用を起こすと予期される薬理学的な理由はない。</p> <p><u>アレルギー性喘息</u></p> <p>臨床試験においてゾレアは通常、吸入及び経口ステロイド、短時間及び長時間作用性吸入 β 刺激薬、ロイコトリエン拮抗薬、テオフィリン、並びに経口抗ヒスタミン薬と併用された。これらの一般的に使用される喘息治療薬によってゾレアの安全性が変化するという所見はなかった。特異的免疫療法（減感作療法）とゾレアの併用に関するデータは限られている。免疫療法とゾレアを併用した臨床試験において、特異的免疫療法と併用したゾレアの安全性及び有効性は、ゾレア単独の場合と差がないことが明らかにされた。</p> <p><u>慢性特発性蕁麻疹（CSU）</u></p> <p>CSU の臨床試験において、ゾレアは抗ヒスタミン剤（H1 及び H2 受容体拮抗薬）及びロイコトリエン受容体拮抗剤（LTRAs）と併用された。アレルギー性喘息における既知の安全性プロファイルの観点から、これらの治療薬によってオマリズマブの安全性が変化するというエビデンスはなかった。さらに、母集団薬物動態分析ではオマリズマブの薬物動態にヒスタミン H2 受容体拮抗薬及び LTRA が関連する影響は見られなかった。</p> <p><u>小児患者集団</u></p> <p>CSU の臨床試験の一部に、ゾレアと抗ヒスタミン剤（H1 及び H2 受容体拮抗薬）及びロイコトリエン受容体拮抗剤（LTRAs）を併用する 12 歳から 17 歳の患者が含まれた。12 歳未満の小児を対象とする試験は行われていない。</p> <p><b>生殖能、妊娠及び授乳</b></p> <p><u>妊娠</u></p> <p>妊婦におけるオマリズマブ使用のデータは限られている。動物試験では生殖毒性に関して直接又は間接の有害作用は示されていない。オマリズマブは胎盤関門を通過するが、胎児に対する有害作用の可能性は不明である。オマリズマブはヒト以外の霊長類において年齢依存的に血小板減少と関連しており、幼若動物において相対感度が高かった。ゾレアは明らかに必要な場合を除いて妊娠中に使用しないこと。</p> <p><u>授乳</u></p> <p>オマリズマブがヒト乳汁中に移行するかは不明である。ヒト以外の霊長類で得られたデータでは、オマリズマブが乳汁中に移行することが示されている。新生児／乳児に対するリスクは除外できない。オマリズマブは授乳中に投与しないこと。</p> |

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| <p>販売名</p> | <p>Xolair 75 mg powder and solvent for solution for injection<br/>Xolair 150 mg powder and solvent for solution for injection<br/>Xolair 75 mg solution for injection<br/>Xolair 150 mg solution for injection</p>   |
|            | <p><u>生殖能</u><br/>オマリズマブのヒト生殖能データはない。ヒト以外の霊長類において特別にデザインした非臨床生殖能試験では、交配試験も含めて、75 mg/kg までの用量のオマリズマブ反復投与後に雄又は雌の生殖能に障害は認められなかった。さらに別の非臨床遺伝毒性試験において、遺伝毒性作用は認められなかった。</p> <p><b>自動車運転及び機械操作に対する影響</b><br/>自動車運転及び機械操作に対するゾレアの影響はほとんどない。</p> <p><b>副作用</b><br/><u>アレルギー性喘息</u><br/><u>安全性プロファイルの要約</u><br/>成人及び12歳以上の青少年における臨床試験で、最も発現頻度が高かった副作用は、頭痛、注射部位疼痛等の注射部位反応、腫脹、紅斑及びびそう痒症であった。6歳以上12歳未満の小児における臨床試験で、最も発現頻度が高かった副作用は、頭痛、発熱及び上腹部痛であった。副作用の大部分は軽度又は中等度であった。</p> <p><u>副作用の一覧</u><br/>表4にゾレアを投与した全安全性評価対象集団において、臨床試験で記録された副作用をMedDRAの器官別大分類及び発現頻度ごとに示す。各発現頻度グループの中では、重症度の高い順に副作用を示す。発現頻度のカテゴリーは、非常に多い(1/10以上)、多い(1/100以上1/10未満)、少ない(1/1,000以上1/100未満)、まれ(1/10,000以上1/1,000未満)及び非常にまれ(1/10,000未満)と定義する。市販後の状況で報告された副作用は頻度不明(利用可能なデータから推定できない)として示す。</p> |

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|--------------------------|---|-------------------|--|-----|-----|----|-------|--------------------|--|----|-------------------|--------------|--|----|---|----|------------------------|--------------|--|----|-----|-----|------------------|-------------|--|-----|-----------|----------------------|--|-----|----------------|----|------|----|---------------------------------------|-------------|--|----|--------|-----|------------------|--------------------|--|-----|-------------------|----|------|----|-----|----------------------|--|----|------------------|----|--------------|--------------------------|--|-------|------|----|-----------------------|-----|-------------------------|
| 販売名                      | Xolair 75 mg powder and solvent for solution for injection<br>Xolair 150 mg powder and solvent for solution for injection<br>Xolair 75 mg solution for injection<br>Xolair 150 mg solution for injection  |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
|                          | <p><b>表 4：アレルギー性喘息における副作用</b></p> <table border="1"> <tr> <td colspan="2"><b>感染症および寄生虫症</b></td> </tr> <tr> <td>少ない</td> <td>咽頭炎</td> </tr> <tr> <td>まれ</td> <td>寄生虫感染</td> </tr> <tr> <td colspan="2"><b>血液およびリンパ系障害</b></td> </tr> <tr> <td>不明</td> <td>特発性血小板減少症（重症例を含む）</td> </tr> <tr> <td colspan="2"><b>免疫系障害</b></td> </tr> <tr> <td>まれ</td> <td>アナフィラキシー反応，その他の重篤なアレルギー性疾患，抗オマリズマブ抗体の発現</td> </tr> <tr> <td>不明</td> <td>血清病（発熱及びリンパ節症を含む場合がある）</td> </tr> <tr> <td colspan="2"><b>神経系障害</b></td> </tr> <tr> <td>多い</td> <td>頭痛*</td> </tr> <tr> <td>少ない</td> <td>失神，錯感覚，傾眠，浮動性めまい</td> </tr> <tr> <td colspan="2"><b>血管障害</b></td> </tr> <tr> <td>少ない</td> <td>体位性低血圧，潮紅</td> </tr> <tr> <td colspan="2"><b>呼吸器，胸郭および縦隔障害</b></td> </tr> <tr> <td>少ない</td> <td>アレルギー性気管支痙攣，咳嗽</td> </tr> <tr> <td>まれ</td> <td>喉頭浮腫</td> </tr> <tr> <td>不明</td> <td>アレルギー性肉芽腫性血管炎（すなわち Churg-Strauss 症候群）</td> </tr> <tr> <td colspan="2"><b>胃腸障害</b></td> </tr> <tr> <td>多い</td> <td>上腹部痛**</td> </tr> <tr> <td>少ない</td> <td>消化不良徴候及び症状，下痢，悪心</td> </tr> <tr> <td colspan="2"><b>皮膚および皮下組織障害</b></td> </tr> <tr> <td>少ない</td> <td>光線過敏症，蕁麻疹，発疹，そう痒症</td> </tr> <tr> <td>まれ</td> <td>血管浮腫</td> </tr> <tr> <td>不明</td> <td>脱毛症</td> </tr> <tr> <td colspan="2"><b>筋骨格系および結合組織障害</b></td> </tr> <tr> <td>まれ</td> <td>全身性エリテマトーデス（SLE）</td> </tr> <tr> <td>不明</td> <td>関節痛，筋肉痛，関節腫脹</td> </tr> <tr> <td colspan="2"><b>一般・全身障害および投与部位の状態</b></td> </tr> <tr> <td>非常に多い</td> <td>発熱**</td> </tr> <tr> <td>多い</td> <td>腫脹，紅斑，疼痛，そう痒症等の注射部位反応</td> </tr> <tr> <td>少ない</td> <td>インフルエンザ様疾患，腕の腫脹，体重増加，疲労</td> </tr> </table> <p>*：6歳以上12歳未満の小児においては非常に多い<br/>**：6歳以上12歳未満の小児において</p> <p><u>慢性特発性蕁麻疹（CSU）</u><br/>安全性プロファイルの要約</p> <p>975名のCSU患者を対象に，オマリズマブ 75 mg，150 mg，300 mg を4週間ごとに投与した場合の安全性及び忍容性を検討し，うち242名にプラセボを投与した。全体として，733名の患者に12週間まで，490名の患者に24週間までオマリズマブでの治療を行った。これらの患者のうち，412名が12週間まで，333名が24週間まで300 mg投与を受けた。</p> | <b>感染症および寄生虫症</b> |  | 少ない | 咽頭炎 | まれ | 寄生虫感染 | <b>血液およびリンパ系障害</b> |  | 不明 | 特発性血小板減少症（重症例を含む） | <b>免疫系障害</b> |  | まれ | アナフィラキシー反応，その他の重篤なアレルギー性疾患，抗オマリズマブ抗体の発現 | 不明 | 血清病（発熱及びリンパ節症を含む場合がある） | <b>神経系障害</b> |  | 多い | 頭痛* | 少ない | 失神，錯感覚，傾眠，浮動性めまい | <b>血管障害</b> |  | 少ない | 体位性低血圧，潮紅 | <b>呼吸器，胸郭および縦隔障害</b> |  | 少ない | アレルギー性気管支痙攣，咳嗽 | まれ | 喉頭浮腫 | 不明 | アレルギー性肉芽腫性血管炎（すなわち Churg-Strauss 症候群） | <b>胃腸障害</b> |  | 多い | 上腹部痛** | 少ない | 消化不良徴候及び症状，下痢，悪心 | <b>皮膚および皮下組織障害</b> |  | 少ない | 光線過敏症，蕁麻疹，発疹，そう痒症 | まれ | 血管浮腫 | 不明 | 脱毛症 | <b>筋骨格系および結合組織障害</b> |  | まれ | 全身性エリテマトーデス（SLE） | 不明 | 関節痛，筋肉痛，関節腫脹 | <b>一般・全身障害および投与部位の状態</b> |  | 非常に多い | 発熱** | 多い | 腫脹，紅斑，疼痛，そう痒症等の注射部位反応 | 少ない | インフルエンザ様疾患，腕の腫脹，体重増加，疲労 |
| <b>感染症および寄生虫症</b>        |   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| 少ない                      | 咽頭炎   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| まれ                       | 寄生虫感染   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| <b>血液およびリンパ系障害</b>       |   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| 不明                       | 特発性血小板減少症（重症例を含む）   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| <b>免疫系障害</b>             |   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| まれ                       | アナフィラキシー反応，その他の重篤なアレルギー性疾患，抗オマリズマブ抗体の発現   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| 不明                       | 血清病（発熱及びリンパ節症を含む場合がある）  |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| <b>神経系障害</b>             |   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| 多い                       | 頭痛*   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| 少ない                      | 失神，錯感覚，傾眠，浮動性めまい  |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| <b>血管障害</b>              |   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| 少ない                      | 体位性低血圧，潮紅   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| <b>呼吸器，胸郭および縦隔障害</b>     |   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| 少ない                      | アレルギー性気管支痙攣，咳嗽  |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| まれ                       | 喉頭浮腫  |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| 不明                       | アレルギー性肉芽腫性血管炎（すなわち Churg-Strauss 症候群）   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| <b>胃腸障害</b>              |   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| 多い                       | 上腹部痛**  |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| 少ない                      | 消化不良徴候及び症状，下痢，悪心  |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| <b>皮膚および皮下組織障害</b>       |   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| 少ない                      | 光線過敏症，蕁麻疹，発疹，そう痒症   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| まれ                       | 血管浮腫  |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| 不明                       | 脱毛症   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| <b>筋骨格系および結合組織障害</b>     |   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| まれ                       | 全身性エリテマトーデス（SLE）  |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| 不明                       | 関節痛，筋肉痛，関節腫脹  |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| <b>一般・全身障害および投与部位の状態</b> |   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| 非常に多い                    | 発熱**  |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| 多い                       | 腫脹，紅斑，疼痛，そう痒症等の注射部位反応   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |
| 少ない                      | インフルエンザ様疾患，腕の腫脹，体重増加，疲労   |                   |  |     |     |    |       |                    |  |    |                   |              |  |    |   |    |                        |              |  |    |     |     |                  |             |  |     |           |                      |  |     |                |    |      |    |                                       |             |  |    |        |     |                  |                    |  |     |                   |    |      |    |     |                      |  |    |                  |    |              |                          |  |       |      |    |                       |     |                         |

| 販売名                      | Xolair 75 mg powder and solvent for solution for injection<br>Xolair 150 mg powder and solvent for solution for injection<br>Xolair 75 mg solution for injection<br>Xolair 150 mg solution for injection  |              |                          |  |            |            |              |                   |  |  |  |      |          |           |    |              |  |  |  |    |          |           |    |                      |  |  |  |     |          |           |    |                          |  |  |  |         |          |           |    |      |                       |  |            |            |              |                   |  |  |  |       |          |           |    |
|--------------------------|---|--------------|--------------------------|--|------------|------------|--------------|-------------------|--|--|--|------|----------|-----------|----|--------------|--|--|--|----|----------|-----------|----|----------------------|--|--|--|-----|----------|-----------|----|--------------------------|--|--|--|---------|----------|-----------|----|------|-----------------------|--|------------|------------|--------------|-------------------|--|--|--|-------|----------|-----------|----|
|                          | <p><u>副作用の一覧</u></p> <p>用量及び治療集団の差 [有意差のある危険因子, 合併症, 併用薬, 及び年齢 (例: 喘息の試験では 6 歳から 12 歳の小児も対象とした)] から生じた, CSU を適応症とした場合の副作用を別表 (表 5) に示す。</p> <p>表 5 は, 第 III 相の併合された 3 試験で 300 mg 投与群に報告された副作用 (医学的な評価後, いずれかの治療群の 1%以上の患者に発現した事象, 及びプラセボ投与群と比較してオマリズマブ投与群で 2%以上の頻度で発現した事象) を示す。これらの副作用は, 12 週間の投与期間及び 24 週間の投与期間に確認された事象の 2 つに分類されている。</p> <p>副作用は MedDRA の器官別大分類ごとに表示する。器官別大分類では最も発現頻度が高い副作用を上から順に示す。それぞれの副作用に対応する発現頻度のカテゴリーは以下の規定により定義する: 非常に多い (1/10 以上), 多い (1/100 以上, 1/10 未満), 少ない (1/1,000 以上, 1/100 未満), まれ (1/10,000 以上, 1/1,000 未満), 非常にまれ (1/10,000 未満), 及び不明 (利用可能なデータから推定不可能)。</p> <p><b>表 5: オマリズマブ 300 mg 投与群の副作用 (併合された CSU 安全性データベース, 1 日目～24 週目のデータ)</b></p> <table border="1" data-bbox="443 1010 1417 1581"> <thead> <tr> <th rowspan="2">12 週</th> <th colspan="2">オマリズマブ試験 1, 2 及び 3 の併合結果</th> <th rowspan="2">発現頻度のカテゴリー</th> </tr> <tr> <th>プラセボ N=242</th> <th>300 mg N=412</th> </tr> </thead> <tbody> <tr> <td colspan="4"><b>感染症および寄生虫症</b></td> </tr> <tr> <td>副鼻腔炎</td> <td>5 (2.1%)</td> <td>20 (4.9%)</td> <td>多い</td> </tr> <tr> <td colspan="4"><b>神経系障害</b></td> </tr> <tr> <td>頭痛</td> <td>7 (2.9%)</td> <td>25 (6.1%)</td> <td>多い</td> </tr> <tr> <td colspan="4"><b>筋骨格系および結合組織障害</b></td> </tr> <tr> <td>関節痛</td> <td>1 (0.4%)</td> <td>12 (2.9%)</td> <td>多い</td> </tr> <tr> <td colspan="4"><b>一般・全身障害および投与部位の状態</b></td> </tr> <tr> <td>注射部位反応*</td> <td>2 (0.8%)</td> <td>11 (2.7%)</td> <td>多い</td> </tr> <tr> <th rowspan="2">24 週</th> <th colspan="2">オマリズマブ試験 1 及び 3 の併合結果</th> <th rowspan="2">発生頻度のカテゴリー</th> </tr> <tr> <th>プラセボ N=163</th> <th>300 mg N=333</th> </tr> <tr> <td colspan="4"><b>感染症および寄生虫症</b></td> </tr> <tr> <td>上気道感染</td> <td>5 (3.1%)</td> <td>19 (5.7%)</td> <td>多い</td> </tr> </tbody> </table> <p>*プラセボとの差が 2%ではないものの, すべての事例で治療薬との関連性があると評価されたため, 注射部位反応が含まれた。</p> <p><u>アレルギー性喘息及び CSU 適応症に関連して選択された副作用の説明</u></p> <p>以下のセクションに変更が必要となる関連データは CSU の臨床試験では得られなかった。</p> <p><u>免疫系障害</u></p> <p>より詳細な情報は警告及び使用上の注意の項を参照。</p> | 12 週         | オマリズマブ試験 1, 2 及び 3 の併合結果 |  | 発現頻度のカテゴリー | プラセボ N=242 | 300 mg N=412 | <b>感染症および寄生虫症</b> |  |  |  | 副鼻腔炎 | 5 (2.1%) | 20 (4.9%) | 多い | <b>神経系障害</b> |  |  |  | 頭痛 | 7 (2.9%) | 25 (6.1%) | 多い | <b>筋骨格系および結合組織障害</b> |  |  |  | 関節痛 | 1 (0.4%) | 12 (2.9%) | 多い | <b>一般・全身障害および投与部位の状態</b> |  |  |  | 注射部位反応* | 2 (0.8%) | 11 (2.7%) | 多い | 24 週 | オマリズマブ試験 1 及び 3 の併合結果 |  | 発生頻度のカテゴリー | プラセボ N=163 | 300 mg N=333 | <b>感染症および寄生虫症</b> |  |  |  | 上気道感染 | 5 (3.1%) | 19 (5.7%) | 多い |
| 12 週                     | オマリズマブ試験 1, 2 及び 3 の併合結果  |              | 発現頻度のカテゴリー               |  |            |            |              |                   |  |  |  |      |          |           |    |              |  |  |  |    |          |           |    |                      |  |  |  |     |          |           |    |                          |  |  |  |         |          |           |    |      |                       |  |            |            |              |                   |  |  |  |       |          |           |    |
|                          | プラセボ N=242  | 300 mg N=412 |                          |  |            |            |              |                   |  |  |  |      |          |           |    |              |  |  |  |    |          |           |    |                      |  |  |  |     |          |           |    |                          |  |  |  |         |          |           |    |      |                       |  |            |            |              |                   |  |  |  |       |          |           |    |
| <b>感染症および寄生虫症</b>        |   |              |                          |  |            |            |              |                   |  |  |  |      |          |           |    |              |  |  |  |    |          |           |    |                      |  |  |  |     |          |           |    |                          |  |  |  |         |          |           |    |      |                       |  |            |            |              |                   |  |  |  |       |          |           |    |
| 副鼻腔炎                     | 5 (2.1%)  | 20 (4.9%)    | 多い                       |  |            |            |              |                   |  |  |  |      |          |           |    |              |  |  |  |    |          |           |    |                      |  |  |  |     |          |           |    |                          |  |  |  |         |          |           |    |      |                       |  |            |            |              |                   |  |  |  |       |          |           |    |
| <b>神経系障害</b>             |   |              |                          |  |            |            |              |                   |  |  |  |      |          |           |    |              |  |  |  |    |          |           |    |                      |  |  |  |     |          |           |    |                          |  |  |  |         |          |           |    |      |                       |  |            |            |              |                   |  |  |  |       |          |           |    |
| 頭痛                       | 7 (2.9%)  | 25 (6.1%)    | 多い                       |  |            |            |              |                   |  |  |  |      |          |           |    |              |  |  |  |    |          |           |    |                      |  |  |  |     |          |           |    |                          |  |  |  |         |          |           |    |      |                       |  |            |            |              |                   |  |  |  |       |          |           |    |
| <b>筋骨格系および結合組織障害</b>     |   |              |                          |  |            |            |              |                   |  |  |  |      |          |           |    |              |  |  |  |    |          |           |    |                      |  |  |  |     |          |           |    |                          |  |  |  |         |          |           |    |      |                       |  |            |            |              |                   |  |  |  |       |          |           |    |
| 関節痛                      | 1 (0.4%)  | 12 (2.9%)    | 多い                       |  |            |            |              |                   |  |  |  |      |          |           |    |              |  |  |  |    |          |           |    |                      |  |  |  |     |          |           |    |                          |  |  |  |         |          |           |    |      |                       |  |            |            |              |                   |  |  |  |       |          |           |    |
| <b>一般・全身障害および投与部位の状態</b> |   |              |                          |  |            |            |              |                   |  |  |  |      |          |           |    |              |  |  |  |    |          |           |    |                      |  |  |  |     |          |           |    |                          |  |  |  |         |          |           |    |      |                       |  |            |            |              |                   |  |  |  |       |          |           |    |
| 注射部位反応*                  | 2 (0.8%)  | 11 (2.7%)    | 多い                       |  |            |            |              |                   |  |  |  |      |          |           |    |              |  |  |  |    |          |           |    |                      |  |  |  |     |          |           |    |                          |  |  |  |         |          |           |    |      |                       |  |            |            |              |                   |  |  |  |       |          |           |    |
| 24 週                     | オマリズマブ試験 1 及び 3 の併合結果   |              | 発生頻度のカテゴリー               |  |            |            |              |                   |  |  |  |      |          |           |    |              |  |  |  |    |          |           |    |                      |  |  |  |     |          |           |    |                          |  |  |  |         |          |           |    |      |                       |  |            |            |              |                   |  |  |  |       |          |           |    |
|                          | プラセボ N=163  | 300 mg N=333 |                          |  |            |            |              |                   |  |  |  |      |          |           |    |              |  |  |  |    |          |           |    |                      |  |  |  |     |          |           |    |                          |  |  |  |         |          |           |    |      |                       |  |            |            |              |                   |  |  |  |       |          |           |    |
| <b>感染症および寄生虫症</b>        |   |              |                          |  |            |            |              |                   |  |  |  |      |          |           |    |              |  |  |  |    |          |           |    |                      |  |  |  |     |          |           |    |                          |  |  |  |         |          |           |    |      |                       |  |            |            |              |                   |  |  |  |       |          |           |    |
| 上気道感染                    | 5 (3.1%)  | 19 (5.7%)    | 多い                       |  |            |            |              |                   |  |  |  |      |          |           |    |              |  |  |  |    |          |           |    |                      |  |  |  |     |          |           |    |                          |  |  |  |         |          |           |    |      |                       |  |            |            |              |                   |  |  |  |       |          |           |    |

|       |  |
|-------|--|
| 販売名   | <p>Xolair 75 mg powder and solvent for solution for injection<br/> Xolair 150 mg powder and solvent for solution for injection<br/> Xolair 75 mg solution for injection<br/> Xolair 150 mg solution for injection</p>  |
|       | <p><u>アナフィラキシー</u><br/> 臨床試験ではアナフィラキシー反応はまれであった。しかし、安全性データベース累積調査後の市販後データによると、総計 898 例にアナフィラキシーがみられた。これは、推定暴露 566,923 患者治療・年とした時、約 0.20%の報告率となる。</p> <p><u>動脈血栓塞栓事象 (ATE)</u><br/> 観察試験の中間解析及び比較対照試験において ATE の数値上の不均衡が認められた。複合エンドポイント ATE の定義は、脳卒中、一過性脳虚血発作、心筋梗塞、不安定狭心症、及び心血管死（原因不明の死亡を含む）が含まれる。観察試験の最終解析で、1,000 患者・年あたりの ATE の発現率はゾレア投与患者が 7.52 (115/15,286 患者・年)、対照患者が 5.12 (51/9,963 患者・年) であった。利用可能なベースラインの心血管リスク因子を調整した多変量解析で、ハザード比は 1.32 (95%信頼区間 0.91-1.91) であった。8 週間以上継続したすべてのランダム化二重盲検プラセボ対照試験を統合した別の解析では、1,000 患者・年あたりの ATE の発現率はゾレア投与患者が 2.69 (5/1,856 患者・年)、プラセボ投与患者が 2.38 (4/1,680 患者・年) であった（発現率の比 1.13, 95%信頼区間 0.24-5.71）。</p> <p><u>血小板</u><br/> 臨床試験において血小板数が基準値の下限を下回った患者はほとんどいなかった。これらの変化は出血事象又はヘモグロビン減少と関連しなかった。市販後の状況で重症例を含む特発性血小板減少症の散発例が報告されているが、ヒト以外の霊長類で認められた、持続的な血小板数減少のパターンは、ヒト（6 歳超の患者）では報告されていない。</p> <p><u>寄生虫感染</u><br/> 寄生虫感染症のリスクが慢性的に高い患者において、プラセボ対照試験でオマリズマブ投与により感染率が数値上わずかに上昇したが、統計学的に有意ではなかった。感染症の経過、重症度、及び治療反応性は変化しなかった。</p> <p><u>全身性エリテマトーデス</u><br/> 臨床試験及び市販後症例で、CSU 患者や中等症から重症の喘息患者において、全身性エリテマトーデス (SLE) が報告されている。SLE の発症機序はよく分かっていない。</p> <p><u>副作用疑いの報告</u><br/> 医薬品承認後の副作用疑いの報告は重要である。それにより医薬品のベネフィット／リスクのバランスを継続的に監視することができる。医療従事者は国内報告システムを介してすべての副作用疑いを報告するよう求められる。</p> <p><u>過量投与</u><br/> ゾレアの最大耐量は決定されていない。患者に対し 4,000 mg までの用量の単回静脈内投与では、用量制限毒性の所見はなかった。患者に対する最高累積投与量は 20 週間で 44,000 mg であり、この用量では好ましくない急性作用は認められなかった。</p> <p>過量投与が疑われる場合は、異常な徴候又は症状がないか患者を観察すること。適切な治療を行うこと。</p> |
| 改訂年月日 | 2016 年 10 月  |

注) 慢性特発性蕁麻疹に係る「効能・効果」, 「用法・用量」, 「使用上の注意」は, 150 mg 製剤のみ該当する。

**Table 2-2 米国の添付文書の概略**

| 販売名              | XOLAIR (omalizumab) for injection, for subcutaneous use  |                  |           |            |  |  |          |           |           |            |                |        |        |        |        |                 |        |        |        |         |                 |        |  |  |                 |  |  |  |  |                 |  |  |  |  |                 |  |  |  |  |
|------------------|--|------------------|-----------|------------|--|--|----------|-----------|-----------|------------|----------------|--------|--------|--------|--------|-----------------|--------|--------|--------|---------|-----------------|--------|--|--|-----------------|--|--|--|--|-----------------|--|--|--|--|-----------------|--|--|--|--|
| 剤型・含量            | 注射用：オマリズマブ 150 mg は無菌の凍結乾燥粉末製剤であり, 単回投与用の 5 mL バイアルに充填されている。   |                  |           |            |  |  |          |           |           |            |                |        |        |        |        |                 |        |        |        |         |                 |        |  |  |                 |  |  |  |  |                 |  |  |  |  |                 |  |  |  |  |
| 効能・効果            | <p><b>喘息</b></p> <p>ゾレアは, 通年性吸入抗原に対する皮膚テスト陽性又は <i>in vitro</i> 反応性を示し, 吸入ステロイド薬で症状を十分にコントロールできない 6 歳以上の中等症～重症持続型喘息患者を適応とする。これらの患者では, 本剤投与により喘息増悪の発現率が低下することが示されている。</p> <p><u>使用に関する制限事項：</u></p> <ul style="list-style-type: none"> <li>● 本剤は急性気管支痙攣又は喘息発作重積の軽減を目的として使用しないこと。</li> <li>● 本剤はその他のアレルギー性疾患の治療には使用しないこと。</li> </ul> <p><b>慢性特発性蕁麻疹 (CIU)</b></p> <p>ゾレアは, ヒスタミン H1 受容体拮抗薬による治療にもかかわらず, 症状が持続的に認められる成人及び 12 歳以上の青少年の慢性特発性蕁麻疹患者を適応とする治療薬である。</p> <p><u>使用に関する制限事項：</u></p> <p>本剤はその他の病型の蕁麻疹の治療には使用しないこと。</p>   |                  |           |            |  |  |          |           |           |            |                |        |        |        |        |                 |        |        |        |         |                 |        |  |  |                 |  |  |  |  |                 |  |  |  |  |                 |  |  |  |  |
| 用法・用量            | <p><b>喘息患者への投与</b></p> <p>ゾレアは, 75～375 mg を 2 週間隔又は 4 週間隔で皮下投与する。用量 (mg) 及び投与頻度は, 投与開始前に測定した血清中総 IgE 濃度 (IU/mL) 及び体重 (kg) に基づいて設定する。投与期間中体重が大幅に変化した場合は用量を調節すること (表 1, 表 2 及び表 3 を参照)。</p> <p>本剤投与中は総 IgE 濃度が上昇し, 投与中止後も最長 1 年間持続する。したがって, 本剤投与中に IgE 濃度を再測定しても, その値を基に用量を再設定することはできない。</p> <ul style="list-style-type: none"> <li>● 投与中断期間が 1 年未満：初回の用量設定時に得られた血清中 IgE 濃度に基づく用量。</li> <li>● 投与中断期間が 1 年以上：患者の年齢に基づき, 表 1, 表 2 及び表 3 を用いて血清中総 IgE 濃度の再測定により用量を設定。</li> </ul> <p>患者の疾患の重症度及び喘息コントロールのレベルに基づいて, 継続投与の必要性を定期的に再評価すること。</p> <p>成人及び 12 歳以上の青少年患者：表 1 又は表 2 に従い投与を開始する。</p> <p><b>表 1. 12 歳以上の喘息患者に対するゾレアの 4 週間隔皮下投与量</b></p> <table border="1" data-bbox="400 1547 1428 1877"> <thead> <tr> <th rowspan="2">投与開始前の血清中 IgE 濃度</th> <th colspan="4">体重</th> </tr> <tr> <th>30～60 kg</th> <th>&gt;60～70 kg</th> <th>&gt;70～90 kg</th> <th>&gt;90～150 kg</th> </tr> </thead> <tbody> <tr> <td>≥ 30～100 IU/mL</td> <td>150 mg</td> <td>150 mg</td> <td>150 mg</td> <td>300 mg</td> </tr> <tr> <td>&gt; 100～200 IU/mL</td> <td>300 mg</td> <td>300 mg</td> <td>300 mg</td> <td rowspan="4" style="text-align: center; vertical-align: middle;">表 2 を参照</td> </tr> <tr> <td>&gt; 200～300 IU/mL</td> <td>300 mg</td> <td colspan="2"></td> </tr> <tr> <td>&gt; 300～400 IU/mL</td> <td colspan="2"></td> <td colspan="2"></td> </tr> <tr> <td>&gt; 400～500 IU/mL</td> <td colspan="2"></td> <td colspan="2"></td> </tr> <tr> <td>&gt; 500～600 IU/mL</td> <td colspan="2"></td> <td colspan="2"></td> </tr> </tbody> </table> | 投与開始前の血清中 IgE 濃度 | 体重        |            |  |  | 30～60 kg | >60～70 kg | >70～90 kg | >90～150 kg | ≥ 30～100 IU/mL | 150 mg | 150 mg | 150 mg | 300 mg | > 100～200 IU/mL | 300 mg | 300 mg | 300 mg | 表 2 を参照 | > 200～300 IU/mL | 300 mg |  |  | > 300～400 IU/mL |  |  |  |  | > 400～500 IU/mL |  |  |  |  | > 500～600 IU/mL |  |  |  |  |
| 投与開始前の血清中 IgE 濃度 | 体重   |                  |           |            |  |  |          |           |           |            |                |        |        |        |        |                 |        |        |        |         |                 |        |  |  |                 |  |  |  |  |                 |  |  |  |  |                 |  |  |  |  |
|                  | 30～60 kg   | >60～70 kg        | >70～90 kg | >90～150 kg |  |  |          |           |           |            |                |        |        |        |        |                 |        |        |        |         |                 |        |  |  |                 |  |  |  |  |                 |  |  |  |  |                 |  |  |  |  |
| ≥ 30～100 IU/mL   | 150 mg   | 150 mg           | 150 mg    | 300 mg     |  |  |          |           |           |            |                |        |        |        |        |                 |        |        |        |         |                 |        |  |  |                 |  |  |  |  |                 |  |  |  |  |                 |  |  |  |  |
| > 100～200 IU/mL  | 300 mg   | 300 mg           | 300 mg    | 表 2 を参照    |  |  |          |           |           |            |                |        |        |        |        |                 |        |        |        |         |                 |        |  |  |                 |  |  |  |  |                 |  |  |  |  |                 |  |  |  |  |
| > 200～300 IU/mL  | 300 mg   |                  |           |            |  |  |          |           |           |            |                |        |        |        |        |                 |        |        |        |         |                 |        |  |  |                 |  |  |  |  |                 |  |  |  |  |                 |  |  |  |  |
| > 300～400 IU/mL  |  |                  |           |            |  |  |          |           |           |            |                |        |        |        |        |                 |        |        |        |         |                 |        |  |  |                 |  |  |  |  |                 |  |  |  |  |                 |  |  |  |  |
| > 400～500 IU/mL  |  |                  |           |            |  |  |          |           |           |            |                |        |        |        |        |                 |        |        |        |         |                 |        |  |  |                 |  |  |  |  |                 |  |  |  |  |                 |  |  |  |  |
| > 500～600 IU/mL  |  |                  |           |            |  |  |          |           |           |            |                |        |        |        |        |                 |        |        |        |         |                 |        |  |  |                 |  |  |  |  |                 |  |  |  |  |                 |  |  |  |  |



|  |   |            |            |             |            |            |            |            |            |             |              |
|--|---|------------|------------|-------------|------------|------------|------------|------------|------------|-------------|--------------|
| 販売名  | XOLAIR (omalizumab) for injection, for subcutaneous use |            |            |             |            |            |            |            |            |             |              |
| <p><b>表 2. 12 歳以上の喘息患者に対するゾレアの 2 週間隔皮下投与量</b></p>                      |   |            |            |             |            |            |            |            |            |             |              |
| 投与開始前の血清中<br>IgE 濃度  | 体重  |            |            |             |            |            |            |            |            |             |              |
|  | 30~60 kg  | > 60~70 kg | > 70~90 kg | > 90~150 kg |            |            |            |            |            |             |              |
| ≥ 30~100 IU/mL   | 表 1 を参照   |            |            |             |            |            |            |            |            |             | 225 mg       |
| > 100~200 IU/mL  |   |            |            |             |            |            |            |            |            |             |              |
| > 200~300 IU/mL  |   |            |            |             |            |            |            |            |            |             | 300 mg       |
| > 300~400 IU/mL  | 225 mg  | 225 mg     | 225 mg     | 300 mg      | 投与しないこと    |            |            |            |            |             |              |
| > 400~500 IU/mL  | 225 mg  | 300 mg     | 375 mg     |             |            |            |            |            |            |             |              |
| > 500~600 IU/mL  | 300 mg  | 375 mg     |            |             |            |            |            |            |            |             |              |
| > 600~700 IU/mL  | 375 mg  |            |            |             |            |            |            |            |            |             |              |
| <p>6 歳以上 12 歳未満の小児患者：表 3 に従い投与を開始する。</p>                               |   |            |            |             |            |            |            |            |            |             |              |
| <p><b>表 3. 6 歳以上 12 歳未満でゾレアを開始する小児喘息患者に対するゾレアの 2 又は 4 週間隔皮下投与量</b></p> |   |            |            |             |            |            |            |            |            |             |              |
| 投与開始前<br>の血清中<br>IgE 濃度<br>(IU/mL)                                     | 投与<br>間隔  | 体重         |            |             |            |            |            |            |            |             |              |
|  |   | ≥20<br>-25 | >25<br>-30 | >30<br>-40  | >40<br>-50 | >50<br>-60 | >60<br>-70 | >70-<br>80 | >80<br>-90 | >90-<br>125 | >125<br>-150 |
|  |   | kg         | kg         | kg          | kg         | kg         | kg         | kg         | kg         | kg          | kg           |
| 用量 (mg)  |   |            |            |             |            |            |            |            |            |             |              |
| 30-100   | 4 週<br>間隔   | 75         | 75         | 75          | 150        | 150        | 150        | 150        | 150        | 300         | 300          |
| >100-200   |   | 150        | 150        | 150         | 300        | 300        | 300        | 300        | 300        | 225         | 300          |
| >200-300   |   | 150        | 150        | 225         | 300        | 300        | 225        | 225        | 225        | 300         | 375          |
| >300-400   |   | 225        | 225        | 300         | 225        | 225        | 225        | 300        | 300        |             |              |
| >400-500   |   | 225        | 300        | 225         | 225        | 300        | 300        | 375        | 375        |             |              |
| >500-600   |   | 300        | 300        | 225         | 300        | 300        | 375        |            |            |             |              |
| >600-700   | 300   | 225        | 225        | 300         | 375        |            |            |            |            |             |              |
| >700-800   | 2 週<br>間隔   | 225        | 225        | 300         | 375        | 投与しないこと    |            |            |            |             |              |
| >800-900   |   | 225        | 225        | 300         | 375        |            |            |            |            |             |              |
| >900-1000  |   | 225        | 300        | 375         |            |            |            |            |            |             |              |
| >1000-1100   |   | 225        | 300        | 375         |            |            |            |            |            |             |              |
| >1100-1200   |   | 300        | 300        |             |            |            |            |            |            |             |              |
| >1200-1300   |   | 300        | 375        |             |            |            |            |            |            |             |              |
| <p>*投与間隔</p> <p>■ 4 週間隔で皮下注投与</p> <p>□ 2 週間隔で皮下注投与</p>                 |   |            |            |             |            |            |            |            |            |             |              |

| 販売名 | XOLAIR (omalizumab) for injection, for subcutaneous use   |
|-----|---|
|     | <p><b>慢性特発性蕁麻疹患者への投与</b></p> <p>ゾレア 150 mg 又は 300 mg を 4 週間隔で皮下投与する。</p> <p>CIU 患者への本剤の投与量は、血清 IgE（遊離 IgE 又は総 IgE）濃度又は体重に基づく必要はない。</p> <p>CIU に対する適切な投与期間については評価していない。継続投与の必要性について、定期的に再評価すること。</p> <p><b>調製</b></p> <p>市販のゾレアの凍結乾燥粉末は、以下の指示に従い、USP 無菌注射用水（SWFI）を用いて調製しなければならない：</p> <ol style="list-style-type: none"> <li>1) 調製する必要のあるバイアル数を事前に決定する（1 バイアルあたり 1.2 mL 中ゾレア 150 mg を送達） [表 4 を参照]。</li> <li>2) 1 インチ長の 18 ゲージ注射針を装着した 3 mL の注射筒を用いて、SWFI（USP）1.4 mL を採取する。</li> <li>3) バイアルを平らな所に真っ直ぐに置き、標準的な無菌的手技を用いて注射針を挿入し、SWFI（USP）を粉末製剤の上に直接注入する。</li> <li>4) バイアルを立てた状態で、約 1 分間ゆっくり回転させ、粉末を均等に湿らせる。この間、バイアルを振らないこと。</li> <li>5) バイアルを約 5 分ごとに 5～10 秒間ゆっくり回し、残りの粉末を溶解させる。<b>凍結乾燥粉末の溶解には 15～20 分かかる。</b>完全に溶解させるのに 20 分以上かかる場合は、溶液中にゲル状の粒子が見えなくなるまで、バイアルを約 5 分ごとに 5～10 秒間ゆっくり回す。バイアルの内容物が 40 分以内に完全に溶解しない場合は使用しないこと。</li> <li>6) 本剤溶解後の溶液にはやや粘性があり、外観は澄明又はわずかに混濁している。バイアルの縁の周囲に小さな気泡や泡が多少あってもさしつかえない。溶液中に目に見えるゲル状の粒子があってはならない。外来粒子がある場合は使用しないこと。</li> <li>7) バイアルを 15 秒間上下逆さにして溶液を止栓の方に流す。</li> <li>8) <b>本剤溶液後、バイアルを 2～8°C（36～46°F）で保存した場合は 8 時間以内に使用し、室温で保存した場合は 4 時間以内に使用すること。</b>溶解後のバイアルは遮光すること。</li> <li>9) 1 インチ長の 18 ゲージ注射針を装着した 3 mL の新しい注射筒を使用して、注射針を逆さにしたバイアルに挿入する。溶液を注射筒に採取する際は、注射針の先端がバイアル栓の溶液の底の位置に来るようにする。本剤溶解後の溶液にはやや粘性がある。注射筒から空気や余分な溶液を抜く操作をする前に、バイアル内の<b>溶液をすべて吸引する</b>。注射針をバイアルから抜く前に、注射筒の末端部までプランジャーを引いて、逆さにしたバイアルから溶液をすべて吸引する。</li> <li>10) 18 ゲージ針を皮下注用の 25 ゲージ針に交換する。</li> <li>11) ゾレア 150 mg の用量に相当する 1.2 mL を採取するためには、空気、大きな気泡及び余分な溶液を抜く。ゾレア 75 mg の用量に相当する 0.6 mL を採取するためには、空気、大きな気泡を抜き、0.6 mL をシリンジから廃棄する。注射筒内の溶液の表面に小さな気泡の薄い層が残っていてもよい。</li> </ol> <p><b>投与时</b></p> <p>ゾレアは皮下注射する。溶液にはやや粘性があるため、注射するのに 5～10 秒を要する場合がある。注射部位 1 箇所あたり 150 mg（1 バイアルの内容量）を超えて投与しないこと。150 mg を超える量を投与する場合は、2～3 箇所に分けて投与すること（表 4）。</p> |

| 販売名      | XOLAIR (omalizumab) for injection, for subcutaneous use  |          |        |       |       |       |   |   |        |        |   |   |        |        |   |   |        |        |   |   |        |        |   |   |        |
|----------|--|----------|--------|-------|-------|-------|---|---|--------|--------|---|---|--------|--------|---|---|--------|--------|---|---|--------|--------|---|---|--------|
|          | <p><b>表 4. バイアル数、注射部位数及び総投与液量</b></p> <table border="1" data-bbox="400 331 1283 555"> <thead> <tr> <th>ゾレアの投与量*</th> <th>バイアル数</th> <th>注射部位数</th> <th>総投与液量</th> </tr> </thead> <tbody> <tr> <td>75 mg</td> <td>1</td> <td>1</td> <td>0.6 mL</td> </tr> <tr> <td>150 mg</td> <td>1</td> <td>1</td> <td>1.2 mL</td> </tr> <tr> <td>225 mg</td> <td>2</td> <td>2</td> <td>1.8 mL</td> </tr> <tr> <td>300 mg</td> <td>2</td> <td>2</td> <td>2.4 mL</td> </tr> <tr> <td>375 mg</td> <td>3</td> <td>3</td> <td>3.0 mL</td> </tr> </tbody> </table> <p>* 本表に記載している投与量は、いずれも喘息患者への投与が承認されている。ゾレア 150 mg 及び 300 mg は CIU 患者に対する投与量である。</p>  | ゾレアの投与量* | バイアル数  | 注射部位数 | 総投与液量 | 75 mg | 1 | 1 | 0.6 mL | 150 mg | 1 | 1 | 1.2 mL | 225 mg | 2 | 2 | 1.8 mL | 300 mg | 2 | 2 | 2.4 mL | 375 mg | 3 | 3 | 3.0 mL |
| ゾレアの投与量* | バイアル数  | 注射部位数    | 総投与液量  |       |       |       |   |   |        |        |   |   |        |        |   |   |        |        |   |   |        |        |   |   |        |
| 75 mg    | 1  | 1        | 0.6 mL |       |       |       |   |   |        |        |   |   |        |        |   |   |        |        |   |   |        |        |   |   |        |
| 150 mg   | 1  | 1        | 1.2 mL |       |       |       |   |   |        |        |   |   |        |        |   |   |        |        |   |   |        |        |   |   |        |
| 225 mg   | 2  | 2        | 1.8 mL |       |       |       |   |   |        |        |   |   |        |        |   |   |        |        |   |   |        |        |   |   |        |
| 300 mg   | 2  | 2        | 2.4 mL |       |       |       |   |   |        |        |   |   |        |        |   |   |        |        |   |   |        |        |   |   |        |
| 375 mg   | 3  | 3        | 3.0 mL |       |       |       |   |   |        |        |   |   |        |        |   |   |        |        |   |   |        |        |   |   |        |
| 使用上の注意   | <p><b>警告：アナフィラキシー</b></p> <p>本剤投与後に、気管支痙攣、低血圧、失神、蕁麻疹及び／又は咽喉又は舌の血管浮腫を呈するアナフィラキシーの発現が報告されている。アナフィラキシーは、早ければ本剤の初回投与後に発現するが、1年以上の定期的な投与後に発現することもある。アナフィラキシーが発現するリスクがあるため、本剤投与後は患者を適切な時間十分に観察すること。生命を脅かす可能性のあるアナフィラキシーの発現に備えて、本剤を投与した医療提供者は救急処置を準備すること。アナフィラキシーの徴候及び症状について患者に説明し、症状が現れた場合には速やかに処置を受けるよう患者に指示すること [警告及び使用上の注意及び副作用を参照]。</p> <p><b>禁忌</b></p> <p>次の患者にはゾレアを投与しないこと：<br/>本剤の有効成分又はその他の添加物に対し、重度の過敏症の既往歴のある患者 [警告及び使用上の注意を参照]。</p> <p><b>警告及び使用上の注意</b></p> <p><b>アナフィラキシー</b></p> <p>市販前の臨床試験及び市販後の自発報告において、本剤投与後にアナフィラキシーの発現が報告されている [警告欄及び副作用を参照]。報告されたこれらの症例における徴候及び症状は、気管支痙攣、低血圧、失神、蕁麻疹及び／又は咽喉又は舌の血管浮腫であった。これらの事象の一部は、生命を脅かす事象であった。喘息患者を対象とした市販前の臨床試験では、3507 例中 3 例の被験者 (0.1%) においてアナフィラキシーの発現が報告された。アナフィラキシーは、2 例の被験者ではゾレアの初回投与時に発現し、1 例の被験者では 4 回目の投与時に発現した。アナフィラキシーの発現時期は、2 例が投与 90 分後、1 例が投与 2 時間後であった。</p> <p>症例対照研究では、アナフィラキシーの既往歴がない被験者と比較して、食物、薬物又はその他の原因物質に対するアナフィラキシーの既往がある被験者では、ゾレアの投与によりアナフィラキシーが発現するリスクが高かった [副作用を参照]。</p> <p>市販後の自発報告では、2003 年 6 月～2006 年 12 月の推定曝露量が約 57,300 例であることを基に算出した本剤投与に起因するアナフィラキシーの発現頻度は、患者の 0.2%以上と推定された。アナフィラキシーは、早ければ本剤の初回投与後に発現したが、1年以上の定期的な投与後に発現した場合もある。</p> <p>本剤は、生命を脅かす可能性のあるアナフィラキシーの発現に備えて救急処置を準備している医療施設においてのみ投与すること。市販前の臨床試験及び市販後の自発報告におけるアナフィラキシーの発現時期を考慮して、本剤投与後は患者を適切な時間十分に観察すること [副作用を参照]。アナフィラキシーの徴候及び症状について患者に説明し、徴候又は症状が現れた場合には速やかに処置を受けるよう患者に指示すること。</p> <p>重度の過敏症が発現した患者には、本剤の投与を中止すること [禁忌を参照]。</p> |          |        |       |       |       |   |   |        |        |   |   |        |        |   |   |        |        |   |   |        |        |   |   |        |

| 販売名 | XOLAIR (omalizumab) for injection, for subcutaneous use   |
|-----|---|
|     | <p><b>悪性腫瘍</b></p> <p>喘息及びその他のアレルギー疾患のある成人及び12歳以上の青少年被験者を対象とした臨床試験では、ゾレアを投与した被験者4127例中20例(0.5%)と、対照被験者2236例中5例(0.2%)において悪性新生物の発現が観察された。本剤を投与した被験者において観察された悪性腫瘍のタイプはさまざまであり、乳癌、非黒色腫皮膚癌、前立腺癌、黒色腫及び耳下腺癌はそれぞれ2例以上に発現し、その他の5種類の腫瘍はそれぞれ1例に発現した。被験者の大半では観察期間が1年未満であった。悪性腫瘍のリスクが高い患者(例:高齢者、喫煙継続者)が本剤に長期曝露又は本剤を長期使用したときの影響については不明である。</p> <p>通年性吸入抗原に対する皮膚テスト陽性又は<i>in vitro</i>反応性を示した中等症～重症持続型喘息で、ゾレアを投与した成人及び青少年被験者5007例及びゾレアを投与しなかった成人及び青少年被験者2829例を対象としたその後の観察研究では、被験者を最長5年間追跡調査した。本試験では、原発性癌の発現率(1000人・年あたり)は、ゾレアを投与した被験者(12.3)及びゾレアを投与しなかった被験者(13.0)とも同等であった[副作用を参照]。しかし、本試験には限界があることから、本剤の投与により悪性腫瘍が発現するリスクを明確に否定することはできない。本試験の限界は次のとおりである:観察研究デザイン、ゾレアへの曝露歴のある患者の登録を許可したことによるバイアス(88%)、癌又は前癌状態の既往歴を本試験の除外基準とした被験者の登録(56%)、試験中止率の高さ(44%)。</p> <p><b>急性喘息症状</b></p> <p>ゾレアを投与しても、喘息増悪は急速に軽減されないことが示されている。本剤を急性気管支痙攣又は喘息発作重積の治療に使用しないこと。</p> <p><b>ステロイド薬の減量</b></p> <p>喘息治療のためのゾレアの投与開始時に、全身又は吸入ステロイド薬の投与を突然中止しないこと。ステロイド薬の減量は、医師の監視下で徐々に行うこと。CIU患者では、本剤とステロイド薬の併用療法について評価を行っていない。</p> <p><b>好酸球性疾患</b></p> <p>まれに、本剤投与中の喘息患者において、全身ステロイド薬にて治療することの多いチャグ・スト劳斯症候群と一致する血管炎の臨床的特徴を呈する重篤な全身性の好酸球増加症が現れることがある。</p> <p>これらの事象は通常は(必ずしもそうとは限らないが)、経口ステロイド薬の減量に伴って発現したものである。医師は、好酸球増加症、血管炎性皮疹、肺症状増悪、心臓合併症及び/又はニューロパチーの発現に注意すること。本剤とこれらの基礎疾患との因果関係は確立されていない。</p> <p><b>発熱、関節痛及び発疹</b></p> <p>承認後の使用経験において、一部の患者にゾレアの初回投与又はその後の投与から1～5日後に、関節炎/関節痛、発疹、発熱及びリンパ節症等の徴候及び症状を呈する特定症状群が発現した。一部の患者では、追加投与後にこれらの徴候及び症状が再発した。これらの症例ではIII型反応と一致する循環免疫複合体又は皮膚生検所見は認められなかったが、これらの徴候及び症状は血清病患者で見られたものと同様である。患者にこれらの徴候及び症状を呈する特定症状群が現れた場合は、本剤の投与を中止すること[副作用を参照]。</p> <p><b>寄生虫感染症</b></p> <p>ゾレアの投与中は、蠕虫感染のリスクが高い患者を注意深く観察すること。本剤の投与中止後に必要となる蠕虫感染の観察期間を設定するためのデータはほとんどない。</p> <p>蠕虫感染(回虫、鉤虫、鞭虫、線虫)のリスクが高い成人及び青少年患者を対象としてブラジル</p> |

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|-----|--|
|     | <p>で実施した1年間の臨床試験では、標準的な便検査を用いた診断による感染症が発現した被験者の割合は、ゾレア投与被験者が53%（68例中36例）であったのに対し、プラセボ対照被験者では42%（69例中29例）であった。感染症のオッズ比の点推定値は1.96、95%信頼区間（0.88, 4.36）であったことから、本試験では、感染症が発現しなかった被験者と比較して、感染症が発現した被験者が本剤の投与を受けた可能性は0.88～4.36倍であったことが示唆された。便中の虫卵数で測定した適切な抗蠕虫感染薬に対する反応については、投与群間に差はなかった。</p> <p><b>臨床検査値</b></p> <p>本剤投与後はゾレア：IgE複合体が形成されるため、血清中総IgE濃度が上昇する〔臨床薬理を参照〕。血清中総IgE濃度の上昇は、ゾレアの投与中止後も最長1年間持続することがある。投与中止後1年以内に測定した血清中総IgE濃度は、定常状態での遊離IgE濃度を反映していない可能性があるため、これらの濃度を喘息患者への投与レジメンの再評価に使用しないこと。〔用法及び用量を参照〕</p> <p><b>副作用</b></p> <p>ゾレアの投与により次の副作用が発現している：</p> <ul style="list-style-type: none"> <li>● アナフィラキシー〔警告欄と警告及び使用上の注意を参照〕</li> <li>● 悪性腫瘍〔警告及び使用上の注意を参照〕</li> </ul> <p><b>臨床試験における経験</b></p> <p>臨床試験はさまざまに異なる条件下で実施しているため、ある薬物の臨床試験で観察された副作用の発現率を他の薬物の臨床試験における発現率と直接比較することはできないほか、使用実態下での発現率を反映しないこともある。</p> <p><u>成人及び12歳以上の青少年喘息患者を対象とした臨床試験における副作用</u></p> <p>以下に記載のデータは、2076例の成人及び12歳以上の青少年被験者（プラセボ対照試験又はその他の喘息の対照試験のいずれかにおいて6ヵ月間曝露した被験者1687例と、1年以上曝露した被験者555例を含む）におけるゾレアへの曝露状況を反映したものである。本剤を投与した被験者の平均年齢は42歳で、134例は65歳以上であった。被験者の60%は女性で、85%は白人であった。被験者には本剤150mg～375mgを2週間隔又は4週間隔で投与し、対照群に割り付けた被験者には、プラセボと併用又は併用せずに標準療法を行った。</p> <p>最も発現頻度が高く臨床介入（例：本剤の投与中止、又は有害事象の治療のため併用薬を投与）が必要となった有害事象は、注射部位反応（45%）、ウイルス感染（23%）、上気道感染（20%）、副鼻腔炎（16%）、頭痛（15%）及び咽頭炎（11%）であった。これらの事象の発現率は、本剤を投与した被験者及び対照被験者とも同等であった。</p> <p>喘息のプラセボ対照試験4試験において、被験者の1%以上に発現し、ゾレアを投与した成人及び12歳以上の青少年被験者の方がプラセボを投与した被験者よりも発現頻度が高かった副作用を表5に示す。有害事象はInternational Medical Nomenclature (IMN) 辞書の基本語を使用して分類した。注射部位反応は他の有害事象の報告とは別に記録した。</p> |

| 販売名            | XOLAIR (omalizumab) for injection, for subcutaneous use   |       |     |     |      |  |       |       |             |  |  |    |    |    |    |    |    |               |  |  |     |    |    |    |    |    |     |    |    |     |    |    |              |  |  |        |    |    |                |  |  |      |    |    |     |    |    |               |  |  |    |    |    |
|----------------|---|-------|-----|-----|------|--|-------|-------|-------------|--|--|----|----|----|----|----|----|---------------|--|--|-----|----|----|----|----|----|-----|----|----|-----|----|----|--------------|--|--|--------|----|----|----------------|--|--|------|----|----|-----|----|----|---------------|--|--|----|----|----|
|                | <p><b>表 5. 喘息のプラセボ対照試験 4 試験のゾレアを投与した成人又は 12 歳以上の青少年被験者において発現頻度が 1%以上であった副作用</b></p> <table border="1"> <thead> <tr> <th>副作用</th> <th>ゾレア</th> <th>プラセボ</th> </tr> </thead> <tbody> <tr> <td></td> <td>738 例</td> <td>717 例</td> </tr> <tr> <td colspan="3"><u>全身障害</u></td> </tr> <tr> <td>疼痛</td> <td>7%</td> <td>5%</td> </tr> <tr> <td>疲労</td> <td>3%</td> <td>2%</td> </tr> <tr> <td colspan="3"><u>筋骨格系障害</u></td> </tr> <tr> <td>関節痛</td> <td>8%</td> <td>6%</td> </tr> <tr> <td>骨折</td> <td>2%</td> <td>1%</td> </tr> <tr> <td>下肢痛</td> <td>4%</td> <td>2%</td> </tr> <tr> <td>上肢痛</td> <td>2%</td> <td>1%</td> </tr> <tr> <td colspan="3"><u>神経系障害</u></td> </tr> <tr> <td>浮動性めまい</td> <td>3%</td> <td>2%</td> </tr> <tr> <td colspan="3"><u>皮膚付属器状態</u></td> </tr> <tr> <td>そう痒症</td> <td>2%</td> <td>1%</td> </tr> <tr> <td>皮膚炎</td> <td>2%</td> <td>1%</td> </tr> <tr> <td colspan="3"><u>特殊感覚異常</u></td> </tr> <tr> <td>耳痛</td> <td>2%</td> <td>1%</td> </tr> </tbody> </table> |       | 副作用 | ゾレア | プラセボ |  | 738 例 | 717 例 | <u>全身障害</u> |  |  | 疼痛 | 7% | 5% | 疲労 | 3% | 2% | <u>筋骨格系障害</u> |  |  | 関節痛 | 8% | 6% | 骨折 | 2% | 1% | 下肢痛 | 4% | 2% | 上肢痛 | 2% | 1% | <u>神経系障害</u> |  |  | 浮動性めまい | 3% | 2% | <u>皮膚付属器状態</u> |  |  | そう痒症 | 2% | 1% | 皮膚炎 | 2% | 1% | <u>特殊感覚異常</u> |  |  | 耳痛 | 2% | 1% |
| 副作用            | ゾレア   | プラセボ  |     |     |      |  |       |       |             |  |  |    |    |    |    |    |    |               |  |  |     |    |    |    |    |    |     |    |    |     |    |    |              |  |  |        |    |    |                |  |  |      |    |    |     |    |    |               |  |  |    |    |    |
|                | 738 例   | 717 例 |     |     |      |  |       |       |             |  |  |    |    |    |    |    |    |               |  |  |     |    |    |    |    |    |     |    |    |     |    |    |              |  |  |        |    |    |                |  |  |      |    |    |     |    |    |               |  |  |    |    |    |
| <u>全身障害</u>    |   |       |     |     |      |  |       |       |             |  |  |    |    |    |    |    |    |               |  |  |     |    |    |    |    |    |     |    |    |     |    |    |              |  |  |        |    |    |                |  |  |      |    |    |     |    |    |               |  |  |    |    |    |
| 疼痛             | 7%  | 5%    |     |     |      |  |       |       |             |  |  |    |    |    |    |    |    |               |  |  |     |    |    |    |    |    |     |    |    |     |    |    |              |  |  |        |    |    |                |  |  |      |    |    |     |    |    |               |  |  |    |    |    |
| 疲労             | 3%  | 2%    |     |     |      |  |       |       |             |  |  |    |    |    |    |    |    |               |  |  |     |    |    |    |    |    |     |    |    |     |    |    |              |  |  |        |    |    |                |  |  |      |    |    |     |    |    |               |  |  |    |    |    |
| <u>筋骨格系障害</u>  |   |       |     |     |      |  |       |       |             |  |  |    |    |    |    |    |    |               |  |  |     |    |    |    |    |    |     |    |    |     |    |    |              |  |  |        |    |    |                |  |  |      |    |    |     |    |    |               |  |  |    |    |    |
| 関節痛            | 8%  | 6%    |     |     |      |  |       |       |             |  |  |    |    |    |    |    |    |               |  |  |     |    |    |    |    |    |     |    |    |     |    |    |              |  |  |        |    |    |                |  |  |      |    |    |     |    |    |               |  |  |    |    |    |
| 骨折             | 2%  | 1%    |     |     |      |  |       |       |             |  |  |    |    |    |    |    |    |               |  |  |     |    |    |    |    |    |     |    |    |     |    |    |              |  |  |        |    |    |                |  |  |      |    |    |     |    |    |               |  |  |    |    |    |
| 下肢痛            | 4%  | 2%    |     |     |      |  |       |       |             |  |  |    |    |    |    |    |    |               |  |  |     |    |    |    |    |    |     |    |    |     |    |    |              |  |  |        |    |    |                |  |  |      |    |    |     |    |    |               |  |  |    |    |    |
| 上肢痛            | 2%  | 1%    |     |     |      |  |       |       |             |  |  |    |    |    |    |    |    |               |  |  |     |    |    |    |    |    |     |    |    |     |    |    |              |  |  |        |    |    |                |  |  |      |    |    |     |    |    |               |  |  |    |    |    |
| <u>神経系障害</u>   |   |       |     |     |      |  |       |       |             |  |  |    |    |    |    |    |    |               |  |  |     |    |    |    |    |    |     |    |    |     |    |    |              |  |  |        |    |    |                |  |  |      |    |    |     |    |    |               |  |  |    |    |    |
| 浮動性めまい         | 3%  | 2%    |     |     |      |  |       |       |             |  |  |    |    |    |    |    |    |               |  |  |     |    |    |    |    |    |     |    |    |     |    |    |              |  |  |        |    |    |                |  |  |      |    |    |     |    |    |               |  |  |    |    |    |
| <u>皮膚付属器状態</u> |   |       |     |     |      |  |       |       |             |  |  |    |    |    |    |    |    |               |  |  |     |    |    |    |    |    |     |    |    |     |    |    |              |  |  |        |    |    |                |  |  |      |    |    |     |    |    |               |  |  |    |    |    |
| そう痒症           | 2%  | 1%    |     |     |      |  |       |       |             |  |  |    |    |    |    |    |    |               |  |  |     |    |    |    |    |    |     |    |    |     |    |    |              |  |  |        |    |    |                |  |  |      |    |    |     |    |    |               |  |  |    |    |    |
| 皮膚炎            | 2%  | 1%    |     |     |      |  |       |       |             |  |  |    |    |    |    |    |    |               |  |  |     |    |    |    |    |    |     |    |    |     |    |    |              |  |  |        |    |    |                |  |  |      |    |    |     |    |    |               |  |  |    |    |    |
| <u>特殊感覚異常</u>  |   |       |     |     |      |  |       |       |             |  |  |    |    |    |    |    |    |               |  |  |     |    |    |    |    |    |     |    |    |     |    |    |              |  |  |        |    |    |                |  |  |      |    |    |     |    |    |               |  |  |    |    |    |
| 耳痛             | 2%  | 1%    |     |     |      |  |       |       |             |  |  |    |    |    |    |    |    |               |  |  |     |    |    |    |    |    |     |    |    |     |    |    |              |  |  |        |    |    |                |  |  |      |    |    |     |    |    |               |  |  |    |    |    |
|                | <p>副作用の発現率については、年齢（65 歳未満の患者）、性別又は人種による差はなかった。</p> <p><i>アナフィラキシーの症例対照研究</i></p> <p>後ろ向き症例対照研究で、ゾレアを投与した喘息被験者における本剤投与によるアナフィラキシー発現の危険因子を調査した。本剤投与によるアナフィラキシーの既往歴が判定されている症例と、こうした既往歴のない対照被験者を比較した。本試験の結果から、自己報告された食物、薬物又はその他の原因物質によるアナフィラキシーの既往歴は、本剤投与によりアナフィラキシーが発現した被験者（30 例の 57%）の方が対照被験者（88 例の 23%）よりも多かった [OR 8.1, 95% CI 2.7~24.3]。本試験は症例対照研究であるため、本試験の結果から本剤を投与した被験者におけるアナフィラキシーの発現率を算出することはできない。その他の情報源では、本剤投与によるアナフィラキシーは、臨床試験の被験者の 0.1%及び市販後の報告における患者の 0.2%以上で発現した [警告及び使用上の注意, 副作用を参照]。</p> <p><i>注射部位反応</i></p> <p>成人及び青少年において、注射部位反応（全重症度）は、ゾレアを投与した被験者の 45%及びプラセボを投与した被験者の 43%に発現した。注射部位反応のタイプは、注射部位内出血、注射部位発赤、注射部位熱感、注射部位灼熱感、注射部位刺痛感、注射部位そう痒感、注射部位蕁麻疹、注射部位疼痛、注射部位硬結、注射部位腫瘍及び注射部位炎症であった。</p> <p>重度の注射部位反応の発現頻度は、ゾレアを投与した被験者の方がプラセボ群の被験者よりも高かった（12%対 9%）。</p> <p>注射部位反応の大半は投与後 1 時間以内に発現し、発現持続期間は 8 日未満であり、その後の投与来院日には発現頻度は概ね減少した。</p> <p><b>6 歳以上 12 歳未満の小児喘息患者を対象とした臨床試験における副作用</b></p> <p>以下に記載のデータは、926 例の 6 歳以上 12 歳未満の小児被験者（プラセボ対照試験又はその</p>                              |       |     |     |      |  |       |       |             |  |  |    |    |    |    |    |    |               |  |  |     |    |    |    |    |    |     |    |    |     |    |    |              |  |  |        |    |    |                |  |  |      |    |    |     |    |    |               |  |  |    |    |    |

| 販売名                  | XOLAIR (omalizumab) for injection, for subcutaneous use   |                  |                       |  |  |                  |                  |                |             |  |  |  |    |          |           |          |                   |  |  |  |      |           |           |           |      |          |           |          |       |          |           |          |            |          |          |        |                      |  |  |  |     |          |           |          |              |  |  |  |    |            |           |          |                      |  |  |  |    |          |          |          |
|----------------------|---|------------------|-----------------------|--|--|------------------|------------------|----------------|-------------|--|--|--|----|----------|-----------|----------|-------------------|--|--|--|------|-----------|-----------|-----------|------|----------|-----------|----------|-------|----------|-----------|----------|------------|----------|----------|--------|----------------------|--|--|--|-----|----------|-----------|----------|--------------|--|--|--|----|------------|-----------|----------|----------------------|--|--|--|----|----------|----------|----------|
|                      | <p>他の喘息の対照試験のいずれかにおいて6ヵ月間曝露した被験者583例と、1年以上曝露した被験者292例を含む)におけるゾレアへの曝露状況を反映したものである。本剤を投与した小児被験者の平均年齢は8.8歳であった。被験者の69%は男性で、64%は白人であった。被験者には本剤75mg~375mgを2週間隔又は4週間隔で投与し、対照群に割り付けた被験者には、プラセボと併用又は併用せずに標準療法を行った。臨床試験において、ゾレアを投与した被験者で悪性腫瘍の報告はなかった。</p> <p>ゾレアを投与した小児被験者の3%以上に発現し、プラセボを投与した被験者よりも発現頻度が高かった副作用は、鼻咽頭炎、頭痛、発熱、上腹部痛、レンサ球菌咽頭炎、中耳炎、ウイルス性胃腸炎、節足動物咬傷、鼻出血であった。</p> <p>最も発現頻度が高く臨床介入(例:本剤の投与中止、又は有害事象の治療のため併用薬を投与)が必要となった有害事象は、気管支炎(0.2%)、頭痛(0.2%)、蕁麻疹(0.2%)であった。これらの事象の発現率は、ゾレアを投与した被験者及び対照被験者とも同等であった。</p> <p><u>慢性特発性蕁麻疹(CIU)患者を対象とした臨床試験における副作用</u></p> <p>CIUの治療におけるゾレアの安全性は、12週間(CIUのTrial 2)及び24週間(CIUのTrials 1及び3)のプラセボ対照反復投与試験3試験で評価した。CIUのTrials 1及び2では、投与期間を通して、被験者にベースラインの用量のヒスタミンH1受容体拮抗薬による治療に加えて、ゾレア75mg, 150mg, 300mg又はプラセボのいずれかを4週間隔で投与した。CIUのTrial 3では、ベースラインの用量のヒスタミンH1受容体拮抗薬による治療に加えて、ゾレア300mg又はプラセボのいずれかを4週間隔で投与する群に被験者を無作為に割り付けた。以下に記載のデータは、3試験に登録し、ゾレアを1回以上投与した733例の被験者(12週間曝露した684例及び24週間曝露した427例を含む)におけるゾレアへの曝露状況を反映したものである。ゾレア300mgを投与した被験者の平均年齢は43歳で、75%は女性であり、89%は白人であった。ゾレア150mg及び75mgを投与した被験者の人口統計学的プロファイルは同等であった。</p> <p>ゾレア(150mg又は300mg)を投与した被験者の2%以上に発現し、プラセボを投与した被験者よりも発現頻度が高かった副作用を表6に示す。副作用は、Trial 2とTrials 1及び3の最初の12週間を併合している。</p> <p><b>表 6. CIU試験でゾレアを投与した被験者の2%以上に発現し、プラセボを投与した被験者よりも発現頻度が高かった副作用(1日目~12週目)</b></p> <table border="1" data-bbox="400 1283 1401 1910"> <thead> <tr> <th rowspan="2">副作用*</th> <th colspan="3">CIUのTrials 1, 2及び3を併合</th> </tr> <tr> <th>150 mg<br/>(175例)</th> <th>300 mg<br/>(412例)</th> <th>プラセボ<br/>(242例)</th> </tr> </thead> <tbody> <tr> <td><u>胃腸障害</u></td> <td></td> <td></td> <td></td> </tr> <tr> <td>悪心</td> <td>2 (1.1%)</td> <td>11 (2.7%)</td> <td>6 (2.5%)</td> </tr> <tr> <td><u>感染症および寄生虫症</u></td> <td></td> <td></td> <td></td> </tr> <tr> <td>鼻咽頭炎</td> <td>16 (9.1%)</td> <td>27 (6.6%)</td> <td>17 (7.0%)</td> </tr> <tr> <td>副鼻腔炎</td> <td>2 (1.1%)</td> <td>20 (4.9%)</td> <td>5 (2.1%)</td> </tr> <tr> <td>上気道感染</td> <td>2 (1.1%)</td> <td>14 (3.4%)</td> <td>5 (2.1%)</td> </tr> <tr> <td>ウイルス性上気道感染</td> <td>4 (2.3%)</td> <td>2 (0.5%)</td> <td>(0.0%)</td> </tr> <tr> <td><u>筋骨格系および結合組織障害</u></td> <td></td> <td></td> <td></td> </tr> <tr> <td>関節痛</td> <td>5 (2.9%)</td> <td>12 (2.9%)</td> <td>1 (0.4%)</td> </tr> <tr> <td><u>神経系障害</u></td> <td></td> <td></td> <td></td> </tr> <tr> <td>頭痛</td> <td>21 (12.0%)</td> <td>25 (6.1%)</td> <td>7 (2.9%)</td> </tr> <tr> <td><u>呼吸器、胸郭および縦隔障害</u></td> <td></td> <td></td> <td></td> </tr> <tr> <td>咳嗽</td> <td>2 (1.1%)</td> <td>9 (2.2%)</td> <td>3 (1.2%)</td> </tr> </tbody> </table> | 副作用*             | CIUのTrials 1, 2及び3を併合 |  |  | 150 mg<br>(175例) | 300 mg<br>(412例) | プラセボ<br>(242例) | <u>胃腸障害</u> |  |  |  | 悪心 | 2 (1.1%) | 11 (2.7%) | 6 (2.5%) | <u>感染症および寄生虫症</u> |  |  |  | 鼻咽頭炎 | 16 (9.1%) | 27 (6.6%) | 17 (7.0%) | 副鼻腔炎 | 2 (1.1%) | 20 (4.9%) | 5 (2.1%) | 上気道感染 | 2 (1.1%) | 14 (3.4%) | 5 (2.1%) | ウイルス性上気道感染 | 4 (2.3%) | 2 (0.5%) | (0.0%) | <u>筋骨格系および結合組織障害</u> |  |  |  | 関節痛 | 5 (2.9%) | 12 (2.9%) | 1 (0.4%) | <u>神経系障害</u> |  |  |  | 頭痛 | 21 (12.0%) | 25 (6.1%) | 7 (2.9%) | <u>呼吸器、胸郭および縦隔障害</u> |  |  |  | 咳嗽 | 2 (1.1%) | 9 (2.2%) | 3 (1.2%) |
| 副作用*                 | CIUのTrials 1, 2及び3を併合   |                  |                       |  |  |                  |                  |                |             |  |  |  |    |          |           |          |                   |  |  |  |      |           |           |           |      |          |           |          |       |          |           |          |            |          |          |        |                      |  |  |  |     |          |           |          |              |  |  |  |    |            |           |          |                      |  |  |  |    |          |          |          |
|                      | 150 mg<br>(175例)  | 300 mg<br>(412例) | プラセボ<br>(242例)        |  |  |                  |                  |                |             |  |  |  |    |          |           |          |                   |  |  |  |      |           |           |           |      |          |           |          |       |          |           |          |            |          |          |        |                      |  |  |  |     |          |           |          |              |  |  |  |    |            |           |          |                      |  |  |  |    |          |          |          |
| <u>胃腸障害</u>          |   |                  |                       |  |  |                  |                  |                |             |  |  |  |    |          |           |          |                   |  |  |  |      |           |           |           |      |          |           |          |       |          |           |          |            |          |          |        |                      |  |  |  |     |          |           |          |              |  |  |  |    |            |           |          |                      |  |  |  |    |          |          |          |
| 悪心                   | 2 (1.1%)  | 11 (2.7%)        | 6 (2.5%)              |  |  |                  |                  |                |             |  |  |  |    |          |           |          |                   |  |  |  |      |           |           |           |      |          |           |          |       |          |           |          |            |          |          |        |                      |  |  |  |     |          |           |          |              |  |  |  |    |            |           |          |                      |  |  |  |    |          |          |          |
| <u>感染症および寄生虫症</u>    |   |                  |                       |  |  |                  |                  |                |             |  |  |  |    |          |           |          |                   |  |  |  |      |           |           |           |      |          |           |          |       |          |           |          |            |          |          |        |                      |  |  |  |     |          |           |          |              |  |  |  |    |            |           |          |                      |  |  |  |    |          |          |          |
| 鼻咽頭炎                 | 16 (9.1%)   | 27 (6.6%)        | 17 (7.0%)             |  |  |                  |                  |                |             |  |  |  |    |          |           |          |                   |  |  |  |      |           |           |           |      |          |           |          |       |          |           |          |            |          |          |        |                      |  |  |  |     |          |           |          |              |  |  |  |    |            |           |          |                      |  |  |  |    |          |          |          |
| 副鼻腔炎                 | 2 (1.1%)  | 20 (4.9%)        | 5 (2.1%)              |  |  |                  |                  |                |             |  |  |  |    |          |           |          |                   |  |  |  |      |           |           |           |      |          |           |          |       |          |           |          |            |          |          |        |                      |  |  |  |     |          |           |          |              |  |  |  |    |            |           |          |                      |  |  |  |    |          |          |          |
| 上気道感染                | 2 (1.1%)  | 14 (3.4%)        | 5 (2.1%)              |  |  |                  |                  |                |             |  |  |  |    |          |           |          |                   |  |  |  |      |           |           |           |      |          |           |          |       |          |           |          |            |          |          |        |                      |  |  |  |     |          |           |          |              |  |  |  |    |            |           |          |                      |  |  |  |    |          |          |          |
| ウイルス性上気道感染           | 4 (2.3%)  | 2 (0.5%)         | (0.0%)                |  |  |                  |                  |                |             |  |  |  |    |          |           |          |                   |  |  |  |      |           |           |           |      |          |           |          |       |          |           |          |            |          |          |        |                      |  |  |  |     |          |           |          |              |  |  |  |    |            |           |          |                      |  |  |  |    |          |          |          |
| <u>筋骨格系および結合組織障害</u> |   |                  |                       |  |  |                  |                  |                |             |  |  |  |    |          |           |          |                   |  |  |  |      |           |           |           |      |          |           |          |       |          |           |          |            |          |          |        |                      |  |  |  |     |          |           |          |              |  |  |  |    |            |           |          |                      |  |  |  |    |          |          |          |
| 関節痛                  | 5 (2.9%)  | 12 (2.9%)        | 1 (0.4%)              |  |  |                  |                  |                |             |  |  |  |    |          |           |          |                   |  |  |  |      |           |           |           |      |          |           |          |       |          |           |          |            |          |          |        |                      |  |  |  |     |          |           |          |              |  |  |  |    |            |           |          |                      |  |  |  |    |          |          |          |
| <u>神経系障害</u>         |   |                  |                       |  |  |                  |                  |                |             |  |  |  |    |          |           |          |                   |  |  |  |      |           |           |           |      |          |           |          |       |          |           |          |            |          |          |        |                      |  |  |  |     |          |           |          |              |  |  |  |    |            |           |          |                      |  |  |  |    |          |          |          |
| 頭痛                   | 21 (12.0%)  | 25 (6.1%)        | 7 (2.9%)              |  |  |                  |                  |                |             |  |  |  |    |          |           |          |                   |  |  |  |      |           |           |           |      |          |           |          |       |          |           |          |            |          |          |        |                      |  |  |  |     |          |           |          |              |  |  |  |    |            |           |          |                      |  |  |  |    |          |          |          |
| <u>呼吸器、胸郭および縦隔障害</u> |   |                  |                       |  |  |                  |                  |                |             |  |  |  |    |          |           |          |                   |  |  |  |      |           |           |           |      |          |           |          |       |          |           |          |            |          |          |        |                      |  |  |  |     |          |           |          |              |  |  |  |    |            |           |          |                      |  |  |  |    |          |          |          |
| 咳嗽                   | 2 (1.1%)  | 9 (2.2%)         | 3 (1.2%)              |  |  |                  |                  |                |             |  |  |  |    |          |           |          |                   |  |  |  |      |           |           |           |      |          |           |          |       |          |           |          |            |          |          |        |                      |  |  |  |     |          |           |          |              |  |  |  |    |            |           |          |                      |  |  |  |    |          |          |          |

|     |  |
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| 販売名 | XOLAIR (omalizumab) for injection, for subcutaneous use  |
|     | <p>* MedDRA (15.1) の器官別大分類及び基本語に従って分類</p> <p>Trials 1 及び 3 の 24 週間の投与期間中に報告のあったその他の反応 [ゾレア (150 mg 又は 300 mg) を投与した被験者の 2%以上に発現し、プラセボを投与した被験者よりも発現頻度が高かった] は、歯痛、真菌感染、尿路感染、筋肉痛、四肢痛、筋骨格痛、末梢性浮腫、発熱、片頭痛、副鼻腔炎に伴う頭痛、不安、口腔咽頭痛、喘息、蕁麻疹及び脱毛症であった。</p> <p><b>注射部位反応</b></p> <p>試験期間中に発現した注射部位反応 (全重症度) の発現頻度は、ゾレアを投与した被験者の方が高く [300 mg が 11 例 (2.7%) , 150 mg が 1 例 (0.6%) ] , プラセボを投与した被験者では 2 例 (0.8%) に発現した。注射部位反応のタイプは、注射部位腫脹、注射部位紅斑、注射部位疼痛、注射部位内出血、注射部位そう痒感、注射部位出血及び注射部位蕁麻疹であった。試験の中止又は投与中断に至った事象はなかった。</p> <p><b>喘息患者を対象とした臨床試験における心血管・脳血管イベント</b></p> <p>通年性吸入抗原に対する皮膚テスト陽性反応を示した 12 歳以上の中等症～重症持続型喘息患者を対象として、5 年間の観察コホート研究を実施し、悪性腫瘍の発現リスクを含め、ゾレアの長期的な安全性を評価した [警告及び使用上の注意を参照]。本試験には、合計でゾレアを投与した被験者 5007 例と、ゾレアを投与しなかった被験者 2829 例を登録した。両コホートにおける喫煙継続者 (5%) 又は元喫煙者 (29%) の割合は同等であった。被験者の平均年齢は 45 歳で、平均追跡調査期間は 3.7 年間であった。重症喘息と診断された被験者の割合は、ゾレアを投与した被験者 (50%) の方がゾレアを投与しなかった被験者 (23%) よりも高く、被験者の 44%は試験を早期に中止した。さらに、ゾレアを投与したコホートの被験者の 88%には、ゾレアへの曝露歴が平均で 8 ヶ月間あった。</p> <p>心血管・脳血管関連の重篤な有害事象 (SAE) の総発現率 (1000 人・年あたり) は、ゾレアを投与した被験者 (13.4) の方がゾレアを投与しなかった被験者 (8.1) よりも高かった。一過性脳虚血発作 (0.7 対 0.1) , 心筋梗塞 (2.1 対 0.8) , 肺高血圧症 (0.5 対 0) , 肺塞栓症・静脈血栓症 (3.2 対 1.5) 及び不安定狭心症 (2.2 対 1.4) の発現率に増加がみられたが、虚血性脳卒中及び心血管死の発現率は両試験コホートとも同等であった。これらの結果から、本剤を投与した被験者において、重篤な心血管・脳血管イベントのリスクが増加する可能性が示唆される。しかし、観察研究という試験デザイン、ゾレアへの曝露歴のある被験者の登録 (88%) , ベースラインの投与群間における心血管危険因子の不均衡、未測定危険因子について未調整、及び試験中止率の高さにより、リスクの規模を数量化できなかった。</p> <p>上述の観察コホート研究における心血管・脳血管 SAE の不均衡について詳細に評価するため、実施期間が 8～52 週間の無作為化、二重盲検、プラセボ対照試験 25 試験の併合解析を実施した。合計でゾレアを投与した被験者 3342 例と、プラセボを投与した被験者 2895 例を併合解析の対象とした。被験者の平均年齢は 38 歳で、平均追跡調査期間は 6.8 ヶ月であった。上に列挙した心血管・脳血管 SAE の発現率に著しい不均衡は観察されなかった。しかし、この併合解析の結果は、観察コホート研究よりも少ない症例数、わずかに若い被験者及び短い追跡調査期間に基づくものであるため、観察コホート研究の所見を確認又は棄却するには不十分である。</p> <p><b>免疫原性</b></p> <p>12 歳以上の喘息を適応症として承認を取得することを目的とし評価された臨床試験において、ゾレアを投与した被験者 1723 例のうち約 1 例 (&lt;0.1%) でゾレア抗体が検出された。3 つの小児の臨床試験において、ゾレアを投与した 6 歳以上 12 歳未満の抗体検査がされた小児被験者 581 例のうち 1 例でゾレア抗体が検出された。CIU の第 III 相臨床試験で本剤を投与した被験者では抗体は検出されなかったが、抗ゾレア抗体用の検体採取時のゾレアの濃度や一部の被験者では検体が紛失したことから、ゾレア抗体はこれらの臨床試験で投与を行った 733 例の被験者の 88%のみでしか測定できなかった。このデータは、ELISA 法による検査結果でゾレア抗体陽性と判定された被験者の割合を反映したものであり、アッセイの感度と特異度に強く左右される。さらに、</p> |



| 販売名 | XOLAIR (omalizumab) for injection, for subcutaneous use   |
|-----|---|
|     | <p>このアッセイにおいて観察された抗体陽性率は、検体の取扱い、検体採取のタイミング、併用薬及び基礎疾患等、いくつかの因子による影響を受けた可能性がある。このため、ゾレア抗体の発現率と他の製剤に対する抗体の発現率を比較した場合、誤解を招くおそれがある。</p> <p><b>市販後の使用経験</b></p> <p>承認後にゾレアを投与した成人患者及び12歳以上の青少年患者において、以下の副作用の発現が確認されている。これらの反応は規模が不明の母集団から自主的に報告されているため、必ずしも確実に発現頻度を推定したり、医薬品への曝露との因果関係を確立できるものではない。</p> <p><u>アナフィラキシー</u>：自発報告及び2003年6月から2006年12月の推定曝露量が約57,300例であることを基に算出したゾレアの投与に起因するアナフィラキシーの発現頻度は、患者の0.2%以上と推計された。アナフィラキシーの診断基準は、皮膚又は粘膜組織浸潤が認められること、随伴する関連症状の有無を問わず気道障害及び/又は血圧低下のいずれかが認められること、ゾレアの投与との間に時間的な関連があり、他に特定可能な原因がないことであった。報告されたこれらの症例における徴候及び症状は、気管支痙攣、低血圧、失神、蕁麻疹、咽喉又は舌の血管浮腫、呼吸困難、咳嗽、胸部絞扼感及び/又は皮膚血管浮腫であった。肺浸潤は症例の89%において報告された。低血圧又は失神は症例の14%において報告された。報告された症例の15%は入院に至った。ゾレアと関連のないアナフィラキシーの既往歴は、症例の24%で報告された。</p> <p>報告のあったゾレアに起因するアナフィラキシーの症例のうち、39%は初回投与時、19%は2回目の投与時、10%は3回目の投与時、残りはその後の投与時に発現した。1例では39回目の投与後に発現した（19ヵ月間連続投与し、3ヵ月間の投与中断後の投与再開時にアナフィラキシーが発現した）。これらの症例におけるアナフィラキシーの発現時期は、投与後30分以内が35%、投与後30分超60分以内が16%、投与後60分超90分以内が2%、投与後90分超120分以内が6%、投与後2時間超6時間以内が5%、投与後6時間超12時間以内が14%、投与後12時間超24時間以内が8%、投与後24時間超4日以内が5%であった。症例の9%では発現時期が不明であった。</p> <p>アナフィラキシーが発現した23例の患者はゾレアの投与を再開したが、18例には同程度のアナフィラキシーの症状が再発した。さらに、以前に蕁麻疹のみが発現した4例では、ゾレアの再投与によりアナフィラキシーが発現した。</p> <p><u>好酸球性疾患</u>：好酸球性疾患の発現が報告されている〔警告及び使用上の注意を参照〕。</p> <p><u>発熱、関節痛及び発疹</u>：ゾレアの承認後の使用経験において、関節炎/関節痛、発疹（蕁麻疹又はその他の病型）、発熱及びリンパ節症等、血清病様の徴候及び症状を呈する特定症状群の発現が報告されている〔警告及び使用上の注意を参照〕。</p> <p><u>血液疾患</u>：重度の血小板減少症が報告されている。</p> <p><u>皮膚疾患</u>：毛髪脱落が報告されている。</p> <p><b>薬物相互作用</b></p> <p>ゾレアの正式な薬物相互作用試験は実施していない。</p> <p>喘息患者では、ゾレアとアレルギー免疫療法の併用は評価していない。</p> <p>CIU患者では、ゾレアと免疫抑制療法の併用は検討していない。</p> <p><b>特別な集団における使用</b></p> <p><b>妊婦</b></p> <p><u>リスクの要約</u></p> <p>妊婦中にゾレアを投与したデータは、薬剤関連リスクの情報を提供する上では不十分である。オマリズマブのようなモノクローナル抗体は妊娠の経過に従って線形性に胎盤を通過して移行する。そのため、胎児への潜在的な影響は、妊娠第2期及び第3期中により大きくなる可能性が高い。</p> <p>動物を用いた生殖試験では、ヒト最大推奨用量（MRHD）の約10倍までの用量のオマリズマブ</p> |

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|-----|---|
|     | <p>を皮下投与したカニクイザルにおいて、胎児への有害作用のエビデンスは認められなかった。<br/> <u>[動物実験データ参照]</u></p> <p>米国の一般住民において、大奇形の推定背景リスクは2~4%、流産は15~20%である。</p> <p><u>臨床的考察</u></p> <p><u>疾患関連の母体、胎児のリスク</u></p> <p>コントロール不良又は不十分な喘息女性において、母体の子癩前症リスク、新生児の未熟児、低体重、胎内発育遅延のリスクが増大することがエビデンスとして示されている。喘息コントロールのレベルは、妊婦において注意深く観察するべきであり、適切にコントロールできるよう治療を調整する必要がある。</p> <p><u>データ</u></p> <p><u>動物実験データ</u></p> <p>カニクイザルを用いた生殖試験を実施している。オマリズマブを器官形成期にMRHDの約10倍（最大75 mg/kg/週の母体皮下注を行ったmg/kg単位）量の用量を投与した結果、母体毒性、胎児毒性又は催奇形性のエビデンスは認められなかった。妊娠後期、分娩及び授乳期にオマリズマブを投与した結果、胎児又は新生児の発育に悪影響は認められなかった。</p> <p><u>授乳</u></p> <p><u>リスクの要約</u></p> <p>ヒト乳汁中へのオマリズマブの移行、乳幼児への影響、及び乳汁産生への影響に関する情報は無い。しかし、オマリズマブはヒトモノクローナル抗体（IgG1κ）であり、免疫グロブリン（IgG）はヒト乳汁中にわずかに存在している。カニクイザルにおいて、子宮内曝露した後、及び28日間授乳した後の新生児のオマリズマブの血清中濃度は、母体血清中濃度の11%~94%であった。オマリズマブの乳汁中濃度は、母体血清中濃度の0.15%であった。</p> <p>授乳による発育上及び健康上の利点については、母親へのゾレアの臨床上的必要性和、オマリズマブ又は母親の基礎疾患が授乳児に及ぼす潜在的な有害作用と併せて考慮すること。</p> <p><u>小児への投与</u></p> <p><u>喘息</u></p> <p>喘息に対するゾレアの安全性及び有効性は、通年性吸入抗原に対する皮膚テスト陽性又は<i>in vitro</i>反応性の結果が得られた6歳以上12歳未満の中等症~重症持続型喘息の小児患者926例（ゾレアが624例、プラセボが302例）を対象とした臨床試験2試験において評価した。1試験は、喘息の成人及び青少年を対象としたTrials 1及び2と試験デザイン及び実施方法が同様の主要試験であった。もう1試験は主に安全性試験であり、有効性の評価は副次的評価項目として実施した。この主要試験では、ゾレアを投与した被験者において、増悪の発現率が統計学的有意に減少した（増悪は、全身ステロイド薬の投与又はベースラインのICSの用量の増倍を必要とする喘息増悪と定義）。<u>[臨床試験を参照]</u></p> <p>6歳未満の小児喘息患者の安全性及び有効性は確立していない。</p> <p><u>慢性特発性蕁麻疹</u></p> <p>青少年CIU患者におけるゾレアの安全性及び有効性は、12~17歳の被験者39例（ゾレアが29例、プラセボが10例）を対象としたCIUの無作為化プラセボ対照試験3試験で評価した。週間そう痒スコアの数値が減少し、副作用は18歳以上の患者で報告された副作用と同等であった。</p> <p>12歳未満の小児CIU患者の安全性及び有効性は確立していない。</p> <p><u>高齢者への投与</u></p> |

|       |   |
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|       | <p>臨床試験では、第 III 相試験で 65 歳以上の喘息の被験者 134 例と、CIU の被験者 37 例にゾレアを投与した。これらの試験では、年齢に伴う明らかな差は認められなかったが、効果が若年患者と異なるかどうかを判定するには、65 歳以上の被験者数が十分ではない。</p> <p><b>過量投与</b></p> <p>本剤の最大耐量は決定されていない。被験者に最大 4,000 mg を静脈内単回投与した際に、用量制限毒性のエビデンスは認められなかった。最大累積用量が 20 週間で 44,000 mg の被験者においても、毒性は認められなかった。</p> |
| 改訂年月日 | 2016 年 7 月  |

## **Core Data Sheet**

[REDACTED]

**XOLAIR<sup>®</sup>** (omalizumab)

[REDACTED]  
[REDACTED]

**Core Data Sheet**

[REDACTED]

|            |
|------------|
| [REDACTED] |
| [REDACTED] |
| [REDACTED] |
| [REDACTED] |
| [REDACTED] |

|            |            |
|------------|------------|
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |

[REDACTED]  
[REDACTED]  
[REDACTED]

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Xolair 75 mg powder and solvent for solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 75 mg of omalizumab\*.

After reconstitution one vial contains 125 mg/ml of omalizumab (75 mg in 0.6 ml).

\*Omalizumab is a humanised monoclonal antibody manufactured by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell line.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: white to off-white lyophilisate

Solvent: clear and colourless solution

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Xolair is indicated in adults, adolescents and children (6 to <12 years of age).

Xolair treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma (see section 4.2).

#### Adults and adolescents (12 years of age and older)

Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV<sub>1</sub> <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

#### Children (6 to <12 years of age)

Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

## 4.2 Posology and method of administration

Xolair treatment should be initiated by physicians experienced in the diagnosis and treatment of severe persistent asthma.

### Posology

The appropriate dose and frequency of Xolair is determined by baseline IgE (IU/ml), measured before the start of treatment, and body weight (kg). Prior to administration of the initial dose, patients should have their IgE level determined by any commercial serum total IgE assay for their dose assignment. Based on these measurements, 75 to 600 mg of Xolair in 1 to 4 injections may be needed for each administration.

Patients with IgE lower than 76 IU/ml were less likely to experience benefit (see section 5.1). Prescribing physicians should ensure that adult and adolescent patients with IgE below 76 IU/ml and children (6 to < 12 years of age) with IgE below 200 IU/ml have unequivocal *in vitro* reactivity (RAST) to a perennial allergen before starting therapy.

See Table 1 for a conversion chart and Tables 2 and 3 for the dose determination charts in adults, adolescents and children (6 to <12 years of age).

Patients whose baseline IgE levels or body weight in kilograms are outside the limits of the dose table should not be given Xolair.

The maximum recommended dose is 600 mg omalizumab every two weeks.

**Table 1: Conversion from dose to number of vials, number of injections and total injection volume for each administration**

| Dose (mg) | Number of vials    |                     | Number of injections | Total injection volume (ml) |
|-----------|--------------------|---------------------|----------------------|-----------------------------|
|           | 75 mg <sup>a</sup> | 150 mg <sup>b</sup> |                      |                             |
| 75        | 1 <sup>c</sup>     | 0                   | 1                    | 0.6                         |
| 150       | 0                  | 1                   | 1                    | 1.2                         |
| 225       | 1 <sup>c</sup>     | 1                   | 2                    | 1.8                         |
| 300       | 0                  | 2                   | 2                    | 2.4                         |
| 375       | 1 <sup>c</sup>     | 2                   | 3                    | 3.0                         |
| 450       | 0                  | 3                   | 3                    | 3.6                         |
| 525       | 1 <sup>c</sup>     | 3                   | 4                    | 4.2                         |
| 600       | 0                  | 4                   | 4                    | 4.8                         |

<sup>a</sup> 0.6 ml = maximum delivered volume per vial (Xolair 75 mg).

<sup>b</sup> 1.2 ml = maximum delivered volume per vial (Xolair 150 mg).

<sup>c</sup> or use 0.6 ml from a 150 mg vial.



**Table 2: ADMINISTRATION EVERY 4 WEEKS. Xolair doses (milligrams per dose) administered by subcutaneous injection every 4 weeks**

| Baseline IgE (IU/ml) | Body weight (kg) |        |        |        |        |        |        |        |         |          |
|----------------------|------------------|--------|--------|--------|--------|--------|--------|--------|---------|----------|
|                      | ≥20-25           | >25-30 | >30-40 | >40-50 | >50-60 | >60-70 | >70-80 | >80-90 | >90-125 | >125-150 |
| ≥30-100              | 75               | 75     | 75     | 150    | 150    | 150    | 150    | 150    | 300     | 300      |
| >100-200             | 150              | 150    | 150    | 300    | 300    | 300    | 300    | 300    | 450     | 600      |
| >200-300             | 150              | 150    | 225    | 300    | 300    | 450    | 450    | 450    | 600     |          |
| >300-400             | 225              | 225    | 300    | 450    | 450    | 450    | 600    | 600    |         |          |
| >400-500             | 225              | 300    | 450    | 450    | 600    | 600    |        |        |         |          |
| >500-600             | 300              | 300    | 450    | 600    | 600    |        |        |        |         |          |
| >600-700             | 300              |        | 450    | 600    |        |        |        |        |         |          |
| >700-800             |                  |        |        |        |        |        |        |        |         |          |
| >800-900             |                  |        |        |        |        |        |        |        |         |          |
| >900-1000            |                  |        |        |        |        |        |        |        |         |          |
| >1000-1100           |                  |        |        |        |        |        |        |        |         |          |

ADMINISTRATION EVERY 2 WEEKS  
SEE TABLE 3

**Table 3: ADMINISTRATION EVERY 2 WEEKS. Xolair doses (milligrams per dose) administered by subcutaneous injection every 2 weeks**

| Baseline IgE (IU/ml) | Body weight (kg)                            |        |        |        |        |  |        |        |         |          |
|----------------------|---|--------|--------|--------|--------|--|--------|--------|---------|----------|
|                      | ≥20-25                                      | >25-30 | >30-40 | >40-50 | >50-60 | >60-70   | >70-80 | >80-90 | >90-125 | >125-150 |
| ≥30-100              | ADMINISTRATION EVERY 4 WEEKS<br>SEE TABLE 2 |        |        |        |        |  |        |        |         |          |
| >100-200             |   |        |        |        |        |  |        |        |         |          |
| >200-300             |   |        |        |        |        |  |        |        |         | 375      |
| >300-400             |   |        |        |        |        |  |        | 450    | 525     |          |
| >400-500             |   |        |        |        |        | 375  | 375    | 525    | 600     |          |
| >500-600             |   |        |        |        | 375    | 450  | 450    | 600    |         |          |
| >600-700             |   | 225    |        |        | 375    | 450  | 450    | 525    |         |          |
| >700-800             | 225   | 225    | 300    | 375    | 450    | 450  | 525    | 600    |         |          |
| >800-900             | 225   | 225    | 300    | 375    | 450    | 525  | 600    |        |         |          |
| >900-1000            | 225   | 300    | 375    | 450    | 525    | 600  |        |        |         |          |
| >1000-1100           | 225   | 300    | 375    | 450    | 600    |  |        |        |         |          |
| >1100-1200           | 300   | 300    | 450    | 525    | 600    | DO NOT ADMINISTER– data is unavailable for dose recommendation |        |        |         |          |
| >1200-1300           | 300   | 375    | 450    | 525    |        |  |        |        |         |          |
| >1300-1500           | 300   | 375    | 525    | 600    |        |  |        |        |         |          |

*Treatment duration, monitoring and dose adjustments*

Xolair is intended for long-term treatment. Clinical trials have demonstrated that it takes at least 12-16 weeks for Xolair treatment to show effectiveness. At 16 weeks after commencing Xolair therapy patients should be assessed by their physician for treatment effectiveness before further injections are administered. The decision to continue Xolair following the 16-week timepoint, or on subsequent occasions, should be based on whether a marked improvement in overall asthma control is seen (see section 5.1, Physician’s overall assessment of treatment effectiveness).

Discontinuation of Xolair treatment generally results in a return to elevated free IgE levels and associated symptoms. Total IgE levels are elevated during treatment and remain elevated for up to one year after the discontinuation of treatment. Therefore, re-testing of IgE levels during Xolair treatment cannot be used as a guide for dose determination. Dose determination after treatment interruptions lasting less than one year should be based on serum IgE levels obtained at the initial dose determination. Total serum IgE levels may be re-tested for dose determination if treatment with Xolair has been interrupted for one year or more.

Doses should be adjusted for significant changes in body weight (see Tables 2 and 3).

### Special populations

#### *Elderly (65 years of age and older)*

There are limited data available on the use of Xolair in patients older than 65 years but there is no evidence that elderly patients require a different dose from younger adult patients.

#### *Renal or hepatic impairment*

There have been no studies on the effect of impaired renal or hepatic function on the pharmacokinetics of Xolair. Because omalizumab clearance at clinical doses is dominated by the reticular endothelial system (RES) it is unlikely to be altered by renal or hepatic impairment. While no particular dose adjustment is recommended for these patients, Xolair should be administered with caution (see section 4.4).

#### *Paediatric population*

The safety and efficacy of Xolair in children below age 6 have not been established. No data are available.

### Method of administration

For subcutaneous administration only. Do not administer by the intravenous or intramuscular route.

The injections are administered subcutaneously in the deltoid region of the arm. Alternatively, the injections can be administered in the thigh if there is any reason precluding administration in the deltoid region.

There is limited experience with self-administration of Xolair. Therefore treatment is intended to be administered by a healthcare provider only.

For instructions on reconstitution of the medicinal product before administration, see section 6.6 and also information for the healthcare professional section of the package leaflet.

## **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## **4.4 Special warnings and precautions for use**

### General

Xolair is not indicated for the treatment of acute asthma exacerbations, acute bronchospasm or status asthmaticus.

Xolair has not been studied in patients with hyperimmunoglobulin E syndrome or allergic bronchopulmonary aspergillosis or for the prevention of anaphylactic reactions, including those provoked by food allergy, atopic dermatitis, or allergic rhinitis. Xolair is not indicated for the treatment of these conditions.

Xolair therapy has not been studied in patients with autoimmune diseases, immune complex-mediated conditions, or pre-existing renal or hepatic impairment (see section 4.2). Caution should be exercised when administering Xolair in these patient populations.

Abrupt discontinuation of systemic or inhaled corticosteroids after initiation of Xolair therapy is not recommended. Decreases in corticosteroids should be performed under the direct supervision of a physician and may need to be performed gradually.

## Immune system disorders

### Allergic reactions type I

Type I local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur when taking omalizumab, also with onset after a long duration of treatment. Most of these reactions occurred within 2 hours after the first and subsequent injections of Xolair but some started beyond 2 hours and even beyond 24 hours after the injection. Therefore medicinal products for the treatment of anaphylactic reactions should always be available for immediate use following administration of Xolair. Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur. A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following Xolair administration.

Antibodies to omalizumab have been detected in a low number of patients in clinical trials (see section 4.8). The clinical relevance of anti-Xolair antibodies is not well understood.

### Serum sickness

Serum sickness and serum sickness-like reactions, which are delayed allergic type III reactions, have been seen in patients treated with humanised monoclonal antibodies including omalizumab. The suggested pathophysiologic mechanism includes immune-complex formation and deposition due to development of antibodies against omalizumab. The onset has typically been 1-5 days after administration of the first or subsequent injections, also after long duration of treatment. Symptoms suggestive of serum sickness include arthritis/arthralgias, rash (urticaria or other forms), fever and lymphadenopathy. Antihistamines and corticosteroids may be useful for preventing or treating this disorder, and patients should be advised to report any suspected symptoms.

### Churg-Strauss syndrome and hypereosinophilic syndrome

Patients with severe asthma may rarely present systemic hypereosinophilic syndrome or allergic eosinophilic granulomatous vasculitis (Churg-Strauss syndrome), both of which are usually treated with systemic corticosteroids.

In rare cases, patients on therapy with anti-asthma medicinal products, including omalizumab, may present or develop systemic eosinophilia and vasculitis. These events are commonly associated with the reduction of oral corticosteroid therapy.

In these patients, physicians should be alert to the development of marked eosinophilia, vasculitic rash, worsening pulmonary symptoms, paranasal sinus abnormalities, cardiac complications, and/or neuropathy.

Discontinuation of omalizumab should be considered in all severe cases with the above mentioned immune system disorders.

### Parasitic (helminth) infections

IgE may be involved in the immunological response to some helminth infections. In patients at chronic high risk of helminth infection, a placebo-controlled trial showed a slight increase in infection rate with omalizumab, although the course, severity, and response to treatment of infection were unaltered. The helminth infection rate in the overall clinical programme, which was not designed to detect such infections, was less than 1 in 1,000 patients. However, caution may be warranted in patients at high risk of helminth infection, in particular when travelling to areas where helminthic infections are endemic. If patients do not respond to recommended anti-helminth treatment, discontinuation of Xolair should be considered.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Since IgE may be involved in the immunological response to some helminth infections, Xolair may indirectly reduce the efficacy of medicinal products for the treatment of helminthic or other parasitic infections (see section 4.4).

Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of omalizumab; thus, there is little potential for drug-drug interactions. Medicinal product or vaccine interaction studies have not been performed with Xolair. There is no pharmacological reason to expect that commonly prescribed medicinal products used in the treatment of asthma will interact with omalizumab.

In clinical studies Xolair was commonly used in conjunction with inhaled and oral corticosteroids, inhaled short-acting and long-acting beta agonists, leukotriene modifiers, theophyllines and oral antihistamines. There was no indication that the safety of Xolair was altered with these other commonly used anti-asthma medicinal products. Limited data are available on the use of Xolair in combination with specific immunotherapy (hypo-sensitisation therapy). In a clinical trial where Xolair was co-administered with immunotherapy, the safety and efficacy of Xolair in combination with specific immunotherapy were found to be no different to that of Xolair alone.

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

There are limited data from the use of omalizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Omalizumab crosses the placental barrier and the potential for harm to the foetus is unknown. Omalizumab has been associated with age-dependent decreases in blood platelets in non-human primates, with a greater relative sensitivity in juvenile animals (see section 5.3). Xolair should not be used during pregnancy unless clearly necessary.

##### Breast-feeding

It is unknown whether omalizumab is excreted in human milk. Available data in non-human primates have shown excretion of omalizumab into milk (see section 5.3). A risk to the newborns/infants cannot be excluded. Omalizumab should not be given during breast-feeding.

##### Fertility

There are no human fertility data for omalizumab. In specifically-designed non-clinical fertility studies in non-human primates, including mating studies, no impairment of male or female fertility was observed following repeated dosing with omalizumab at dose levels up to 75 mg/kg. Furthermore, no genotoxic effects were observed in separate non-clinical genotoxicity studies (see section 5.3).

#### **4.7 Effects on ability to drive and use machines**

Xolair has no or negligible influence on the ability to drive and use machines.

#### **4.8 Undesirable effects**

##### Summary of the safety profile

During clinical trials in adult and adolescent patients 12 years of age and older, the most commonly reported adverse reactions were headaches and injection site reactions, including injection site pain, swelling, erythema and pruritus. In clinical trials in children 6 to <12 years of age, the most commonly reported adverse reactions were headache, pyrexia and upper abdominal pain. Most of the reactions were mild or moderate in severity.

### Tabulated list of adverse reactions

Table 4 lists the adverse reactions recorded in clinical studies in the total safety population treated with Xolair by MedDRA system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequency categories are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and very rare ( $< 1/10,000$ ). Reactions reported in the post-marketing setting are listed with frequency not known (cannot be estimated from the available data).

**Table 4: Adverse reactions**

|   |  |
|---|--|
| <b>Infections and infestations</b>                          |  |
| Uncommon  | Pharyngitis  |
| Rare  | Parasitic infection  |
| <b>Blood and lymphatic system disorders</b>                 |  |
| Not known   | Idiopathic thrombocytopenia, including severe cases  |
| <b>Immune system disorders</b>                              |  |
| Rare  | Anaphylactic reaction, other serious allergic conditions, anti-omalizumab antibody development |
| Not known   | Serum sickness, may include fever and lymphadenopathy  |
| <b>Nervous system disorders</b>                             |  |
| Common  | Headache*  |
| Uncommon  | Syncope, paraesthesia, somnolence, dizziness   |
| <b>Vascular disorders</b>                                   |  |
| Uncommon  | Postural hypotension, flushing   |
| <b>Respiratory, thoracic and mediastinal disorders</b>      |  |
| Uncommon  | Allergic bronchospasm, coughing  |
| Rare  | Laryngoedema   |
| Not known   | Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome)                                |
| <b>Gastrointestinal disorders</b>                           |  |
| Common  | Abdominal pain upper**   |
| Uncommon  | Dyspeptic signs and symptoms, diarrhoea, nausea  |
| <b>Skin and subcutaneous tissue disorders</b>               |  |
| Uncommon  | Photosensitivity, urticaria, rash, pruritus  |
| Rare  | Angioedema   |
| Not known   | Alopecia   |
| <b>Musculoskeletal and connective tissue disorders</b>      |  |
| Rare  | Systemic lupus erythematosus (SLE)   |
| Not known   | Arthralgia, myalgia, joint swelling  |
| <b>General disorders and administration site conditions</b> |  |
| Very common   | Pyrexia**  |
| Common  | Injection site reactions such as swelling, erythema, pain, pruritus                            |
| Uncommon  | Influenza-like illness, swelling arms, weight increase, fatigue                                |

\*: Very common in children 6 to <12 years of age

\*\* : In children 6 to <12 years of age

### Description of selected adverse reactions

#### Immune system disorders

For further information, see section 4.4.

#### Anaphylaxis

Anaphylactic reactions were rare in clinical trials. However, post-marketing data following a cumulative search in the safety database retrieved a total of 898 anaphylaxis cases. Based on an estimated exposure of 566,923 patient treatment years, this results in a reporting rate of approximately 0.20%.

### Arterial thromboembolic events (ATE)

In controlled clinical trials and during interim analyses of an observational study, a numerical imbalance of ATE was observed. The definition of the composite endpoint ATE included stroke, transient ischaemic attack, myocardial infarction, unstable angina, and cardiovascular death (including death from unknown cause). In the final analysis of the observational study, the rate of ATE per 1,000 patient years was 7.52 (115/15,286 patient years) for Xolair-treated patients and 5.12 (51/9,963 patient years) for control patients. In a multivariate analysis controlling for available baseline cardiovascular risk factors, the hazard ratio was 1.32 (95% confidence interval 0.91-1.91). In a separate analysis of pooled clinical trials, which included all randomised double-blind, placebo-controlled clinical trials lasting 8 or more weeks, the rate of ATE per 1,000 patient years was 2.69 (5/1,856 patient years) for Xolair-treated patients and 2.38 (4/1,680 patient years) for placebo patients (rate ratio 1.13, 95% confidence interval 0.24-5.71).

### Platelets

In clinical trials few patients had platelet counts below the lower limit of the normal laboratory range. None of these changes were associated with bleeding episodes or a decrease in haemoglobin. No pattern of persistent decrease in platelet counts, as observed in non-human primates (see section 5.3), has been reported in humans (patients above 6 years of age), even though isolated cases of idiopathic thrombocytopenia, including severe cases, have been reported in the post-marketing setting.

### Parasitic infections

In patients at chronic high risk of helminth infection, a placebo-controlled trial showed a slight numerical increase in infection rate with omalizumab that was not statistically significant. The course, severity, and response to treatment of infections were unaltered (see section 4.4).

### Systemic lupus erythematosus

Clinical trial and post-marketing cases of systemic lupus erythematosus (SLE) have been reported in patients with moderate to severe asthma and CSU. The pathogenesis of SLE is not well understood.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions **via the national reporting system listed in [Appendix V](#)**.

## **4.9 Overdose**

Maximum tolerated dose of Xolair has not been determined. Single intravenous doses up to 4,000 mg have been administered to patients without evidence of dose-limiting toxicities. The highest cumulative dose administered to patients was 44,000 mg over a 20-week period and this dose did not result in any untoward acute effects.

If an overdose is suspected, the patient should be monitored for any abnormal signs or symptoms. Medical treatment should be sought and instituted appropriately.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Drugs for obstructive airway diseases, other systemic drugs for obstructive airway diseases, ATC code: R03DX05

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (IgE). The antibody is an IgG1 kappa that contains human framework regions with the complementary-determining regions of a murine parent antibody that binds to IgE.

### Mechanism of action

Omalizumab binds to IgE and prevents binding of IgE to FcεRI (high-affinity IgE receptor), thereby reducing the amount of free IgE that is available to trigger the allergic cascade. Treatment of atopic subjects with omalizumab resulted in a marked down-regulation of FcεRI receptors on basophils.

### Pharmacodynamic effects

The *in vitro* histamine release from basophils isolated from Xolair-treated subjects was reduced by approximately 90% following stimulation with an allergen compared to pre-treatment values.

In clinical studies, serum free IgE levels were reduced in a dose-dependent manner within one hour following the first dose and maintained between doses. One year after discontinuation of Xolair dosing, the IgE levels had returned to pre-treatment levels with no observed rebound in IgE levels after washout of the medicinal product.

### Clinical efficacy and safety

#### Adults and adolescents ≥12 years of age

The efficacy and safety of Xolair were demonstrated in a 28-week double-blind placebo-controlled study (study 1) involving 419 severe allergic asthmatics, ages 12-79 years, who had reduced lung function (FEV<sub>1</sub> 40-80% predicted) and poor asthma symptom control despite receiving high dose inhaled corticosteroids and a long-acting beta2-agonist. Eligible patients had experienced multiple asthma exacerbations requiring systemic corticosteroid treatment or had been hospitalised or attended an emergency room due to a severe asthma exacerbation in the past year despite continuous treatment with high-dose inhaled corticosteroids and a long-acting beta2-agonist. Subcutaneous Xolair or placebo were administered as add-on therapy to >1,000 micrograms beclomethasone dipropionate (or equivalent) plus a long-acting beta2-agonist. Oral corticosteroid, theophylline and leukotriene-modifier maintenance therapies were allowed (22%, 27%, and 35% of patients, respectively).

The rate of asthma exacerbations requiring treatment with bursts of systemic corticosteroids was the primary endpoint. Omalizumab reduced the rate of asthma exacerbations by 19% (p = 0.153). Further evaluations which did show statistical significance (p<0.05) in favour of Xolair included reductions in severe exacerbations (where patient's lung function was reduced to below 60% of personal best and requiring systemic corticosteroids) and asthma-related emergency visits (comprised of hospitalisations, emergency room, and unscheduled doctor visits), and improvements in Physician's overall assessment of treatment effectiveness, Asthma-related Quality of Life (AQL), asthma symptoms and lung function.



In a subgroup analysis, patients with pre-treatment total IgE  $\geq 76$  IU/ml were more likely to experience clinically meaningful benefit to Xolair. In these patients in study 1 Xolair reduced the rate of asthma exacerbations by 40% ( $p = 0.002$ ). In addition more patients had clinically meaningful responses in the total IgE  $\geq 76$  IU/ml population across the Xolair severe asthma programme. Table 5 includes results in the study 1 population.

**Table 5: Results of study 1**

|                                       | Whole study 1 population |                  |
|---------------------------------------|--------------------------|------------------|
|                                       | Xolair<br>N=209          | Placebo<br>N=210 |
| <b>Asthma exacerbations</b>           |                          |                  |
| Rate per 28-week period               | 0.74                     | 0.92             |
| % reduction, p-value for rate ratio   | 19.4%, $p = 0.153$       |                  |
| <b>Severe asthma exacerbations</b>    |                          |                  |
| Rate per 28-week period               | 0.24                     | 0.48             |
| % reduction, p-value for rate ratio   | 50.1%, $p = 0.002$       |                  |
| <b>Emergency visits</b>               |                          |                  |
| Rate per 28-week period               | 0.24                     | 0.43             |
| % reduction, p-value for rate ratio   | 43.9%, $p = 0.038$       |                  |
| <b>Physician's overall assessment</b> |                          |                  |
| % responders*                         | 60.5%                    | 42.8%            |
| p-value**                             | $<0.001$                 |                  |
| <b>AQL improvement</b>                |                          |                  |
| % of patients $\geq 0.5$ improvement  | 60.8%                    | 47.8%            |
| p-value                               | 0.008                    |                  |

\* marked improvement or complete control

\*\* p-value for overall distribution of assessment

Study 2 assessed the efficacy and safety of Xolair in a population of 312 severe allergic asthmatics which matched the population in study 1. Treatment with Xolair in this open label study led to a 61% reduction in clinically significant asthma exacerbation rate compared to current asthma therapy alone.

Four additional large placebo-controlled supportive studies of 28 to 52 weeks duration in 1,722 adults and adolescents (studies 3, 4, 5, 6) assessed the efficacy and safety of Xolair in patients with severe persistent asthma. Most patients were inadequately controlled but were receiving less concomitant asthma therapy than patients in studies 1 or 2. Studies 3-5 used exacerbation as primary endpoint, whereas study 6 primarily evaluated inhaled corticosteroid sparing.

In studies 3, 4 and 5 patients treated with Xolair had respective reductions in asthma exacerbation rates of 37.5% ( $p = 0.027$ ), 40.3% ( $p < 0.001$ ) and 57.6% ( $p < 0.001$ ) compared to placebo.

In study 6, significantly more severe allergic asthma patients on Xolair were able to reduce their fluticasone dose to  $\leq 500$  micrograms/day without deterioration of asthma control (60.3%) compared to the placebo group (45.8%,  $p < 0.05$ ).

Quality of life scores were measured using the Juniper Asthma-related Quality of Life Questionnaire. For all six studies there was a statistically significant improvement from baseline in quality of life scores for Xolair patients versus the placebo or control group.

Physician's overall assessment of treatment effectiveness:

Physician's overall assessment was performed in five of the above studies as a broad measure of asthma control performed by the treating physician. The physician was able to take into account PEF (peak expiratory flow), day and night time symptoms, rescue medication use, spirometry and exacerbations. In all five studies a significantly greater proportion of Xolair treated patients were judged to have achieved either a marked improvement or complete control of their asthma compared to placebo patients.

#### Children 6 to <12 years of age

The primary support for safety and efficacy of Xolair in the group aged 6 to <12 years comes from one randomised, double-blind, placebo-controlled, multi-centre trial (study 7).

Study 7 was a placebo-controlled trial which included a specific subgroup (n=235) of patients as defined in the present indication, who were treated with high-dose inhaled corticosteroids ( $\geq 500$   $\mu\text{g/day}$  fluticasone equivalent) plus long-acting beta agonist.

A clinically significant exacerbation was defined as a worsening of asthma symptoms as judged clinically by the investigator, requiring doubling of the baseline inhaled corticosteroid dose for at least 3 days and/or treatment with rescue systemic (oral or intravenous) corticosteroids for at least 3 days.

In the specific subgroup of patients on high dose inhaled corticosteroids, the omalizumab group had a statistically significantly lower rate of clinically significant asthma exacerbations than the placebo group. At 24 weeks, the difference in rates between treatment groups represented a 34% (rate ratio 0.662,  $p = 0.047$ ) decrease relative to placebo for omalizumab patients. In the second double-blind 28-week treatment period the difference in rates between treatment groups represented a 63% (rate ratio 0.37,  $p < 0.001$ ) decrease relative to placebo for omalizumab patients.

During the 52-week double-blind treatment period (including the 24-week fixed-dose steroid phase and the 28-week steroid adjustment phase) the difference in rates between treatment groups represented a 50% (rate ratio 0.504,  $p < 0.001$ ) relative decrease in exacerbations for omalizumab patients.

The omalizumab group showed greater decreases in beta-agonist rescue medication use than the placebo group at the end of the 52-week treatment period, although the difference between treatment groups was not statistically significant. For the global evaluation of treatment effectiveness at the end of the 52-week double-blind treatment period in the subgroup of severe patients on high-dose inhaled corticosteroids plus long-acting beta agonists, the proportion of patients rated as having 'excellent' treatment effectiveness was higher, and the proportions having 'moderate' or 'poor' treatment effectiveness lower in the omalizumab group compared to the placebo group; the difference between groups was statistically significant ( $p < 0.001$ ), while there were no differences between the omalizumab and placebo groups for patients' subjective Quality of Life ratings.

## 5.2 Pharmacokinetic properties

The pharmacokinetics of omalizumab have been studied in adult and adolescent patients with allergic asthma.

### Absorption

After subcutaneous administration, omalizumab is absorbed with an average absolute bioavailability of 62%. Following a single subcutaneous dose in adult and adolescent patients with asthma, omalizumab was absorbed slowly, reaching peak serum concentrations after an average of 7-8 days. The pharmacokinetics of omalizumab are linear at doses greater than 0.5 mg/kg. Following multiple doses of omalizumab, areas under the serum concentration-time curve from Day 0 to Day 14 at steady state were up to 6-fold of those after the first dose.

Administration of Xolair manufactured as a lyophilised or liquid formulation resulted in similar serum concentration-time profiles of omalizumab.

### Distribution

*In vitro*, omalizumab forms complexes of limited size with IgE. Precipitating complexes and complexes larger than one million Daltons in molecular weight are not observed *in vitro* or *in vivo*. The apparent volume of distribution in patients following subcutaneous administration was  $78 \pm 32$  ml/kg.

### Elimination

Clearance of omalizumab involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG includes degradation in the reticuloendothelial system and endothelial cells. Intact IgG is also excreted in bile. In asthma patients the omalizumab serum elimination half-life averaged 26 days, with apparent clearance averaging  $2.4 \pm 1.1$  ml/kg/day. In addition, doubling of body weight approximately doubled apparent clearance.

### Characteristics in patient populations

#### *Age, Race/Ethnicity, Gender, Body Mass Index*

The population pharmacokinetics of Xolair were analysed to evaluate the effects of demographic characteristics. Analyses of these limited data suggest that no dose adjustments are necessary for age (6-76 years), race/ethnicity, gender or Body Mass Index (see section 4.2).

#### *Renal and hepatic impairment*

There are no pharmacokinetic or pharmacodynamic data in patients with renal or hepatic impairment (see sections 4.2 and 4.4).

## 5.3 Preclinical safety data

The safety of omalizumab has been studied in the cynomolgus monkey, since omalizumab binds to cynomolgus and human IgE with similar affinity. Antibodies to omalizumab were detected in some monkeys following repeated subcutaneous or intravenous administration. However, no apparent toxicity, such as immune complex-mediated disease or complement-dependent cytotoxicity, was seen. There was no evidence of an anaphylactic response due to mast-cell degranulation in cynomolgus monkeys.

Chronic administration of omalizumab at dose levels of up to 250 mg/kg (at least 14 times the highest recommended clinical dose in mg/kg according to the recommended dosing table) was well tolerated in non-human primates (both adult and juvenile animals), with the exception of a dose-related and age-dependent decrease in blood platelets, with a greater sensitivity in juvenile animals. The serum concentration required to attain a 50% drop in platelets from baseline in adult cynomolgus monkeys was roughly 4- to 20-fold higher than anticipated maximum clinical serum concentrations. In addition, acute haemorrhage and inflammation were observed at injection sites in cynomolgus monkeys.

Formal carcinogenicity studies have not been conducted with omalizumab.

In reproduction studies in cynomolgus monkeys, subcutaneous doses up to 75 mg/kg per week (at least 8 times the highest recommended clinical dose in mg/kg over a 4-week period) did not elicit maternal toxicity, embryotoxicity or teratogenicity when administered throughout organogenesis and did not elicit adverse effects on foetal or neonatal growth when administered throughout late gestation, delivery and nursing.

Omalizumab is excreted in breast milk in cynomolgus monkeys. Milk levels of omalizumab were 0.15% of the maternal serum concentration.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Powder

Sucrose

L-histidine

L-histidine hydrochloride monohydrate

Polysorbate 20

#### Solvent

Water for injections

### **6.2 Incompatibilities**

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### **6.3 Shelf life**

4 years.

#### After reconstitution

The chemical and physical stability of the reconstituted medicinal product have been demonstrated for 8 hours at 2°C to 8°C and for 4 hours at 30°C.

From a microbiological point of view, the medicinal product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 8 hours at 2°C to 8°C or 2 hours at 25°C.

### **6.4 Special precautions for storage**

Store in a refrigerator (2°C - 8°C).

Do not freeze.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

## 6.5 Nature and contents of container

Powder vial: Clear, colourless type I glass vial with a butyl rubber stopper and grey flip-off seal.

Solvent ampoule: Clear, colourless type I glass ampoule containing 2 ml water for injections.

Pack containing one vial of powder for solution for injection and one ampoule of water for injections.

## 6.6 Special precautions for disposal and other handling

The lyophilised medicinal product takes 15-20 minutes to dissolve, although in some cases it may take longer. The fully reconstituted medicinal product will appear clear to slightly opalescent, colourless to pale brownish-yellow and may have a few small bubbles or foam around the edge of the vial. Because of the viscosity of the reconstituted medicinal product care must be taken to withdraw all of the medicinal product from the vial before expelling any air or excess solution from the syringe in order to obtain the 0.6 ml.

To prepare Xolair 75 mg vials for subcutaneous administration, please adhere to the following instructions:

1. Draw 0.9 ml of water for injections from the ampoule into a syringe equipped with a large-bore 18-gauge needle.
2. With the vial placed upright on a flat surface, insert the needle and transfer the water for injections into the vial containing the lyophilised powder using standard aseptic techniques, directing the water for injections directly on to the powder.
3. Keeping the vial in an upright position, vigorously swirl it (do not shake) for approximately 1 minute to evenly wet the powder.
4. To aid in dissolution after completing step 3, gently swirl the vial for 5-10 seconds approximately every 5 minutes in order to dissolve any remaining solids.

Note that in some cases it may take longer than 20 minutes for the powder to dissolve completely. If this is the case, repeat step 4 until there are no visible gel-like particles in the solution.

When the medicinal product is fully dissolved, there should be no visible gel-like particles in the solution. Small bubbles or foam around the edge of the vial are common. The reconstituted medicinal product will appear clear to slightly opalescent, colourless to pale brownish-yellow. Do not use if solid particles are present.

5. Invert the vial for at least 15 seconds in order to allow the solution to drain towards the stopper. Using a new 3-ml syringe equipped with a large-bore, 18-gauge needle, insert the needle into the inverted vial. Keeping the vial inverted position the needle tip at the very bottom of the solution in the vial when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove all of the solution from the inverted vial.
6. Replace the 18-gauge needle with a 25-gauge needle for subcutaneous injection.

7. Expel air, large bubbles, and any excess solution in order to obtain the required 0.6 ml dose. A thin layer of small bubbles may remain at the top of the solution in the syringe. Because the solution is slightly viscous, it may take 5-10 seconds to administer the solution by subcutaneous injection.

The vial delivers 0.6 ml (75 mg) of Xolair.

8. The injections are administered subcutaneously in the deltoid region of the arm or the thigh.

Xolair 75 mg powder for solution for injection is supplied in a single-use vial.

From a microbiological point of view, the medicinal product should be used immediately after reconstitution (see section 6.3).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Frimley Business Park  
Camberley GU16 7SR  
United Kingdom

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/001

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 25 October 2005

Date of latest renewal: 22 June 2015

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

## 1. NAME OF THE MEDICINAL PRODUCT

Xolair 150 mg powder and solvent for solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 150 mg of omalizumab\*.

After reconstitution one vial contains 125 mg/ml of omalizumab (150 mg in 1.2 ml).

\*Omalizumab is a humanised monoclonal antibody manufactured by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell line.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: white to off-white lyophilisate

Solvent: clear and colourless solution

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

#### Allergic asthma

Xolair is indicated in adults, adolescents and children (6 to <12 years of age).

Xolair treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma (see section 4.2).

#### Adults and adolescents (12 years of age and older)

Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV<sub>1</sub> <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

#### Children (6 to <12 years of age)

Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

#### Chronic spontaneous urticaria (CSU)

Xolair is indicated as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment.

## 4.2 Posology and method of administration

Xolair treatment should be initiated by physicians experienced in the diagnosis and treatment of severe persistent asthma or chronic spontaneous urticaria.

### Allergic asthma

#### Posology

The appropriate dose and frequency of Xolair is determined by baseline IgE (IU/ml), measured before the start of treatment, and body weight (kg). Prior to administration of the initial dose, patients should have their IgE level determined by any commercial serum total IgE assay for their dose assignment. Based on these measurements, 75 to 600 mg of Xolair in 1 to 4 injections may be needed for each administration.

Patients with IgE lower than 76 IU/ml were less likely to experience benefit (see section 5.1). Prescribing physicians should ensure that adult and adolescent patients with IgE below 76 IU/ml and children (6 to < 12 years of age) with IgE below 200 IU/ml have unequivocal *in vitro* reactivity (RAST) to a perennial allergen before starting therapy.

See Table 1 for a conversion chart and Tables 2 and 3 for the dose determination charts in adults, adolescents and children (6 to <12 years of age).

Patients whose baseline IgE levels or body weight in kilograms are outside the limits of the dose table should not be given Xolair.

The maximum recommended dose is 600 mg omalizumab every two weeks.

**Table 1: Conversion from dose to number of vials, number of injections and total injection volume for each administration**

| Dose (mg) | Number of vials    |                     | Number of injections | Total injection volume (ml) |
|-----------|--------------------|---------------------|----------------------|-----------------------------|
|           | 75 mg <sup>a</sup> | 150 mg <sup>b</sup> |                      |                             |
| 75        | 1 <sup>c</sup>     | 0                   | 1                    | 0.6                         |
| 150       | 0                  | 1                   | 1                    | 1.2                         |
| 225       | 1 <sup>c</sup>     | 1                   | 2                    | 1.8                         |
| 300       | 0                  | 2                   | 2                    | 2.4                         |
| 375       | 1 <sup>c</sup>     | 2                   | 3                    | 3.0                         |
| 450       | 0                  | 3                   | 3                    | 3.6                         |
| 525       | 1 <sup>c</sup>     | 3                   | 4                    | 4.2                         |
| 600       | 0                  | 4                   | 4                    | 4.8                         |

<sup>a</sup> 0.6 ml = maximum delivered volume per vial (Xolair 75 mg).

<sup>b</sup> 1.2 ml = maximum delivered volume per vial (Xolair 150 mg).

<sup>c</sup> or use 0.6 ml from a 150 mg vial.



**Table 2: ADMINISTRATION EVERY 4 WEEKS. Xolair doses (milligrams per dose) administered by subcutaneous injection every 4 weeks**

| Baseline IgE (IU/ml) | Body weight (kg) |        |        |        |        |        |        |        |         |          |
|----------------------|------------------|--------|--------|--------|--------|--------|--------|--------|---------|----------|
|                      | ≥20-25           | >25-30 | >30-40 | >40-50 | >50-60 | >60-70 | >70-80 | >80-90 | >90-125 | >125-150 |
| ≥30-100              | 75               | 75     | 75     | 150    | 150    | 150    | 150    | 150    | 300     | 300      |
| >100-200             | 150              | 150    | 150    | 300    | 300    | 300    | 300    | 300    | 450     | 600      |
| >200-300             | 150              | 150    | 225    | 300    | 300    | 450    | 450    | 450    | 600     |          |
| >300-400             | 225              | 225    | 300    | 450    | 450    | 450    | 600    | 600    |         |          |
| >400-500             | 225              | 300    | 450    | 450    | 600    | 600    |        |        |         |          |
| >500-600             | 300              | 300    | 450    | 600    | 600    |        |        |        |         |          |
| >600-700             | 300              |        | 450    | 600    |        |        |        |        |         |          |
| >700-800             |                  |        |        |        |        |        |        |        |         |          |
| >800-900             |                  |        |        |        |        |        |        |        |         |          |
| >900-1000            |                  |        |        |        |        |        |        |        |         |          |
| >1000-1100           |                  |        |        |        |        |        |        |        |         |          |

ADMINISTRATION EVERY 2 WEEKS  
SEE TABLE 3

**Table 3: ADMINISTRATION EVERY 2 WEEKS. Xolair doses (milligrams per dose) administered by subcutaneous injection every 2 weeks**

| Baseline IgE (IU/ml) | Body weight (kg)             |        |        |        |        |  |        |        |         |          |
|----------------------|------------------------------|--------|--------|--------|--------|--|--------|--------|---------|----------|
|                      | ≥20-25                       | >25-30 | >30-40 | >40-50 | >50-60 | >60-70   | >70-80 | >80-90 | >90-125 | >125-150 |
| ≥30-100              | ADMINISTRATION EVERY 4 WEEKS |        |        |        |        |  |        |        |         |          |
| >100-200             | SEE TABLE 2                  |        |        |        |        |  |        |        |         |          |
| >200-300             |                              |        |        |        |        |  |        |        |         | 375      |
| >300-400             |                              |        |        |        |        |  |        | 450    |         | 525      |
| >400-500             |                              |        |        |        |        | 375  | 375    | 525    |         | 600      |
| >500-600             |                              |        |        |        | 375    | 450  | 450    | 600    |         |          |
| >600-700             |                              | 225    |        |        | 375    | 450  | 450    | 525    |         |          |
| >700-800             | 225                          | 225    | 300    | 375    | 450    | 450  | 525    | 600    |         |          |
| >800-900             | 225                          | 225    | 300    | 375    | 450    | 525  | 600    |        |         |          |
| >900-1000            | 225                          | 300    | 375    | 450    | 525    | 600  |        |        |         |          |
| >1000-1100           | 225                          | 300    | 375    | 450    | 600    |  |        |        |         |          |
| >1100-1200           | 300                          | 300    | 450    | 525    | 600    | DO NOT ADMINISTER– data is unavailable for dose recommendation |        |        |         |          |
| >1200-1300           | 300                          | 375    | 450    | 525    |        |  |        |        |         |          |
| >1300-1500           | 300                          | 375    | 525    | 600    |        |  |        |        |         |          |

*Treatment duration, monitoring and dose adjustments*

Xolair is intended for long-term treatment. Clinical trials have demonstrated that it takes at least 12-16 weeks for Xolair treatment to show effectiveness. At 16 weeks after commencing Xolair therapy patients should be assessed by their physician for treatment effectiveness before further injections are administered. The decision to continue Xolair following the 16-week timepoint, or on subsequent occasions, should be based on whether a marked improvement in overall asthma control is seen (see section 5.1, Physician’s overall assessment of treatment effectiveness).

Discontinuation of Xolair treatment generally results in a return to elevated free IgE levels and associated symptoms. Total IgE levels are elevated during treatment and remain elevated for up to one year after the discontinuation of treatment. Therefore, re-testing of IgE levels during Xolair treatment cannot be used as a guide for dose determination. Dose determination after treatment interruptions lasting less than one year should be based on serum IgE levels obtained at the initial dose determination. Total serum IgE levels may be re-tested for dose determination if treatment with Xolair has been interrupted for one year or more.

Doses should be adjusted for significant changes in body weight (see Tables 2 and 3).

### Chronic spontaneous urticaria (CSU)

#### Posology

The recommended dose is 300 mg by subcutaneous injection every four weeks.

Prescribers are advised to periodically reassess the need for continued therapy.

Clinical trial experience of long-term treatment beyond 6 months in this indication is limited.

#### Special populations

##### Elderly (65 years of age and older)

There are limited data available on the use of Xolair in patients older than 65 years but there is no evidence that elderly patients require a different dose from younger adult patients.

##### Renal or hepatic impairment

There have been no studies on the effect of impaired renal or hepatic function on the pharmacokinetics of omalizumab. Because omalizumab clearance at clinical doses is dominated by the reticular endothelial system (RES) it is unlikely to be altered by renal or hepatic impairment. While no particular dose adjustment is recommended for these patients, Xolair should be administered with caution (see section 4.4).

##### Paediatric population

In allergic asthma, the safety and efficacy of Xolair in paediatric patients below the age of 6 years have not been established. No data are available.

In CSU, the safety and efficacy of Xolair in paediatric patients below the age of 12 years have not been established.

#### Method of administration

For subcutaneous administration only. Do not administer by the intravenous or intramuscular route.

The injections are administered subcutaneously in the deltoid region of the arm. Alternatively, the injections can be administered in the thigh if there is any reason precluding administration in the deltoid region.

There is limited experience with self-administration of Xolair. Therefore treatment is intended to be administered by a healthcare provider only.

For instructions on reconstitution of the medicinal product before administration, see section 6.6 and also information for the healthcare professional section of the package leaflet.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

#### 4.4 Special warnings and precautions for use

##### General

Xolair is not indicated for the treatment of acute asthma exacerbations, acute bronchospasm or status asthmaticus.

Xolair has not been studied in patients with hyperimmunoglobulin E syndrome or allergic bronchopulmonary aspergillosis or for the prevention of anaphylactic reactions, including those provoked by food allergy, atopic dermatitis, or allergic rhinitis. Xolair is not indicated for the treatment of these conditions.

Xolair therapy has not been studied in patients with autoimmune diseases, immune complex-mediated conditions, or pre-existing renal or hepatic impairment (see section 4.2). Caution should be exercised when administering Xolair in these patient populations.

Abrupt discontinuation of systemic or inhaled corticosteroids after initiation of Xolair therapy is not recommended. Decreases in corticosteroids should be performed under the direct supervision of a physician and may need to be performed gradually.

##### Immune system disorders

###### Allergic reactions type I

Type I local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur when taking omalizumab, also with onset after a long duration of treatment. Most of these reactions occurred within 2 hours after the first and subsequent injections of Xolair but some started beyond 2 hours and even beyond 24 hours after the injection. Therefore medicinal products for the treatment of anaphylactic reactions should always be available for immediate use following administration of Xolair. Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur. A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following Xolair administration.

Antibodies to omalizumab have been detected in a low number of patients in clinical trials (see section 4.8). The clinical relevance of anti-Xolair antibodies is not well understood.

###### Serum sickness

Serum sickness and serum sickness-like reactions, which are delayed allergic type III reactions, have been seen in patients treated with humanised monoclonal antibodies including omalizumab. The suggested pathophysiologic mechanism includes immune-complex formation and deposition due to development of antibodies against omalizumab. The onset has typically been 1-5 days after administration of the first or subsequent injections, also after long duration of treatment. Symptoms suggestive of serum sickness include arthritis/arthralgias, rash (urticaria or other forms), fever and lymphadenopathy. Antihistamines and corticosteroids may be useful for preventing or treating this disorder, and patients should be advised to report any suspected symptoms.

###### Churg-Strauss syndrome and hypereosinophilic syndrome

Patients with severe asthma may rarely present systemic hypereosinophilic syndrome or allergic eosinophilic granulomatous vasculitis (Churg-Strauss syndrome), both of which are usually treated with systemic corticosteroids.

In rare cases, patients on therapy with anti-asthma medicinal products, including omalizumab, may present or develop systemic eosinophilia and vasculitis. These events are commonly associated with the reduction of oral corticosteroid therapy.

In these patients, physicians should be alert to the development of marked eosinophilia, vasculitic rash, worsening pulmonary symptoms, paranasal sinus abnormalities, cardiac complications, and/or neuropathy.

Discontinuation of omalizumab should be considered in all severe cases with the above mentioned immune system disorders.

#### Parasitic (helminth) infections

IgE may be involved in the immunological response to some helminth infections. In patients at chronic high risk of helminth infection, a placebo-controlled trial in allergic patients showed a slight increase in infection rate with omalizumab, although the course, severity, and response to treatment of infection were unaltered. The helminth infection rate in the overall clinical programme, which was not designed to detect such infections, was less than 1 in 1,000 patients. However, caution may be warranted in patients at high risk of helminth infection, in particular when travelling to areas where helminthic infections are endemic. If patients do not respond to recommended anti-helminth treatment, discontinuation of Xolair should be considered.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Since IgE may be involved in the immunological response to some helminth infections, Xolair may indirectly reduce the efficacy of medicinal products for the treatment of helminthic or other parasitic infections (see section 4.4).

Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of omalizumab; thus, there is little potential for drug-drug interactions. Medicinal product or vaccine interaction studies have not been performed with Xolair. There is no pharmacological reason to expect that commonly prescribed medicinal products used in the treatment of asthma or CSU will interact with omalizumab.

#### Allergic asthma

In clinical studies Xolair was commonly used in conjunction with inhaled and oral corticosteroids, inhaled short-acting and long-acting beta agonists, leukotriene modifiers, theophyllines and oral antihistamines. There was no indication that the safety of Xolair was altered with these other commonly used anti-asthma medicinal products. Limited data are available on the use of Xolair in combination with specific immunotherapy (hypo-sensitisation therapy). In a clinical trial where Xolair was co-administered with immunotherapy, the safety and efficacy of Xolair in combination with specific immunotherapy were found to be no different to that of Xolair alone.

#### Chronic spontaneous urticaria (CSU)

In clinical studies in CSU, Xolair was used in conjunction with antihistamines (anti-H1, anti-H2) and leukotriene receptor antagonists (LTRAs). There was no evidence that the safety of omalizumab was altered when used with these medicinal products relative to its known safety profile in allergic asthma. In addition, a population pharmacokinetic analysis showed no relevant effect of H2 antihistamines and LTRAs on omalizumab pharmacokinetics (see section 5.2).

#### Paediatric population

Clinical studies in CSU included some patients aged 12 to 17 years taking Xolair in conjunction with antihistamines (anti-H1, anti-H2) and LTRAs. No studies have been performed in children under 12 years.

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

There are limited data from the use of omalizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Omalizumab crosses the placental barrier and the potential for harm to the foetus is unknown. Omalizumab has been associated with age-dependent decreases in blood platelets in non-human primates, with a greater relative sensitivity in juvenile animals (see section 5.3). Xolair should not be used during pregnancy unless clearly necessary.

### Breast-feeding

It is unknown whether omalizumab is excreted in human milk. Available data in non-human primates have shown excretion of omalizumab into milk (see section 5.3). A risk to the newborns/infants cannot be excluded. Omalizumab should not be given during breast-feeding.

### Fertility

There are no human fertility data for omalizumab. In specifically-designed non-clinical fertility studies, in non-human primates including mating studies, no impairment of male or female fertility was observed following repeated dosing with omalizumab at dose levels up to 75 mg/kg. Furthermore, no genotoxic effects were observed in separate non-clinical genotoxicity studies (see section 5.3).

## **4.7 Effects on ability to drive and use machines**

Xolair has no or negligible influence on the ability to drive and use machines.

## **4.8 Undesirable effects**

### Allergic asthma

#### Summary of safety profile

During clinical trials in adult and adolescent patients 12 years of age and older, the most commonly reported adverse reactions were headaches and injection site reactions, including injection site pain, swelling, erythema and pruritus. In clinical trials in children 6 to <12 years of age, the most commonly reported adverse reactions were headache, pyrexia and upper abdominal pain. Most of the reactions were mild or moderate in severity.

*Tabulated list of adverse reactions*

Table 4 lists the adverse reactions recorded in clinical studies in the total safety population treated with Xolair by MedDRA system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequency categories are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and very rare ( $< 1/10,000$ ). Reactions reported in the post-marketing setting are listed with frequency not known (cannot be estimated from the available data).

**Table 4: Adverse reactions in allergic asthma**

|   |  |
|---|--|
| <b>Infections and infestations</b>                          |  |
| Uncommon  | Pharyngitis  |
| Rare  | Parasitic infection  |
| <b>Blood and lymphatic system disorders</b>                 |  |
| Not known   | Idiopathic thrombocytopenia, including severe cases  |
| <b>Immune system disorders</b>                              |  |
| Rare  | Anaphylactic reaction, other serious allergic conditions, anti-omalizumab antibody development |
| Not known   | Serum sickness, may include fever and lymphadenopathy  |
| <b>Nervous system disorders</b>                             |  |
| Common  | Headache*  |
| Uncommon  | Syncope, paraesthesia, somnolence, dizziness   |
| <b>Vascular disorders</b>                                   |  |
| Uncommon  | Postural hypotension, flushing   |
| <b>Respiratory, thoracic and mediastinal disorders</b>      |  |
| Uncommon  | Allergic bronchospasm, coughing  |
| Rare  | Laryngoedema   |
| Not known   | Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome)                                |
| <b>Gastrointestinal disorders</b>                           |  |
| Common  | Abdominal pain upper**   |
| Uncommon  | Dyspeptic signs and symptoms, diarrhoea, nausea  |
| <b>Skin and subcutaneous tissue disorders</b>               |  |
| Uncommon  | Photosensitivity, urticaria, rash, pruritus  |
| Rare  | Angioedema   |
| Not known   | Alopecia   |
| <b>Musculoskeletal and connective tissue disorders</b>      |  |
| Rare  | Systemic lupus erythematosus (SLE)   |
| Not known   | Arthralgia, myalgia, joint swelling  |
| <b>General disorders and administration site conditions</b> |  |
| Very common   | Pyrexia**  |
| Common  | Injection site reactions such as swelling, erythema, pain, pruritus                            |
| Uncommon  | Influenza-like illness, swelling arms, weight increase, fatigue                                |

\*: Very common in children 6 to <12 years of age

\*\* : In children 6 to <12 years of age

**Chronic spontaneous urticaria (CSU)**

*Summary of safety profile*

The safety and tolerability of omalizumab were investigated with doses of 75 mg, 150 mg and 300 mg every four weeks in 975 CSU patients, 242 of whom received placebo. Overall, 733 patients were treated with omalizumab for up to 12 weeks and 490 patients for up to 24 weeks. Of those, 412 patients were treated for up to 12 weeks and 333 patients were treated for up to 24 weeks at the 300 mg dose.

### Tabulated list of adverse reactions

A separate table (Table 5) shows the adverse reactions for the CSU indication resulting from differences in dosages and treatment populations (with significantly different risk factors, comorbidities, co-medications and ages [e.g. asthma trials included children from 6-12 years of age]).

Table 5 lists the adverse reactions (events occurring in  $\geq 1\%$  of patients in any treatment group and  $\geq 2\%$  more frequently in any omalizumab treatment group than with placebo (after medical review)) reported with 300 mg in the three pooled phase III studies. The adverse reactions presented are divided into two groups: those identified in the 12-week and the 24-week treatment periods.

The adverse reactions are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions listed first. The corresponding frequency category for each adverse reaction is based on the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data).

**Table 5: Adverse reactions from the pooled CSU safety database (day 1 to week 24) at 300 mg omalizumab**

| 12-Week  | Omalizumab studies 1, 2 and 3 Pooled |              | Frequency category |
|--|--------------------------------------|--------------|--------------------|
|  | Placebo N=242                        | 300 mg N=412 |                    |
| <b>Infections and infestations</b>                         |                                      |              |                    |
| Sinusitis  | 5 (2.1%)                             | 20 (4.9%)    | Common             |
| <b>Nervous system disorders</b>                            |                                      |              |                    |
| Headache   | 7 (2.9%)                             | 25 (6.1%)    | Common             |
| <b>Musculoskeletal and connective tissue disorders</b>     |                                      |              |                    |
| Arthralgia   | 1 (0.4%)                             | 12 (2.9%)    | Common             |
| <b>General disorder and administration site conditions</b> |                                      |              |                    |
| Injection site reaction*                                   | 2 (0.8%)                             | 11 (2.7%)    | Common             |
| 24-Week  | Omalizumab studies 1 and 3 Pooled    |              | Frequency category |
|  | Placebo N=163                        | 300 mg N=333 |                    |
| <b>Infections and infestations</b>                         |                                      |              |                    |
| Upper respiratory tract infection                          | 5 (3.1%)                             | 19 (5.7%)    | Common             |

\* Despite not showing a 2% difference to placebo, injection site reactions were included as all cases were assessed causally related to study treatment.

### Description of selected adverse reactions pertinent to allergic asthma and CSU indications

No relevant data was obtained in clinical studies in CSU that would require a modification of the sections below.

### Immune system disorders

For further information, see section 4.4.

### Anaphylaxis

Anaphylactic reactions were rare in clinical trials. However, post-marketing data following a cumulative search in the safety database retrieved a total of 898 anaphylaxis cases. Based on an estimated exposure of 566,923 patient treatment years, this results in a reporting rate of approximately 0.20%.



### Arterial thromboembolic events (ATE)

In controlled clinical trials and during interim analyses of an observational study, a numerical imbalance of ATE was observed. The definition of the composite endpoint ATE included stroke, transient ischaemic attack, myocardial infarction, unstable angina, and cardiovascular death (including death from unknown cause). In the final analysis of the observational study, the rate of ATE per 1,000 patient years was 7.52 (115/15,286 patient years) for Xolair-treated patients and 5.12 (51/9,963 patient years) for control patients. In a multivariate analysis controlling for available baseline cardiovascular risk factors, the hazard ratio was 1.32 (95% confidence interval 0.91-1.91). In a separate analysis of pooled clinical trials, which included all randomised double-blind, placebo-controlled clinical trials lasting 8 or more weeks, the rate of ATE per 1,000 patient years was 2.69 (5/1,856 patient years) for Xolair-treated patients and 2.38 (4/1,680 patient years) for placebo patients (rate ratio 1.13, 95% confidence interval 0.24-5.71).

### Platelets

In clinical trials few patients had platelet counts below the lower limit of the normal laboratory range. None of these changes were associated with bleeding episodes or a decrease in haemoglobin. No pattern of persistent decrease in platelet counts, as observed in non-human primates (see section 5.3), has been reported in humans (patients above 6 years of age), even though isolated cases of idiopathic thrombocytopenia, including severe cases, have been reported in the post-marketing setting.

### Parasitic infections

In allergic patients at chronic high risk of helminth infection, a placebo-controlled trial showed a slight numerical increase in infection rate with omalizumab that was not statistically significant. The course, severity, and response to treatment of infections were unaltered (see section 4.4).

### Systemic lupus erythematosus

Clinical trial and post-marketing cases of systemic lupus erythematosus (SLE) have been reported in patients with moderate to severe asthma and CSU. The pathogenesis of SLE is not well understood.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

## **4.9 Overdose**

Maximum tolerated dose of Xolair has not been determined. Single intravenous doses up to 4,000 mg have been administered to patients without evidence of dose-limiting toxicities. The highest cumulative dose administered to patients was 44,000 mg over a 20-week period and this dose did not result in any untoward acute effects.

If an overdose is suspected, the patient should be monitored for any abnormal signs or symptoms. Medical treatment should be sought and instituted appropriately.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Drugs for obstructive airway diseases, other systemic drugs for obstructive airway diseases, ATC code: R03DX05

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (IgE). The antibody is an IgG1 kappa that contains human framework regions with the complementary-determining regions of a murine parent antibody that binds to IgE.

## Allergic asthma

### Mechanism of action

Omalizumab binds to IgE and prevents binding of IgE to FcεRI (high-affinity IgE receptor) on basophils and mast cells, thereby reducing the amount of free IgE that is available to trigger the allergic cascade. Treatment of atopic subjects with omalizumab resulted in a marked down-regulation of FcεRI receptors on basophils.

### Pharmacodynamic effects

The *in vitro* histamine release from basophils isolated from Xolair-treated subjects was reduced by approximately 90% following stimulation with an allergen compared to pre-treatment values.

In clinical studies in allergic asthma patients, serum free IgE levels were reduced in a dose-dependent manner within one hour following the first dose and maintained between doses. One year after discontinuation of Xolair dosing, the IgE levels had returned to pre-treatment levels with no observed rebound in IgE levels after washout of the medicinal product.

## Chronic spontaneous urticaria (CSU)

### Mechanism of action

Omalizumab binds to IgE and lowers free IgE levels. Subsequently, IgE receptors (FcεRI) on cells down-regulate. It is not entirely understood how this results in an improvement of CSU symptoms.

### Pharmacodynamic effect

In clinical studies in CSU patients, maximum suppression of free IgE was observed 3 days after the first subcutaneous dose. After repeated dosing once every 4 weeks, pre-dose serum free IgE levels remained stable between 12 and 24 weeks of treatment. After discontinuation of Xolair, free IgE levels increased towards pre-treatment levels over a 16-week treatment-free follow-up period.

## Clinical efficacy and safety in allergic asthma

### Adults and adolescents ≥12 years of age

The efficacy and safety of Xolair were demonstrated in a 28-week double-blind placebo-controlled study (study 1) involving 419 severe allergic asthmatics, ages 12-79 years, who had reduced lung function (FEV<sub>1</sub> 40-80% predicted) and poor asthma symptom control despite receiving high dose inhaled corticosteroids and a long-acting beta2-agonist. Eligible patients had experienced multiple asthma exacerbations requiring systemic corticosteroid treatment or had been hospitalised or attended an emergency room due to a severe asthma exacerbation in the past year despite continuous treatment with high-dose inhaled corticosteroids and a long-acting beta2-agonist. Subcutaneous Xolair or placebo were administered as add-on therapy to >1,000 micrograms beclomethasone dipropionate (or equivalent) plus a long-acting beta2-agonist. Oral corticosteroid, theophylline and leukotriene-modifier maintenance therapies were allowed (22%, 27%, and 35% of patients, respectively).

The rate of asthma exacerbations requiring treatment with bursts of systemic corticosteroids was the primary endpoint. Omalizumab reduced the rate of asthma exacerbations by 19% (p = 0.153). Further evaluations which did show statistical significance (p<0.05) in favour of Xolair included reductions in severe exacerbations (where patient's lung function was reduced to below 60% of personal best and requiring systemic corticosteroids) and asthma-related emergency visits (comprised of hospitalisations, emergency room, and unscheduled doctor visits), and improvements in Physician's overall assessment of treatment effectiveness, Asthma-related Quality of Life (AQL), asthma symptoms and lung function.

In a subgroup analysis, patients with pre-treatment total IgE  $\geq 76$  IU/ml were more likely to experience clinically meaningful benefit to Xolair. In these patients in study 1 Xolair reduced the rate of asthma exacerbations by 40% ( $p = 0.002$ ). In addition more patients had clinically meaningful responses in the total IgE  $\geq 76$  IU/ml population across the Xolair severe asthma programme. Table 6 includes results in the study 1 population.

**Table 6: Results of study 1**

|                                       | Whole study 1 population |                  |
|---------------------------------------|--------------------------|------------------|
|                                       | Xolair<br>N=209          | Placebo<br>N=210 |
| <b>Asthma exacerbations</b>           |                          |                  |
| Rate per 28-week period               | 0.74                     | 0.92             |
| % reduction, p-value for rate ratio   | 19.4%, $p = 0.153$       |                  |
| <b>Severe asthma exacerbations</b>    |                          |                  |
| Rate per 28-week period               | 0.24                     | 0.48             |
| % reduction, p-value for rate ratio   | 50.1%, $p = 0.002$       |                  |
| <b>Emergency visits</b>               |                          |                  |
| Rate per 28-week period               | 0.24                     | 0.43             |
| % reduction, p-value for rate ratio   | 43.9%, $p = 0.038$       |                  |
| <b>Physician's overall assessment</b> |                          |                  |
| % responders*                         | 60.5%                    | 42.8%            |
| p-value**                             | $<0.001$                 |                  |
| <b>AQL improvement</b>                |                          |                  |
| % of patients $\geq 0.5$ improvement  | 60.8%                    | 47.8%            |
| p-value                               | 0.008                    |                  |

\* marked improvement or complete control

\*\* p-value for overall distribution of assessment

Study 2 assessed the efficacy and safety of Xolair in a population of 312 severe allergic asthmatics which matched the population in study 1. Treatment with Xolair in this open label study led to a 61% reduction in clinically significant asthma exacerbation rate compared to current asthma therapy alone.

Four additional large placebo-controlled supportive studies of 28 to 52 weeks duration in 1,722 adults and adolescents (studies 3, 4, 5, 6) assessed the efficacy and safety of Xolair in patients with severe persistent asthma. Most patients were inadequately controlled but were receiving less concomitant asthma therapy than patients in studies 1 or 2. Studies 3-5 used exacerbation as primary endpoint, whereas study 6 primarily evaluated inhaled corticosteroid sparing.

In studies 3, 4 and 5 patients treated with Xolair had respective reductions in asthma exacerbation rates of 37.5% ( $p = 0.027$ ), 40.3% ( $p < 0.001$ ) and 57.6% ( $p < 0.001$ ) compared to placebo.

In study 6, significantly more severe allergic asthma patients on Xolair were able to reduce their fluticasone dose to  $\leq 500$  micrograms/day without deterioration of asthma control (60.3%) compared to the placebo group (45.8%,  $p < 0.05$ ).

Quality of life scores were measured using the Juniper Asthma-related Quality of Life Questionnaire. For all six studies there was a statistically significant improvement from baseline in quality of life scores for Xolair patients versus the placebo or control group.

Physician's overall assessment of treatment effectiveness:

Physician's overall assessment was performed in five of the above studies as a broad measure of asthma control performed by the treating physician. The physician was able to take into account PEF (peak expiratory flow), day and night time symptoms, rescue medication use, spirometry and exacerbations. In all five studies a significantly greater proportion of Xolair treated patients were judged to have achieved either a marked improvement or complete control of their asthma compared to placebo patients.

#### Children 6 to <12 years of age

The primary support for safety and efficacy of Xolair in the group aged 6 to <12 years comes from one randomised, double-blind, placebo-controlled, multi-centre trial (study 7).

Study 7 was a placebo-controlled trial which included a specific subgroup (n=235) of patients as defined in the present indication, who were treated with high-dose inhaled corticosteroids ( $\geq 500$   $\mu\text{g}/\text{day}$  fluticasone equivalent) plus long-acting beta agonist.

A clinically significant exacerbation was defined as a worsening of asthma symptoms as judged clinically by the investigator, requiring doubling of the baseline inhaled corticosteroid dose for at least 3 days and/or treatment with rescue systemic (oral or intravenous) corticosteroids for at least 3 days.

In the specific subgroup of patients on high dose inhaled corticosteroids, the omalizumab group had a statistically significantly lower rate of clinically significant asthma exacerbations than the placebo group. At 24 weeks, the difference in rates between treatment groups represented a 34% (rate ratio 0.662,  $p = 0.047$ ) decrease relative to placebo for omalizumab patients. In the second double-blind 28-week treatment period the difference in rates between treatment groups represented a 63% (rate ratio 0.37,  $p < 0.001$ ) decrease relative to placebo for omalizumab patients.

During the 52-week double-blind treatment period (including the 24-week fixed-dose steroid phase and the 28-week steroid adjustment phase) the difference in rates between treatment groups represented a 50% (rate ratio 0.504,  $p < 0.001$ ) relative decrease in exacerbations for omalizumab patients.

The omalizumab group showed greater decreases in beta-agonist rescue medication use than the placebo group at the end of the 52-week treatment period, although the difference between treatment groups was not statistically significant. For the global evaluation of treatment effectiveness at the end of the 52-week double-blind treatment period in the subgroup of severe patients on high-dose inhaled corticosteroids plus long-acting beta agonists, the proportion of patients rated as having 'excellent' treatment effectiveness was higher, and the proportions having 'moderate' or 'poor' treatment effectiveness lower in the omalizumab group compared to the placebo group; the difference between groups was statistically significant ( $p < 0.001$ ), while there were no differences between the omalizumab and placebo groups for patients' subjective Quality of Life ratings.

#### Clinical efficacy and safety in chronic spontaneous urticaria (CSU)

The efficacy and safety of Xolair were demonstrated in two randomised, placebo-controlled phase III studies (study 1 and 2) in patients with CSU who remained symptomatic despite H1 antihistamine therapy at the approved dose. A third study (study 3) primarily evaluated the safety of Xolair in patients with CSU who remained symptomatic despite treatment with H1 antihistamines at up to four times the approved dose and H2 antihistamine and/or LTRA treatment. The three studies enrolled 975 patients aged between 12 and 75 years (mean age 42.3 years; 39 patients 12-17 years, 54 patients  $\geq 65$  years; 259 males and 716 females). All patients were required to have inadequate symptom control, as assessed by a weekly urticaria activity score (UAS7, range 0-42) of  $\geq 16$ , and a weekly itch severity score (which is a component of the UAS7; range 0-21) of  $\geq 8$  for the 7 days prior to randomisation, despite having used an antihistamine for at least 2 weeks beforehand.

In studies 1 and 2, patients had a mean weekly itch severity score of between 13.7 and 14.5 at baseline and a mean UAS7 score of 29.5 and 31.7 respectively. Patients in safety study 3 had a mean weekly itch severity score of 13.8 and a mean UAS7 score of 31.2 at baseline. Across all three studies, patients reported receiving on average 4 to 6 medications (including H1 antihistamines) for CSU symptoms prior to study enrollment. Patients received Xolair at 75 mg, 150 mg or 300 mg or placebo by subcutaneous injection every 4 weeks for 24 and 12 weeks in studies 1 and 2, respectively, and 300 mg or placebo by subcutaneous injection every 4 weeks for 24 weeks in study 3. All studies had a 16-week treatment-free follow-up period.

The primary endpoint was the change from baseline to week 12 in weekly itch severity score. Omalizumab at 300 mg reduced the weekly itch severity score by 8.55 to 9.77 ( $p < 0.0001$ ) compared to a reduction of 3.63 to 5.14 for placebo (see Table 7). Statistically significant results were further observed in the responder rates for  $UAS7 \leq 6$  (at week 12) which were higher for the 300 mg treatment groups, ranging from 52-66% ( $p < 0.0001$ ) compared to 11-19% for the placebo groups, and complete response ( $UAS7=0$ ) was achieved by 34-44% ( $p < 0.0001$ ) of patients treated with 300 mg compared to 5-9% of patients in the placebo groups. Patients in the 300 mg treatment groups achieved the highest mean proportion of angioedema-free days from week 4 to week 12, (91.0-96.1%;  $p < 0.001$ ) compared to the placebo groups (88.1-89.2%). Mean change from baseline to week 12 in the overall DLQI for the 300 mg treatment groups was greater ( $p < 0.001$ ) than for placebo showing an improvement ranging from 9.7-10.3 points compared to 5.1-6.1 points for the corresponding placebo groups.

**Table 7: Change from baseline to week 12 in weekly itch severity score, studies 1, 2 and 3 (mITT population\*)**

|   | Placebo      | Omalizumab<br>300 mg |
|---|--------------|----------------------|
| <b>Study 1</b>                                  |              |                      |
| N   | 80           | 81                   |
| Mean (SD)                                       | -3.63 (5.22) | -9.40 (5.73)         |
| Difference in LS means vs. placebo <sup>1</sup> | -            | -5.80                |
| 95% CI for difference                           | -            | -7.49, -4.10         |
| P-value vs. placebo <sup>2</sup>                | -            | <0.0001              |
| <b>Study 2</b>                                  |              |                      |
| N   | 79           | 79                   |
| Mean (SD)                                       | -5.14 (5.58) | -9.77 (5.95)         |
| Difference in LS means vs. placebo <sup>1</sup> | -            | -4.81                |
| 95% CI for difference                           | -            | -6.49, -3.13         |
| P-value vs. placebo <sup>2</sup>                | -            | <0.0001              |
| <b>Study 3</b>                                  |              |                      |
| N   | 83           | 252                  |
| Mean (SD)                                       | -4.01 (5.87) | -8.55 (6.01)         |
| Difference in LS means vs. placebo <sup>1</sup> | -            | -4.52                |
| 95% CI for difference                           | -            | -5.97, -3.08         |
| P-value vs. placebo <sup>2</sup>                | -            | <0.0001              |

\*Modified intent-to-treat (mITT) population: included all patients who were randomised and received at least one dose of study medication.

BOCF (Baseline Observation Carried Forward) was used to impute missing data.

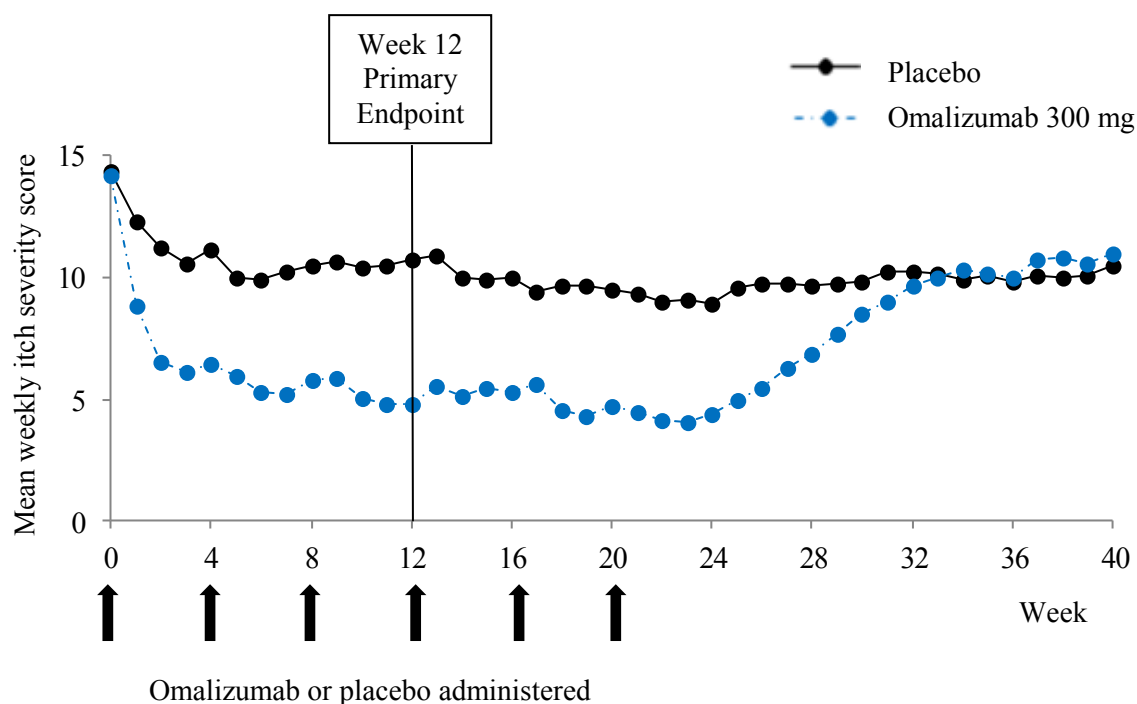
<sup>1</sup> The LS mean was estimated using an ANCOVA model. The strata were baseline weekly itch severity score (<13 vs. ≥13) and baseline weight (<80 kg vs. ≥80 kg).

<sup>2</sup> p-value is derived from ANCOVA t-test.

Figure 1 shows the mean weekly itch severity score over time in study 1. The mean weekly itch severity scores significantly decreased with a maximum effect around week 12 that was sustained over the 24-week treatment period. The results were similar in study 3.

In all three studies the mean weekly itch severity score increased gradually during the 16-week treatment-free follow-up period, consistent with symptom re-occurrence. Mean values at the end of the follow-up period were similar to the placebo group, but lower than respective mean baseline values.

**Figure 1: Mean weekly itch severity score over time, study 1 (mITT population)**



BOCF=baseline observation carried forward; mITT=modified intention-to-treat population

Efficacy after 24 weeks of treatment

The magnitude of the efficacy outcomes observed at week 24 of treatment was comparable to that observed at week 12:

For 300 mg, in studies 1 and 3, the mean decrease from baseline in weekly itch severity score was 9.8 and 8.6, the proportion of patients with UAS7≤6 was 61.7% and 55.6%, and the proportion of patients with complete response (UAS7=0) was 48.1% and 42.5%, respectively, (all p<0.0001, when compared to placebo).

There is limited clinical experience in re-treatment of patients with omalizumab.

Clinical trial data on adolescents (12 to 17 years) included a total of 39 patients, of whom 11 received the 300 mg dose. Results for the 300 mg are available for 9 patients at week 12 and 6 patients at week 24, and show a similar magnitude of response to omalizumab treatment compared to the adult population. Mean change from baseline in weekly itch severity score showed a reduction of 8.25 at week 12 and of 8.95 at week 24. The responder rates were: 33% at week 12 and 67% at week 24 for UAS7=0, and 56% at week 12 and 67% at week 24 for UAS7≤6.

## 5.2 Pharmacokinetic properties

The pharmacokinetics of omalizumab have been studied in adult and adolescent patients with allergic asthma as well as in adult and adolescent patients with CSU. The general pharmacokinetic characteristics of omalizumab are similar in these populations.

### Absorption

After subcutaneous administration, omalizumab is absorbed with an average absolute bioavailability of 62%. Following a single subcutaneous dose in adult and adolescent patients with asthma or CSU, omalizumab was absorbed slowly, reaching peak serum concentrations after an average of 6-8 days. In patients with asthma, following multiple doses of omalizumab, areas under the serum concentration-time curve from Day 0 to Day 14 at steady state were up to 6-fold of those after the first dose.

The pharmacokinetics of omalizumab are linear at doses greater than 0.5 mg/kg. Following doses of 75 mg, 150 mg or 300 mg every 4 weeks in patients with CSU, trough serum concentrations of omalizumab increased proportionally with the dose level.

Administration of Xolair manufactured as a lyophilised or liquid formulation resulted in similar serum concentration-time profiles of omalizumab.

### Distribution

*In vitro*, omalizumab forms complexes of limited size with IgE. Precipitating complexes and complexes larger than one million Daltons in molecular weight are not observed *in vitro* or *in vivo*. Based on population pharmacokinetics, distribution of omalizumab was similar in patients with allergic asthma and patients with CSU. The apparent volume of distribution in patients with asthma following subcutaneous administration was  $78 \pm 32$  ml/kg.

### Elimination

Clearance of omalizumab involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG includes degradation in the reticuloendothelial system and endothelial cells. Intact IgG is also excreted in bile. In asthma patients the omalizumab serum elimination half-life averaged 26 days, with apparent clearance averaging  $2.4 \pm 1.1$  ml/kg/day. Doubling of body weight approximately doubled apparent clearance. In CSU patients, based on population pharmacokinetic simulations, omalizumab serum elimination half-life at steady state averaged 24 days and apparent clearance at steady state for a patient of 80 kg weight was 3.0 ml/kg/day.

### Characteristics in patient populations

*Patients with asthma:* The population pharmacokinetics of omalizumab were analysed to evaluate the effects of demographic characteristics. Analyses of these limited data suggest that no dose adjustments are necessary in patients with asthma for age (6-76 years), race/ethnicity, gender or body mass index (see section 4.2).

*Patients with CSU:* The effects of demographic characteristics and other factors on omalizumab exposure were evaluated based on population pharmacokinetics. In addition, covariate effects were evaluated by analysing the relationship between omalizumab concentrations and clinical responses. These analyses suggest that no dose adjustments are necessary in patients with CSU for age (12-75 years), race/ethnicity, gender, body weight, body mass index, baseline IgE, anti-FcεRI autoantibodies or concomitant use of H2 antihistamines or LTRAs.

### Renal and hepatic impairment

There are no pharmacokinetic or pharmacodynamic data in allergic asthma or CSU patients with renal or hepatic impairment (see sections 4.2 and 4.4).

### **5.3 Preclinical safety data**

The safety of omalizumab has been studied in the cynomolgus monkey, since omalizumab binds to cynomolgus and human IgE with similar affinity. Antibodies to omalizumab were detected in some monkeys following repeated subcutaneous or intravenous administration. However, no apparent toxicity, such as immune complex-mediated disease or complement-dependent cytotoxicity, was seen. There was no evidence of an anaphylactic response due to mast-cell degranulation in cynomolgus monkeys.

Chronic administration of omalizumab at dose levels of up to 250 mg/kg (at least 14 times the highest recommended clinical dose in mg/kg according to the recommended dosing table) was well tolerated in non-human primates (both adult and juvenile animals), with the exception of a dose-related and age-dependent decrease in blood platelets, with a greater sensitivity in juvenile animals. The serum concentration required to attain a 50% drop in platelets from baseline in adult cynomolgus monkeys was roughly 4- to 20-fold higher than anticipated maximum clinical serum concentrations. In addition, acute haemorrhage and inflammation were observed at injection sites in cynomolgus monkeys.

Formal carcinogenicity studies have not been conducted with omalizumab.

In reproduction studies in cynomolgus monkeys, subcutaneous doses up to 75 mg/kg per week (at least 8 times the highest recommended clinical dose in mg/kg over a 4-week period) did not elicit maternal toxicity, embryotoxicity or teratogenicity when administered throughout organogenesis and did not elicit adverse effects on foetal or neonatal growth when administered throughout late gestation, delivery and nursing.

Omalizumab is excreted in breast milk in cynomolgus monkeys. Milk levels of omalizumab were 0.15% of the maternal serum concentration.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Powder

Sucrose

L-histidine

L-histidine hydrochloride monohydrate

Polysorbate 20

#### Solvent

Water for injections

### **6.2 Incompatibilities**

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.



### **6.3 Shelf life**

4 years.

#### After reconstitution

The chemical and physical stability of the reconstituted medicinal product have been demonstrated for 8 hours at 2°C to 8°C and for 4 hours at 30°C.

From a microbiological point of view, the medicinal product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 8 hours at 2°C to 8°C or 2 hours at 25°C.

### **6.4 Special precautions for storage**

Store in a refrigerator (2°C - 8°C).

Do not freeze.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

### **6.5 Nature and contents of container**

Powder vial: Clear, colourless type I glass vial with a butyl rubber stopper and blue flip-off seal.

Solvent ampoule: Clear, colourless type I glass ampoule containing 2 ml water for injections.

Pack containing 1 vial of powder and 1 ampoule of water for injections, and multipacks containing 4 (4 packs of 1+1) or 10 (10 packs of 1+1) vials of powder and ampoules of water for injections.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

The lyophilised medicinal product takes 15-20 minutes to dissolve, although in some cases it may take longer. The fully reconstituted medicinal product will appear clear to slightly opalescent, colourless to pale brownish-yellow and may have a few small bubbles or foam around the edge of the vial. Because of the viscosity of the reconstituted medicinal product care must be taken to withdraw all of the medicinal product from the vial before expelling any air or excess solution from the syringe in order to obtain the 1.2 ml.

To prepare Xolair 150 mg vials for subcutaneous administration, please adhere to the following instructions:

1. Draw 1.4 ml of water for injections from the ampoule into a syringe equipped with a large-bore 18-gauge needle.
2. With the vial placed upright on a flat surface, insert the needle and transfer the water for injections into the vial containing the lyophilised powder using standard aseptic techniques, directing the water for injections directly on to the powder.
3. Keeping the vial in an upright position, vigorously swirl it (do not shake) for approximately 1 minute to evenly wet the powder.

4. To aid in dissolution after completing step 3, gently swirl the vial for 5-10 seconds approximately every 5 minutes in order to dissolve any remaining solids.

Note that in some cases it may take longer than 20 minutes for the powder to dissolve completely. If this is the case, repeat step 4 until there are no visible gel-like particles in the solution.

When the medicinal product is fully dissolved, there should be no visible gel-like particles in the solution. Small bubbles or foam around the edge of the vial are common. The reconstituted medicinal product will appear clear to slightly opalescent, colourless to pale brownish-yellow. Do not use if solid particles are present.

5. Invert the vial for at least 15 seconds in order to allow the solution to drain towards the stopper. Using a new 3-ml syringe equipped with a large-bore, 18-gauge needle, insert the needle into the inverted vial. Keeping the vial inverted position the needle tip at the very bottom of the solution in the vial when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove all of the solution from the inverted vial.
6. Replace the 18-gauge needle with a 25-gauge needle for subcutaneous injection.
7. Expel air, large bubbles, and any excess solution in order to obtain the required 1.2 ml dose. A thin layer of small bubbles may remain at the top of the solution in the syringe. Because the solution is slightly viscous, it may take 5-10 seconds to administer the solution by subcutaneous injection.

The vial delivers 1.2 ml (150 mg) of Xolair. For a 75 mg dose, draw up 0.6 ml into the syringe and discard the remaining solution.

8. The injections are administered subcutaneously in the deltoid region of the arm or the thigh.

Xolair 150 mg powder for solution for injection is supplied in a single-use vial.

From a microbiological point of view, the medicinal product should be used immediately after reconstitution (see section 6.3).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Frimley Business Park  
Camberley GU16 7SR  
United Kingdom

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/002  
EU/1/05/319/003  
EU/1/05/319/004

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 25 October 2005

Date of latest renewal: 22 June 2015

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

## 1. NAME OF THE MEDICINAL PRODUCT

Xolair 75 mg solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe of 0.5 ml solution contains 75 mg of omalizumab\*.

\*Omalizumab is a humanised monoclonal antibody manufactured by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell line.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection.

Clear to slightly opalescent, colourless to pale brownish-yellow solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Xolair is indicated in adults, adolescents and children (6 to <12 years of age).

Xolair treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma (see section 4.2).

#### Adults and adolescents (12 years of age and older)

Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV<sub>1</sub> <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

#### Children (6 to <12 years of age)

Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

## 4.2 Posology and method of administration

Xolair treatment should be initiated by physicians experienced in the diagnosis and treatment of severe persistent asthma.

### Posology

The appropriate dose and frequency of Xolair is determined by baseline IgE (IU/ml), measured before the start of treatment, and body weight (kg). Prior to administration of the initial dose, patients should have their IgE level determined by any commercial serum total IgE assay for their dose assignment. Based on these measurements, 75 to 600 mg of Xolair in 1 to 4 injections may be needed for each administration.

Patients with IgE lower than 76 IU/ml were less likely to experience benefit (see section 5.1). Prescribing physicians should ensure that adult and adolescent patients with IgE below 76 IU/ml and children (6 to < 12 years of age) with IgE below 200 IU/ml have unequivocal *in vitro* reactivity (RAST) to a perennial allergen before starting therapy.

See Table 1 for a conversion chart and Tables 2 and 3 for the dose determination charts in adults, adolescents and children (6 to <12 years of age).

Patients whose baseline IgE levels or body weight in kilograms are outside the limits of the dose table should not be given Xolair.

The maximum recommended dose is 600 mg omalizumab every two weeks.

**Table 1: Conversion from dose to number of syringes, number of injections and total injection volume for each administration**

| Dose (mg) | Number of syringes |        | Number of injections | Total injection volume (ml) |
|-----------|--------------------|--------|----------------------|-----------------------------|
|           | 75 mg              | 150 mg |                      |                             |
| 75        | 1                  | 0      | 1                    | 0.5                         |
| 150       | 0                  | 1      | 1                    | 1.0                         |
| 225       | 1                  | 1      | 2                    | 1.5                         |
| 300       | 0                  | 2      | 2                    | 2.0                         |
| 375       | 1                  | 2      | 3                    | 2.5                         |
| 450       | 0                  | 3      | 3                    | 3.0                         |
| 525       | 1                  | 3      | 4                    | 3.5                         |
| 600       | 0                  | 4      | 4                    | 4.0                         |

**Table 2: ADMINISTRATION EVERY 4 WEEKS. Xolair doses (milligrams per dose) administered by subcutaneous injection every 4 weeks**

| <b>Baseline IgE (IU/ml)</b> | <b>Body weight (kg)</b>                     |        |        |        |        |        |        |        |         |          |
|-----------------------------|---|--------|--------|--------|--------|--------|--------|--------|---------|----------|
|                             | ≥20-25                                      | >25-30 | >30-40 | >40-50 | >50-60 | >60-70 | >70-80 | >80-90 | >90-125 | >125-150 |
| ≥30-100                     | 75  | 75     | 75     | 150    | 150    | 150    | 150    | 150    | 300     | 300      |
| >100-200                    | 150   | 150    | 150    | 300    | 300    | 300    | 300    | 300    | 450     | 600      |
| >200-300                    | 150   | 150    | 225    | 300    | 300    | 450    | 450    | 450    | 600     |          |
| >300-400                    | 225   | 225    | 300    | 450    | 450    | 450    | 600    | 600    |         |          |
| >400-500                    | 225   | 300    | 450    | 450    | 600    | 600    |        |        |         |          |
| >500-600                    | 300   | 300    | 450    | 600    | 600    |        |        |        |         |          |
| >600-700                    | 300   |        | 450    | 600    |        |        |        |        |         |          |
| >700-800                    |   |        |        |        |        |        |        |        |         |          |
| >800-900                    | ADMINISTRATION EVERY 2 WEEKS<br>SEE TABLE 3 |        |        |        |        |        |        |        |         |          |
| >900-1000                   | ADMINISTRATION EVERY 2 WEEKS<br>SEE TABLE 3 |        |        |        |        |        |        |        |         |          |
| >1000-1100                  | ADMINISTRATION EVERY 2 WEEKS<br>SEE TABLE 3 |        |        |        |        |        |        |        |         |          |

**Table 3: ADMINISTRATION EVERY 2 WEEKS. Xolair doses (milligrams per dose) administered by subcutaneous injection every 2 weeks**

| Baseline IgE (IU/ml) | Body weight (kg)             |        |        |        |        |  |        |        |         |          |
|----------------------|------------------------------|--------|--------|--------|--------|--|--------|--------|---------|----------|
|                      | ≥20-25                       | >25-30 | >30-40 | >40-50 | >50-60 | >60-70   | >70-80 | >80-90 | >90-125 | >125-150 |
| ≥30-100              | ADMINISTRATION EVERY 4 WEEKS |        |        |        |        |  |        |        |         |          |
| >100-200             | SEE TABLE 2                  |        |        |        |        |  |        |        |         |          |
| >200-300             |                              |        |        |        |        |  |        |        |         | 375      |
| >300-400             |                              |        |        |        |        |  |        | 450    |         | 525      |
| >400-500             |                              |        |        |        |        | 375  | 375    | 525    |         | 600      |
| >500-600             |                              |        |        |        | 375    | 450  | 450    | 600    |         |          |
| >600-700             |                              | 225    |        |        | 375    | 450  | 450    | 525    |         |          |
| >700-800             | 225                          | 225    | 300    | 375    | 450    | 450  | 525    | 600    |         |          |
| >800-900             | 225                          | 225    | 300    | 375    | 450    | 525  | 600    |        |         |          |
| >900-1000            | 225                          | 300    | 375    | 450    | 525    | 600  |        |        |         |          |
| >1000-1100           | 225                          | 300    | 375    | 450    | 600    |  |        |        |         |          |
| >1100-1200           | 300                          | 300    | 450    | 525    | 600    | DO NOT ADMINISTER– data is unavailable for dose recommendation |        |        |         |          |
| >1200-1300           | 300                          | 375    | 450    | 525    |        |  |        |        |         |          |
| >1300-1500           | 300                          | 375    | 525    | 600    |        |  |        |        |         |          |

*Treatment duration, monitoring and dose adjustments*

Xolair is intended for long-term treatment. Clinical trials have demonstrated that it takes at least 12-16 weeks for Xolair treatment to show effectiveness. At 16 weeks after commencing Xolair therapy patients should be assessed by their physician for treatment effectiveness before further injections are administered. The decision to continue Xolair following the 16-week timepoint, or on subsequent occasions, should be based on whether a marked improvement in overall asthma control is seen (see section 5.1, Physician’s overall assessment of treatment effectiveness).

Discontinuation of Xolair treatment generally results in a return to elevated free IgE levels and associated symptoms. Total IgE levels are elevated during treatment and remain elevated for up to one year after the discontinuation of treatment. Therefore, re-testing of IgE levels during Xolair treatment cannot be used as a guide for dose determination. Dose determination after treatment interruptions lasting less than one year should be based on serum IgE levels obtained at the initial dose determination. Total serum IgE levels may be re-tested for dose determination if treatment with Xolair has been interrupted for one year or more.

Doses should be adjusted for significant changes in body weight (see Tables 2 and 3).

### Special populations

#### *Elderly (65 years of age and older)*

There are limited data available on the use of Xolair in patients older than 65 years but there is no evidence that elderly patients require a different dose from younger adult patients.

#### *Renal or hepatic impairment*

There have been no studies on the effect of impaired renal or hepatic function on the pharmacokinetics of Xolair. Because omalizumab clearance at clinical doses is dominated by the reticular endothelial system (RES) it is unlikely to be altered by renal or hepatic impairment. While no particular dose adjustment is recommended for these patients, Xolair should be administered with caution (see section 4.4).

#### *Paediatric population*

The safety and efficacy of Xolair in children below age 6 have not been established. No data are available.

### Method of administration

For subcutaneous administration only. Do not administer by the intravenous or intramuscular route.

The injections are administered subcutaneously in the deltoid region of the arm. Alternatively, the injections can be administered in the thigh if there is any reason precluding administration in the deltoid region.

There is limited experience with self-administration of Xolair. Therefore treatment is intended to be administered by a healthcare provider only (see section 6.6 and also information for the healthcare professional section of the package leaflet).

## **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## **4.4 Special warnings and precautions for use**

### General

Xolair is not indicated for the treatment of acute asthma exacerbations, acute bronchospasm or status asthmaticus.

Xolair has not been studied in patients with hyperimmunoglobulin E syndrome or allergic bronchopulmonary aspergillosis or for the prevention of anaphylactic reactions, including those provoked by food allergy, atopic dermatitis, or allergic rhinitis. Xolair is not indicated for the treatment of these conditions.

Xolair therapy has not been studied in patients with autoimmune diseases, immune complex-mediated conditions, or pre-existing renal or hepatic impairment (see section 4.2). Caution should be exercised when administering Xolair in these patient populations.

Abrupt discontinuation of systemic or inhaled corticosteroids after initiation of Xolair therapy is not recommended. Decreases in corticosteroids should be performed under the direct supervision of a physician and may need to be performed gradually.



## Immune system disorders

### Allergic reactions type I

Type I local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur when taking omalizumab, also with onset after a long duration of treatment. Most of these reactions occurred within 2 hours after the first and subsequent injections of Xolair but some started beyond 2 hours and even beyond 24 hours after the injection. Therefore medicinal products for the treatment of anaphylactic reactions should always be available for immediate use following administration of Xolair. Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur. A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following Xolair administration.

Antibodies to omalizumab have been detected in a low number of patients in clinical trials (see section 4.8). The clinical relevance of anti-Xolair antibodies is not well understood.

### Serum sickness

Serum sickness and serum sickness-like reactions, which are delayed allergic type III reactions, have been seen in patients treated with humanised monoclonal antibodies including omalizumab. The suggested pathophysiologic mechanism includes immune-complex formation and deposition due to development of antibodies against omalizumab. The onset has typically been 1-5 days after administration of the first or subsequent injections, also after long duration of treatment. Symptoms suggestive of serum sickness include arthritis/arthralgias, rash (urticaria or other forms), fever and lymphadenopathy. Antihistamines and corticosteroids may be useful for preventing or treating this disorder, and patients should be advised to report any suspected symptoms.

### Churg-Strauss syndrome and hypereosinophilic syndrome

Patients with severe asthma may rarely present systemic hypereosinophilic syndrome or allergic eosinophilic granulomatous vasculitis (Churg-Strauss syndrome), both of which are usually treated with systemic corticosteroids.

In rare cases, patients on therapy with anti-asthma medicinal products, including omalizumab, may present or develop systemic eosinophilia and vasculitis. These events are commonly associated with the reduction of oral corticosteroid therapy.

In these patients, physicians should be alert to the development of marked eosinophilia, vasculitic rash, worsening pulmonary symptoms, paranasal sinus abnormalities, cardiac complications, and/or neuropathy.

Discontinuation of omalizumab should be considered in all severe cases with the above mentioned immune system disorders.

### Parasitic (helminth) infections

IgE may be involved in the immunological response to some helminth infections. In patients at chronic high risk of helminth infection, a placebo-controlled trial showed a slight increase in infection rate with omalizumab, although the course, severity, and response to treatment of infection were unaltered. The helminth infection rate in the overall clinical programme, which was not designed to detect such infections, was less than 1 in 1,000 patients. However, caution may be warranted in patients at high risk of helminth infection, in particular when travelling to areas where helminthic infections are endemic. If patients do not respond to recommended anti-helminth treatment, discontinuation of Xolair should be considered.

### Latex-sensitive individuals

The removable needle cap of this pre-filled syringe contains a derivative of natural rubber latex. No natural rubber latex has to date been detected in the removable needle cap. Nevertheless, the use of Xolair solution for injection in pre-filled syringe in latex-sensitive individuals has not been studied and thus there is a potential risk for hypersensitivity reactions which cannot be completely ruled out.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Since IgE may be involved in the immunological response to some helminth infections, Xolair may indirectly reduce the efficacy of medicinal products for the treatment of helminthic or other parasitic infections (see section 4.4).

Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of omalizumab; thus, there is little potential for drug-drug interactions. Medicinal product or vaccine interaction studies have not been performed with Xolair. There is no pharmacological reason to expect that commonly prescribed medicinal products used in the treatment of asthma will interact with omalizumab.

In clinical studies Xolair was commonly used in conjunction with inhaled and oral corticosteroids, inhaled short-acting and long-acting beta agonists, leukotriene modifiers, theophyllines and oral antihistamines. There was no indication that the safety of Xolair was altered with these other commonly used anti-asthma medicinal products. Limited data are available on the use of Xolair in combination with specific immunotherapy (hypo-sensitisation therapy). In a clinical trial where Xolair was co-administered with immunotherapy, the safety and efficacy of Xolair in combination with specific immunotherapy were found to be no different to that of Xolair alone.

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

There are limited data from the use of omalizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Omalizumab crosses the placental barrier and the potential for harm to the foetus is unknown. Omalizumab has been associated with age-dependent decreases in blood platelets in non-human primates, with a greater relative sensitivity in juvenile animals (see section 5.3). Xolair should not be used during pregnancy unless clearly necessary.

##### Breast-feeding

It is unknown whether omalizumab is excreted in human milk. Available data in non-human primates have shown excretion of omalizumab into milk (see section 5.3). A risk to the newborns/infants cannot be excluded. Omalizumab should not be given during breast-feeding.

##### Fertility

There are no human fertility data for omalizumab. In specifically-designed non-clinical fertility studies in non-human primates, including mating studies, no impairment of male or female fertility was observed following repeated dosing with omalizumab at dose levels up to 75 mg/kg. Furthermore, no genotoxic effects were observed in separate non-clinical genotoxicity studies (see section 5.3).

#### **4.7 Effects on ability to drive and use machines**

Xolair has no or negligible influence on the ability to drive and use machines.

#### **4.8 Undesirable effects**

##### Summary of the safety profile

During clinical trials in adult and adolescent patients 12 years of age and older, the most commonly reported adverse reactions were headaches and injection site reactions, including injection site pain, swelling, erythema and pruritus. In clinical trials in children 6 to <12 years of age, the most commonly reported adverse reactions were headache, pyrexia and upper abdominal pain. Most of the reactions were mild or moderate in severity.

### Tabulated list of adverse reactions

Table 4 lists the adverse reactions recorded in clinical studies in the total safety population treated with Xolair by MedDRA system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequency categories are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and very rare ( $< 1/10,000$ ). Reactions reported in the post-marketing setting are listed with frequency not known (cannot be estimated from the available data).

**Table 4: Adverse reactions**

|   |  |
|---|--|
| <b>Infections and infestations</b>                          |  |
| Uncommon  | Pharyngitis  |
| Rare  | Parasitic infection  |
| <b>Blood and lymphatic system disorders</b>                 |  |
| Not known   | Idiopathic thrombocytopenia, including severe cases  |
| <b>Immune system disorders</b>                              |  |
| Rare  | Anaphylactic reaction, other serious allergic conditions, anti-omalizumab antibody development |
| Not known   | Serum sickness, may include fever and lymphadenopathy  |
| <b>Nervous system disorders</b>                             |  |
| Common  | Headache*  |
| Uncommon  | Syncope, paraesthesia, somnolence, dizziness   |
| <b>Vascular disorders</b>                                   |  |
| Uncommon  | Postural hypotension, flushing   |
| <b>Respiratory, thoracic and mediastinal disorders</b>      |  |
| Uncommon  | Allergic bronchospasm, coughing  |
| Rare  | Laryngoedema   |
| Not known   | Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome)                                |
| <b>Gastrointestinal disorders</b>                           |  |
| Common  | Abdominal pain upper**   |
| Uncommon  | Dyspeptic signs and symptoms, diarrhoea, nausea  |
| <b>Skin and subcutaneous tissue disorders</b>               |  |
| Uncommon  | Photosensitivity, urticaria, rash, pruritus  |
| Rare  | Angioedema   |
| Not known   | Alopecia   |
| <b>Musculoskeletal and connective tissue disorders</b>      |  |
| Rare  | Systemic lupus erythematosus (SLE)   |
| Not known   | Arthralgia, myalgia, joint swelling  |
| <b>General disorders and administration site conditions</b> |  |
| Very common   | Pyrexia**  |
| Common  | Injection site reactions such as swelling, erythema, pain, pruritus                            |
| Uncommon  | Influenza-like illness, swelling arms, weight increase, fatigue                                |

\*: Very common in children 6 to <12 years of age

\*\* : In children 6 to <12 years of age

### Description of selected adverse reactions

#### Immune system disorders

For further information, see section 4.4.

#### Anaphylaxis

Anaphylactic reactions were rare in clinical trials. However, post-marketing data following a cumulative search in the safety database retrieved a total of 898 anaphylaxis cases. Based on an estimated exposure of 566,923 patient treatment years, this results in a reporting rate of approximately 0.20%.

### Arterial thromboembolic events (ATE)

In controlled clinical trials and during interim analyses of an observational study, a numerical imbalance of ATE was observed. The definition of the composite endpoint ATE included stroke, transient ischaemic attack, myocardial infarction, unstable angina, and cardiovascular death (including death from unknown cause). In the final analysis of the observational study, the rate of ATE per 1,000 patient years was 7.52 (115/15,286 patient years) for Xolair-treated patients and 5.12 (51/9,963 patient years) for control patients. In a multivariate analysis controlling for available baseline cardiovascular risk factors, the hazard ratio was 1.32 (95% confidence interval 0.91-1.91). In a separate analysis of pooled clinical trials, which included all randomised double-blind, placebo-controlled clinical trials lasting 8 or more weeks, the rate of ATE per 1,000 patient years was 2.69 (5/1,856 patient years) for Xolair-treated patients and 2.38 (4/1,680 patient years) for placebo patients (rate ratio 1.13, 95% confidence interval 0.24-5.71).

### Platelets

In clinical trials few patients had platelet counts below the lower limit of the normal laboratory range. None of these changes were associated with bleeding episodes or a decrease in haemoglobin. No pattern of persistent decrease in platelet counts, as observed in non-human primates (see section 5.3), has been reported in humans (patients above 6 years of age), even though isolated cases of idiopathic thrombocytopenia, including severe cases, have been reported in the post-marketing setting.

### Parasitic infections

In patients at chronic high risk of helminth infection, a placebo-controlled trial showed a slight numerical increase in infection rate with omalizumab that was not statistically significant. The course, severity, and response to treatment of infections were unaltered (see section 4.4).

### Systemic lupus erythematosus

Clinical trial and post-marketing cases of systemic lupus erythematosus (SLE) have been reported in patients with moderate to severe asthma and CSU. The pathogenesis of SLE is not well understood.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

## **4.9 Overdose**

Maximum tolerated dose of Xolair has not been determined. Single intravenous doses up to 4,000 mg have been administered to patients without evidence of dose-limiting toxicities. The highest cumulative dose administered to patients was 44,000 mg over a 20-week period and this dose did not result in any untoward acute effects.

If an overdose is suspected, the patient should be monitored for any abnormal signs or symptoms. Medical treatment should be sought and instituted appropriately.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, other systemic drugs for obstructive airway diseases, ATC code: R03DX05

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (IgE). The antibody is an IgG1 kappa that contains human framework regions with the complementary-determining regions of a murine parent antibody that binds to IgE.

#### Mechanism of action

Omalizumab binds to IgE and prevents binding of IgE to FcεRI (high-affinity IgE receptor), thereby reducing the amount of free IgE that is available to trigger the allergic cascade. Treatment of atopic subjects with omalizumab resulted in a marked down-regulation of FcεRI receptors on basophils.

#### Pharmacodynamic effects

The *in vitro* histamine release from basophils isolated from Xolair-treated subjects was reduced by approximately 90% following stimulation with an allergen compared to pre-treatment values.

In clinical studies, serum free IgE levels were reduced in a dose-dependent manner within one hour following the first dose and maintained between doses. One year after discontinuation of Xolair dosing, the IgE levels had returned to pre-treatment levels with no observed rebound in IgE levels after washout of the medicinal product.

#### Clinical efficacy and safety

##### Adults and adolescents ≥12 years of age

The efficacy and safety of Xolair were demonstrated in a 28-week double-blind placebo-controlled study (study 1) involving 419 severe allergic asthmatics, ages 12-79 years, who had reduced lung function (FEV<sub>1</sub> 40-80% predicted) and poor asthma symptom control despite receiving high dose inhaled corticosteroids and a long-acting beta2-agonist. Eligible patients had experienced multiple asthma exacerbations requiring systemic corticosteroid treatment or had been hospitalised or attended an emergency room due to a severe asthma exacerbation in the past year despite continuous treatment with high-dose inhaled corticosteroids and a long-acting beta2-agonist. Subcutaneous Xolair or placebo were administered as add-on therapy to >1,000 micrograms beclomethasone dipropionate (or equivalent) plus a long-acting beta2-agonist. Oral corticosteroid, theophylline and leukotriene-modifier maintenance therapies were allowed (22%, 27%, and 35% of patients, respectively).

The rate of asthma exacerbations requiring treatment with bursts of systemic corticosteroids was the primary endpoint. Omalizumab reduced the rate of asthma exacerbations by 19% (p = 0.153). Further evaluations which did show statistical significance (p<0.05) in favour of Xolair included reductions in severe exacerbations (where patient's lung function was reduced to below 60% of personal best and requiring systemic corticosteroids) and asthma-related emergency visits (comprised of hospitalisations, emergency room, and unscheduled doctor visits), and improvements in Physician's overall assessment of treatment effectiveness, Asthma-related Quality of Life (AQL), asthma symptoms and lung function.

In a subgroup analysis, patients with pre-treatment total IgE  $\geq 76$  IU/ml were more likely to experience clinically meaningful benefit to Xolair. In these patients in study 1 Xolair reduced the rate of asthma exacerbations by 40% ( $p = 0.002$ ). In addition more patients had clinically meaningful responses in the total IgE  $\geq 76$  IU/ml population across the Xolair severe asthma programme. Table 5 includes results in the study 1 population.

**Table 5: Results of study 1**

|                                       | Whole study 1 population |                  |
|---------------------------------------|--------------------------|------------------|
|                                       | Xolair<br>N=209          | Placebo<br>N=210 |
| <b>Asthma exacerbations</b>           |                          |                  |
| Rate per 28-week period               | 0.74                     | 0.92             |
| % reduction, p-value for rate ratio   | 19.4%, $p = 0.153$       |                  |
| <b>Severe asthma exacerbations</b>    |                          |                  |
| Rate per 28-week period               | 0.24                     | 0.48             |
| % reduction, p-value for rate ratio   | 50.1%, $p = 0.002$       |                  |
| <b>Emergency visits</b>               |                          |                  |
| Rate per 28-week period               | 0.24                     | 0.43             |
| % reduction, p-value for rate ratio   | 43.9%, $p = 0.038$       |                  |
| <b>Physician's overall assessment</b> |                          |                  |
| % responders*                         | 60.5%                    | 42.8%            |
| p-value**                             | <0.001                   |                  |
| <b>AQL improvement</b>                |                          |                  |
| % of patients $\geq 0.5$ improvement  | 60.8%                    | 47.8%            |
| p-value                               | 0.008                    |                  |

\* marked improvement or complete control

\*\* p-value for overall distribution of assessment

Study 2 assessed the efficacy and safety of Xolair in a population of 312 severe allergic asthmatics which matched the population in study 1. Treatment with Xolair in this open label study led to a 61% reduction in clinically significant asthma exacerbation rate compared to current asthma therapy alone.

Four additional large placebo-controlled supportive studies of 28 to 52 weeks duration in 1,722 adults and adolescents (studies 3, 4, 5, 6) assessed the efficacy and safety of Xolair in patients with severe persistent asthma. Most patients were inadequately controlled but were receiving less concomitant asthma therapy than patients in studies 1 or 2. Studies 3-5 used exacerbation as primary endpoint, whereas study 6 primarily evaluated inhaled corticosteroid sparing.

In studies 3, 4 and 5 patients treated with Xolair had respective reductions in asthma exacerbation rates of 37.5% ( $p = 0.027$ ), 40.3% ( $p < 0.001$ ) and 57.6% ( $p < 0.001$ ) compared to placebo.

In study 6, significantly more severe allergic asthma patients on Xolair were able to reduce their fluticasone dose to  $\leq 500$  micrograms/day without deterioration of asthma control (60.3%) compared to the placebo group (45.8%,  $p < 0.05$ ).

Quality of life scores were measured using the Juniper Asthma-related Quality of Life Questionnaire. For all six studies there was a statistically significant improvement from baseline in quality of life scores for Xolair patients versus the placebo or control group.

Physician's overall assessment of treatment effectiveness:

Physician's overall assessment was performed in five of the above studies as a broad measure of asthma control performed by the treating physician. The physician was able to take into account PEF (peak expiratory flow), day and night time symptoms, rescue medication use, spirometry and exacerbations. In all five studies a significantly greater proportion of Xolair treated patients were judged to have achieved either a marked improvement or complete control of their asthma compared to placebo patients.

#### Children 6 to <12 years of age

The primary support for safety and efficacy of Xolair in the group aged 6 to <12 years comes from one randomised, double-blind, placebo-controlled, multi-centre trial (study 7).

Study 7 was a placebo-controlled trial which included a specific subgroup (n=235) of patients as defined in the present indication, who were treated with high-dose inhaled corticosteroids ( $\geq 500$   $\mu\text{g}/\text{day}$  fluticasone equivalent) plus long-acting beta agonist.

A clinically significant exacerbation was defined as a worsening of asthma symptoms as judged clinically by the investigator, requiring doubling of the baseline inhaled corticosteroid dose for at least 3 days and/or treatment with rescue systemic (oral or intravenous) corticosteroids for at least 3 days.

In the specific subgroup of patients on high dose inhaled corticosteroids, the omalizumab group had a statistically significantly lower rate of clinically significant asthma exacerbations than the placebo group. At 24 weeks, the difference in rates between treatment groups represented a 34% (rate ratio 0.662,  $p = 0.047$ ) decrease relative to placebo for omalizumab patients. In the second double-blind 28-week treatment period the difference in rates between treatment groups represented a 63% (rate ratio 0.37,  $p < 0.001$ ) decrease relative to placebo for omalizumab patients.

During the 52-week double-blind treatment period (including the 24-week fixed-dose steroid phase and the 28-week steroid adjustment phase) the difference in rates between treatment groups represented a 50% (rate ratio 0.504,  $p < 0.001$ ) relative decrease in exacerbations for omalizumab patients.

The omalizumab group showed greater decreases in beta-agonist rescue medication use than the placebo group at the end of the 52-week treatment period, although the difference between treatment groups was not statistically significant. For the global evaluation of treatment effectiveness at the end of the 52-week double-blind treatment period in the subgroup of severe patients on high-dose inhaled corticosteroids plus long-acting beta agonists, the proportion of patients rated as having 'excellent' treatment effectiveness was higher, and the proportions having 'moderate' or 'poor' treatment effectiveness lower in the omalizumab group compared to the placebo group; the difference between groups was statistically significant ( $p < 0.001$ ), while there were no differences between the omalizumab and placebo groups for patients' subjective Quality of Life ratings.

## **5.2 Pharmacokinetic properties**

The pharmacokinetics of omalizumab have been studied in adult and adolescent patients with allergic asthma.

### Absorption

After subcutaneous administration, omalizumab is absorbed with an average absolute bioavailability of 62%. Following a single subcutaneous dose in adult and adolescent patients with asthma, omalizumab was absorbed slowly, reaching peak serum concentrations after an average of 7-8 days. The pharmacokinetics of omalizumab are linear at doses greater than 0.5 mg/kg. Following multiple doses of omalizumab, areas under the serum concentration-time curve from Day 0 to Day 14 at steady state were up to 6-fold of those after the first dose.

Administration of Xolair manufactured as a lyophilised or liquid formulation resulted in similar serum concentration-time profiles of omalizumab.

#### Distribution

*In vitro*, omalizumab forms complexes of limited size with IgE. Precipitating complexes and complexes larger than one million Daltons in molecular weight are not observed *in vitro* or *in vivo*. The apparent volume of distribution in patients following subcutaneous administration was  $78 \pm 32$  ml/kg.

#### Elimination

Clearance of omalizumab involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG includes degradation in the reticuloendothelial system and endothelial cells. Intact IgG is also excreted in bile. In asthma patients the omalizumab serum elimination half-life averaged 26 days, with apparent clearance averaging  $2.4 \pm 1.1$  ml/kg/day. In addition, doubling of body weight approximately doubled apparent clearance.

#### Characteristics in patient populations

##### *Age, Race/Ethnicity, Gender, Body Mass Index*

The population pharmacokinetics of Xolair were analysed to evaluate the effects of demographic characteristics. Analyses of these limited data suggest that no dose adjustments are necessary for age (6-76 years), race/ethnicity, gender or Body Mass Index (see section 4.2).

##### *Renal and hepatic impairment*

There are no pharmacokinetic or pharmacodynamic data in patients with renal or hepatic impairment (see sections 4.2 and 4.4).

### **5.3 Preclinical safety data**

The safety of omalizumab has been studied in the cynomolgus monkey, since omalizumab binds to cynomolgus and human IgE with similar affinity. Antibodies to omalizumab were detected in some monkeys following repeated subcutaneous or intravenous administration. However, no apparent toxicity, such as immune complex-mediated disease or complement-dependent cytotoxicity, was seen. There was no evidence of an anaphylactic response due to mast-cell degranulation in cynomolgus monkeys.

Chronic administration of omalizumab at dose levels of up to 250 mg/kg (at least 14 times the highest recommended clinical dose in mg/kg according to the recommended dosing table) was well tolerated in non-human primates (both adult and juvenile animals), with the exception of a dose-related and age-dependent decrease in blood platelets, with a greater sensitivity in juvenile animals. The serum concentration required to attain a 50% drop in platelets from baseline in adult cynomolgus monkeys was roughly 4- to 20-fold higher than anticipated maximum clinical serum concentrations. In addition, acute haemorrhage and inflammation were observed at injection sites in cynomolgus monkeys.

Formal carcinogenicity studies have not been conducted with omalizumab.

In reproduction studies in cynomolgus monkeys, subcutaneous doses up to 75 mg/kg per week (at least 8 times the highest recommended clinical dose in mg/kg over a 4-week period) did not elicit maternal toxicity, embryotoxicity or teratogenicity when administered throughout organogenesis and did not elicit adverse effects on foetal or neonatal growth when administered throughout late gestation, delivery and nursing.

Omalizumab is excreted in breast milk in cynomolgus monkeys. Milk levels of omalizumab were 0.15% of the maternal serum concentration.



## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

L-arginine hydrochloride  
L-histidine hydrochloride  
L-histidine  
Polysorbate 20  
Water for injections

### **6.2 Incompatibilities**

This medicinal product must not be mixed with other medicinal products.

### **6.3 Shelf life**

15 months.

The shelf life includes potential temperature excursions. The product may be kept for a total of 4 hours at 25°C. If necessary, the product may be returned to the refrigerator for later use, but this must not be done more than once.

### **6.4 Special precautions for storage**

Store in a refrigerator (2°C - 8°C).  
Do not freeze.  
Store in the original package in order to protect from light.

### **6.5 Nature and contents of container**

0.5 ml solution in a pre-filled syringe barrel (type I glass) with staked needle (stainless steel), (type I) plunger stopper and needle cap.

Pack containing 1 pre-filled syringe, and multipacks containing 4 (4 packs of 1) or 10 (10 packs of 1) pre-filled syringes.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

Prior to completion of the injection, avoid contact with the device activation clips to keep from prematurely covering the needle with the needle guard.

#### Using the syringe

1. Holding the syringe with the needle pointing upwards, carefully pull off the needle cap from the syringe and discard it. Do not touch the exposed needle. Then, gently tap the syringe with your finger until the air bubble rises to the top of the syringe. Slowly push the plunger up to force the air bubble out of the syringe without inadvertently expelling solution.
2. Gently pinch the skin at the injection site and insert the needle.
3. Holding onto the finger flange, slowly depress the plunger as far as it will go. If any solution leaks from the injection site, insert the needle further.
4. Keeping the plunger fully depressed, carefully lift the needle straight out from the injection site.
5. Slowly release the plunger and allow the needle guard to automatically cover the exposed needle.

Disposal instructions

Dispose of the used syringe immediately in a sharps container.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Frimley Business Park  
Camberley GU16 7SR  
United Kingdom

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/005  
EU/1/05/319/006  
EU/1/05/319/007

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 25 October 2005  
Date of latest renewal: 22 June 2015

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

## 1. NAME OF THE MEDICINAL PRODUCT

Xolair 150 mg solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe of 1 ml solution contains 150 mg of omalizumab\*.

\*Omalizumab is a humanised monoclonal antibody manufactured by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell line.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection.

Clear to slightly opalescent, colourless to pale brownish-yellow solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

#### Allergic asthma

Xolair is indicated in adults, adolescents and children (6 to <12 years of age).

Xolair treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma (see section 4.2).

#### Adults and adolescents (12 years of age and older)

Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV<sub>1</sub> <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

#### Children (6 to <12 years of age)

Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

#### Chronic spontaneous urticaria (CSU)

Xolair is indicated as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment.

### 4.2 Posology and method of administration

Xolair treatment should be initiated by physicians experienced in the diagnosis and treatment of severe persistent asthma or chronic spontaneous urticaria.

## Allergic asthma

### Posology

The appropriate dose and frequency of Xolair is determined by baseline IgE (IU/ml), measured before the start of treatment, and body weight (kg). Prior to administration of the initial dose, patients should have their IgE level determined by any commercial serum total IgE assay for their dose assignment. Based on these measurements, 75 to 600 mg of Xolair in 1 to 4 injections may be needed for each administration.

Patients with IgE lower than 76 IU/ml were less likely to experience benefit (see section 5.1). Prescribing physicians should ensure that adult and adolescent patients with IgE below 76 IU/ml and children (6 to < 12 years of age) with IgE below 200 IU/ml have unequivocal *in vitro* reactivity (RAST) to a perennial allergen before starting therapy.

See Table 1 for a conversion chart and Tables 2 and 3 for the dose determination charts in adults, adolescents and children (6 to <12 years of age).

Patients whose baseline IgE levels or body weight in kilograms are outside the limits of the dose table should not be given Xolair.

The maximum recommended dose is 600 mg omalizumab every two weeks.

**Table 1: Conversion from dose to number of syringes, number of injections and total injection volume for each administration**

| Dose (mg) | Number of syringes |        | Number of injections | Total injection volume (ml) |
|-----------|--------------------|--------|----------------------|-----------------------------|
|           | 75 mg              | 150 mg |                      |                             |
| 75        | 1                  | 0      | 1                    | 0.5                         |
| 150       | 0                  | 1      | 1                    | 1.0                         |
| 225       | 1                  | 1      | 2                    | 1.5                         |
| 300       | 0                  | 2      | 2                    | 2.0                         |
| 375       | 1                  | 2      | 3                    | 2.5                         |
| 450       | 0                  | 3      | 3                    | 3.0                         |
| 525       | 1                  | 3      | 4                    | 3.5                         |
| 600       | 0                  | 4      | 4                    | 4.0                         |

**Table 2: ADMINISTRATION EVERY 4 WEEKS. Xolair doses (milligrams per dose) administered by subcutaneous injection every 4 weeks**

| Baseline IgE (IU/ml) | Body weight (kg)                            |        |        |        |        |        |        |        |         |          |
|----------------------|---|--------|--------|--------|--------|--------|--------|--------|---------|----------|
|                      | ≥20-25                                      | >25-30 | >30-40 | >40-50 | >50-60 | >60-70 | >70-80 | >80-90 | >90-125 | >125-150 |
| ≥30-100              | 75  | 75     | 75     | 150    | 150    | 150    | 150    | 150    | 300     | 300      |
| >100-200             | 150   | 150    | 150    | 300    | 300    | 300    | 300    | 300    | 450     | 600      |
| >200-300             | 150   | 150    | 225    | 300    | 300    | 450    | 450    | 450    | 600     |          |
| >300-400             | 225   | 225    | 300    | 450    | 450    | 450    | 600    | 600    |         |          |
| >400-500             | 225   | 300    | 450    | 450    | 600    | 600    |        |        |         |          |
| >500-600             | 300   | 300    | 450    | 600    | 600    |        |        |        |         |          |
| >600-700             | 300   |        | 450    | 600    |        |        |        |        |         |          |
| >700-800             | ADMINISTRATION EVERY 2 WEEKS<br>SEE TABLE 3 |        |        |        |        |        |        |        |         |          |
| >800-900             |   |        |        |        |        |        |        |        |         |          |
| >900-1000            |   |        |        |        |        |        |        |        |         |          |
| >1000-1100           |   |        |        |        |        |        |        |        |         |          |

**Table 3: ADMINISTRATION EVERY 2 WEEKS. Xolair doses (milligrams per dose) administered by subcutaneous injection every 2 weeks**

| Baseline IgE (IU/ml) | Body weight (kg)             |        |        |        |        |  |        |        |         |          |
|----------------------|------------------------------|--------|--------|--------|--------|--|--------|--------|---------|----------|
|                      | ≥20-25                       | >25-30 | >30-40 | >40-50 | >50-60 | >60-70   | >70-80 | >80-90 | >90-125 | >125-150 |
| ≥30-100              | ADMINISTRATION EVERY 4 WEEKS |        |        |        |        |  |        |        |         |          |
| >100-200             | SEE TABLE 2                  |        |        |        |        |  |        |        |         |          |
| >200-300             |                              |        |        |        |        |  |        |        |         | 375      |
| >300-400             |                              |        |        |        |        |  |        | 450    |         | 525      |
| >400-500             |                              |        |        |        |        | 375  | 375    | 525    |         | 600      |
| >500-600             |                              |        |        |        | 375    | 450  | 450    | 600    |         |          |
| >600-700             |                              | 225    |        |        | 375    | 450  | 450    | 525    |         |          |
| >700-800             | 225                          | 225    | 300    | 375    | 450    | 450  | 525    | 600    |         |          |
| >800-900             | 225                          | 225    | 300    | 375    | 450    | 525  | 600    |        |         |          |
| >900-1000            | 225                          | 300    | 375    | 450    | 525    | 600  |        |        |         |          |
| >1000-1100           | 225                          | 300    | 375    | 450    | 600    |  |        |        |         |          |
| >1100-1200           | 300                          | 300    | 450    | 525    | 600    | DO NOT ADMINISTER– data is unavailable for dose recommendation |        |        |         |          |
| >1200-1300           | 300                          | 375    | 450    | 525    |        |  |        |        |         |          |
| >1300-1500           | 300                          | 375    | 525    | 600    |        |  |        |        |         |          |

*Treatment duration, monitoring and dose adjustments*

Xolair is intended for long-term treatment. Clinical trials have demonstrated that it takes at least 12-16 weeks for Xolair treatment to show effectiveness. At 16 weeks after commencing Xolair therapy patients should be assessed by their physician for treatment effectiveness before further injections are administered. The decision to continue Xolair following the 16-week timepoint, or on subsequent occasions, should be based on whether a marked improvement in overall asthma control is seen (see section 5.1, Physician’s overall assessment of treatment effectiveness).

Discontinuation of Xolair treatment generally results in a return to elevated free IgE levels and associated symptoms. Total IgE levels are elevated during treatment and remain elevated for up to one year after the discontinuation of treatment. Therefore, re-testing of IgE levels during Xolair treatment cannot be used as a guide for dose determination. Dose determination after treatment interruptions lasting less than one year should be based on serum IgE levels obtained at the initial dose determination. Total serum IgE levels may be re-tested for dose determination if treatment with Xolair has been interrupted for one year or more.

Doses should be adjusted for significant changes in body weight (see Tables 2 and 3).

### Chronic spontaneous urticaria (CSU)

#### Posology

The recommended dose is 300 mg by subcutaneous injection every four weeks.

Prescribers are advised to periodically reassess the need for continued therapy.

Clinical trial experience of long-term treatment beyond 6 months in this indication is limited.

#### Special populations

##### Elderly (65 years of age and older)

There are limited data available on the use of Xolair in patients older than 65 years but there is no evidence that elderly patients require a different dose from younger adult patients.

##### Renal or hepatic impairment

There have been no studies on the effect of impaired renal or hepatic function on the pharmacokinetics of omalizumab. Because omalizumab clearance at clinical doses is dominated by the reticular endothelial system (RES) it is unlikely to be altered by renal or hepatic impairment. While no particular dose adjustment is recommended for these patients, Xolair should be administered with caution (see section 4.4).

##### Paediatric population

In allergic asthma, the safety and efficacy of Xolair in paediatric patients below the age of 6 years have not been established. No data are available.

In CSU, the safety and efficacy of Xolair in paediatric patients below the age of 12 years have not been established.

#### Method of administration

For subcutaneous administration only. Do not administer by the intravenous or intramuscular route.

The injections are administered subcutaneously in the deltoid region of the arm. Alternatively, the injections can be administered in the thigh if there is any reason precluding administration in the deltoid region.

There is limited experience with self-administration of Xolair. Therefore treatment is intended to be administered by a healthcare provider only (see section 6.6 and also information for the healthcare professional section of the package leaflet).

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### General

Xolair is not indicated for the treatment of acute asthma exacerbations, acute bronchospasm or status asthmaticus.

Xolair has not been studied in patients with hyperimmunoglobulin E syndrome or allergic bronchopulmonary aspergillosis or for the prevention of anaphylactic reactions, including those provoked by food allergy, atopic dermatitis, or allergic rhinitis. Xolair is not indicated for the treatment of these conditions.

Xolair therapy has not been studied in patients with autoimmune diseases, immune complex-mediated conditions, or pre-existing renal or hepatic impairment (see section 4.2). Caution should be exercised when administering Xolair in these patient populations.

Abrupt discontinuation of systemic or inhaled corticosteroids after initiation of Xolair therapy is not recommended. Decreases in corticosteroids should be performed under the direct supervision of a physician and may need to be performed gradually.

#### Immune system disorders

##### Allergic reactions type I

Type I local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur when taking omalizumab, also with onset after a long duration of treatment. Most of these reactions occurred within 2 hours after the first and subsequent injections of Xolair but some started beyond 2 hours and even beyond 24 hours after the injection. Therefore medicinal products for the treatment of anaphylactic reactions should always be available for immediate use following administration of Xolair. Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur. A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following Xolair administration.

Antibodies to omalizumab have been detected in a low number of patients in clinical trials (see section 4.8). The clinical relevance of anti-Xolair antibodies is not well understood.

##### Serum sickness

Serum sickness and serum sickness-like reactions, which are delayed allergic type III reactions, have been seen in patients treated with humanised monoclonal antibodies including omalizumab. The suggested pathophysiologic mechanism includes immune-complex formation and deposition due to development of antibodies against omalizumab. The onset has typically been 1-5 days after administration of the first or subsequent injections, also after long duration of treatment. Symptoms suggestive of serum sickness include arthritis/arthralgias, rash (urticaria or other forms), fever and lymphadenopathy. Antihistamines and corticosteroids may be useful for preventing or treating this disorder, and patients should be advised to report any suspected symptoms.

##### Churg-Strauss syndrome and hypereosinophilic syndrome

Patients with severe asthma may rarely present systemic hypereosinophilic syndrome or allergic eosinophilic granulomatous vasculitis (Churg-Strauss syndrome), both of which are usually treated with systemic corticosteroids.

In rare cases, patients on therapy with anti-asthma medicinal products, including omalizumab, may present or develop systemic eosinophilia and vasculitis. These events are commonly associated with the reduction of oral corticosteroid therapy.

In these patients, physicians should be alert to the development of marked eosinophilia, vasculitic rash, worsening pulmonary symptoms, paranasal sinus abnormalities, cardiac complications, and/or neuropathy.

Discontinuation of omalizumab should be considered in all severe cases with the above mentioned immune system disorders.



### Parasitic (helminth) infections

IgE may be involved in the immunological response to some helminth infections. In patients at chronic high risk of helminth infection, a placebo-controlled trial in allergic patients showed a slight increase in infection rate with omalizumab, although the course, severity, and response to treatment of infection were unaltered. The helminth infection rate in the overall clinical programme, which was not designed to detect such infections, was less than 1 in 1,000 patients. However, caution may be warranted in patients at high risk of helminth infection, in particular when travelling to areas where helminthic infections are endemic. If patients do not respond to recommended anti-helminth treatment, discontinuation of Xolair should be considered.

### Latex-sensitive individuals

The removable needle cap of this pre-filled syringe contains a derivative of natural rubber latex. No natural rubber latex has to date been detected in the removable needle cap. Nevertheless, the use of Xolair solution for injection in pre-filled syringe in latex-sensitive individuals has not been studied and thus there is a potential risk for hypersensitivity reactions which cannot be completely ruled out.

## **4.5 Interaction with other medicinal products and other forms of interaction**

Since IgE may be involved in the immunological response to some helminth infections, Xolair may indirectly reduce the efficacy of medicinal products for the treatment of helminthic or other parasitic infections (see section 4.4).

Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of omalizumab; thus, there is little potential for drug-drug interactions. Medicinal product or vaccine interaction studies have not been performed with Xolair. There is no pharmacological reason to expect that commonly prescribed medicinal products used in the treatment of asthma or CSU will interact with omalizumab.

### Allergic asthma

In clinical studies Xolair was commonly used in conjunction with inhaled and oral corticosteroids, inhaled short-acting and long-acting beta agonists, leukotriene modifiers, theophyllines and oral antihistamines. There was no indication that the safety of Xolair was altered with these other commonly used anti-asthma medicinal products. Limited data are available on the use of Xolair in combination with specific immunotherapy (hypo-sensitisation therapy). In a clinical trial where Xolair was co-administered with immunotherapy, the safety and efficacy of Xolair in combination with specific immunotherapy were found to be no different to that of Xolair alone.

### Chronic spontaneous urticaria (CSU)

In clinical studies in CSU, Xolair was used in conjunction with antihistamines (anti-H1, anti-H2) and leukotriene receptor antagonists (LTRAs). There was no evidence that the safety of omalizumab was altered when used with these medicinal products relative to its known safety profile in allergic asthma. In addition, a population pharmacokinetic analysis showed no relevant effect of H2 antihistamines and LTRAs on omalizumab pharmacokinetics (see section 5.2).

### Paediatric population

Clinical studies in CSU included some patients aged 12 to 17 years taking Xolair in conjunction with antihistamines (anti-H1, anti-H2) and LTRAs. No studies have been performed in children under 12 years.

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

There are limited data from the use of omalizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Omalizumab crosses the placental barrier and the potential for harm to the foetus is unknown. Omalizumab has been associated with age-dependent decreases in blood platelets in non-human primates, with a greater relative sensitivity in juvenile animals (see section 5.3). Xolair should not be used during pregnancy unless clearly necessary.

### Breast-feeding

It is unknown whether omalizumab is excreted in human milk. Available data in non-human primates have shown excretion of omalizumab into milk (see section 5.3). A risk to the newborns/infants cannot be excluded. Omalizumab should not be given during breast-feeding.

### Fertility

There are no human fertility data for omalizumab. In specifically-designed non-clinical fertility studies in non-human primates, including mating studies, no impairment of male or female fertility was observed following repeated dosing with omalizumab at dose levels up to 75 mg/kg. Furthermore, no genotoxic effects were observed in separate non-clinical genotoxicity studies (see section 5.3).

## **4.7 Effects on ability to drive and use machines**

Xolair has no or negligible influence on the ability to drive and use machines.

## **4.8 Undesirable effects**

### Allergic asthma

#### *Summary of the safety profile*

During clinical trials in adult and adolescent patients 12 years of age and older, the most commonly reported adverse reactions were headaches and injection site reactions, including injection site pain, swelling, erythema and pruritus. In clinical trials in children 6 to <12 years of age, the most commonly reported adverse reactions were headache, pyrexia and upper abdominal pain. Most of the reactions were mild or moderate in severity.

Tabulated list of adverse reactions

Table 4 lists the adverse reactions recorded in clinical studies in the total safety population treated with Xolair by MedDRA system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequency categories are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and very rare ( $< 1/10,000$ ). Reactions reported in the post-marketing setting are listed with frequency not known (cannot be estimated from the available data).

**Table 4: Adverse reactions in allergic asthma**

|   |  |
|---|--|
| <b>Infections and infestations</b>                          |  |
| Uncommon  | Pharyngitis  |
| Rare  | Parasitic infection  |
| <b>Blood and lymphatic system disorders</b>                 |  |
| Not known   | Idiopathic thrombocytopenia, including severe cases  |
| <b>Immune system disorders</b>                              |  |
| Rare  | Anaphylactic reaction, other serious allergic conditions, anti-omalizumab antibody development |
| Not known   | Serum sickness, may include fever and lymphadenopathy  |
| <b>Nervous system disorders</b>                             |  |
| Common  | Headache*  |
| Uncommon  | Syncope, paraesthesia, somnolence, dizziness   |
| <b>Vascular disorders</b>                                   |  |
| Uncommon  | Postural hypotension, flushing   |
| <b>Respiratory, thoracic and mediastinal disorders</b>      |  |
| Uncommon  | Allergic bronchospasm, coughing  |
| Rare  | Laryngoedema   |
| Not known   | Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome)                                |
| <b>Gastrointestinal disorders</b>                           |  |
| Common  | Abdominal pain upper**   |
| Uncommon  | Dyspeptic signs and symptoms, diarrhoea, nausea  |
| <b>Skin and subcutaneous tissue disorders</b>               |  |
| Uncommon  | Photosensitivity, urticaria, rash, pruritus  |
| Rare  | Angioedema   |
| Not known   | Alopecia   |
| <b>Musculoskeletal and connective tissue disorders</b>      |  |
| Rare  | Systemic lupus erythematosus (SLE)   |
| Not known   | Arthralgia, myalgia, joint swelling  |
| <b>General disorders and administration site conditions</b> |  |
| Very common   | Pyrexia**  |
| Common  | Injection site reactions such as swelling, erythema, pain, pruritus                            |
| Uncommon  | Influenza-like illness, swelling arms, weight increase, fatigue                                |

\*: Very common in children 6 to <12 years of age

\*\* : In children 6 to <12 years of age

Chronic spontaneous urticaria (CSU)

Summary of the safety profile

The safety and tolerability of omalizumab were investigated with doses of 75 mg, 150 mg and 300 mg every four weeks in 975 CSU patients, 242 of whom received placebo. Overall, 733 patients were treated with omalizumab for up to 12 weeks and 490 patients for up to 24 weeks. Of those, 412 patients were treated for up to 12 weeks and 333 patients were treated for up to 24 weeks at the 300 mg dose.

### Tabulated list of adverse reactions

A separate table (Table 5) shows the adverse reactions for the CSU indication resulting from differences in dosages and treatment populations (with significantly different risk factors, comorbidities, co-medications and ages [e.g. asthma trials included children from 6-12 years of age]).

Table 5 lists the adverse reactions (events occurring in  $\geq 1\%$  of patients in any treatment group and  $\geq 2\%$  more frequently in any omalizumab treatment group than with placebo (after medical review)) reported with 300 mg in the three pooled phase III studies. The adverse reactions presented are divided into two groups: those identified in the 12-week and the 24-week treatment periods.

The adverse reactions are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions listed first. The corresponding frequency category for each adverse reaction is based on the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data).

**Table 5: Adverse reactions from the pooled CSU safety database (day 1 to week 24) at 300 mg omalizumab**

| 12-Week  | Omalizumab studies 1, 2 and 3 Pooled |              | Frequency category |
|--|--------------------------------------|--------------|--------------------|
|  | Placebo N=242                        | 300 mg N=412 |                    |
| <b>Infections and infestations</b>                         |                                      |              |                    |
| Sinusitis  | 5 (2.1%)                             | 20 (4.9%)    | Common             |
| <b>Nervous system disorders</b>                            |                                      |              |                    |
| Headache   | 7 (2.9%)                             | 25 (6.1%)    | Common             |
| <b>Musculoskeletal and connective tissue disorders</b>     |                                      |              |                    |
| Arthralgia   | 1 (0.4%)                             | 12 (2.9%)    | Common             |
| <b>General disorder and administration site conditions</b> |                                      |              |                    |
| Injection site reaction*                                   | 2 (0.8%)                             | 11 (2.7%)    | Common             |
| 24-Week  | Omalizumab studies 1 and 3 Pooled    |              | Frequency category |
|  | Placebo N=163                        | 300 mg N=333 |                    |
| <b>Infections and infestations</b>                         |                                      |              |                    |
| Upper respiratory tract infection                          | 5 (3.1%)                             | 19 (5.7%)    | Common             |

\* Despite not showing a 2% difference to placebo, injection site reactions were included as all cases were assessed causally related to study treatment.

### Description of selected adverse reactions pertinent to allergic asthma and CSU indications

No relevant data was obtained in clinical studies in CSU that would require a modification of the sections below.

#### Immune system disorders

For further information, see section 4.4.

#### Anaphylaxis

Anaphylactic reactions were rare in clinical trials. However, post-marketing data following a cumulative search in the safety database retrieved a total of 898 anaphylaxis cases. Based on an estimated exposure of 566,923 patient treatment years, this results in a reporting rate of approximately 0.20%.

### Arterial thromboembolic events (ATE)

In controlled clinical trials and during interim analyses of an observational study, a numerical imbalance of ATE was observed. The definition of the composite endpoint ATE included stroke, transient ischaemic attack, myocardial infarction, unstable angina, and cardiovascular death (including death from unknown cause). In the final analysis of the observational study, the rate of ATE per 1,000 patient years was 7.52 (115/15,286 patient years) for Xolair-treated patients and 5.12 (51/9,963 patient years) for control patients. In a multivariate analysis controlling for available baseline cardiovascular risk factors, the hazard ratio was 1.32 (95% confidence interval 0.91-1.91). In a separate analysis of pooled clinical trials, which included all randomised double-blind, placebo-controlled clinical trials lasting 8 or more weeks, the rate of ATE per 1,000 patient years was 2.69 (5/1,856 patient years) for Xolair-treated patients and 2.38 (4/1,680 patient years) for placebo patients (rate ratio 1.13, 95% confidence interval 0.24-5.71).

### Platelets

In clinical trials few patients had platelet counts below the lower limit of the normal laboratory range. None of these changes were associated with bleeding episodes or a decrease in haemoglobin. No pattern of persistent decrease in platelet counts, as observed in non-human primates (see section 5.3), has been reported in humans (patients above 6 years of age), even though isolated cases of idiopathic thrombocytopenia, including severe cases, have been reported in the post-marketing setting.

### Parasitic infections

In allergic patients at chronic high risk of helminth infection, a placebo-controlled trial showed a slight numerical increase in infection rate with omalizumab that was not statistically significant. The course, severity, and response to treatment of infections were unaltered (see section 4.4).

### Systemic lupus erythematosus

Clinical trial and post-marketing cases of systemic lupus erythematosus (SLE) have been reported in patients with moderate to severe asthma and CSU. The pathogenesis of SLE is not well understood.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

## **4.9 Overdose**

Maximum tolerated dose of Xolair has not been determined. Single intravenous doses up to 4,000 mg have been administered to patients without evidence of dose-limiting toxicities. The highest cumulative dose administered to patients was 44,000 mg over a 20-week period and this dose did not result in any untoward acute effects.

If an overdose is suspected, the patient should be monitored for any abnormal signs or symptoms. Medical treatment should be sought and instituted appropriately.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Drugs for obstructive airway diseases, other systemic drugs for obstructive airway diseases, ATC code: R03DX05

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (IgE). The antibody is an IgG1 kappa that contains human framework regions with the complementary-determining regions of a murine parent antibody that binds to IgE.

## Allergic asthma

### Mechanism of action

Omalizumab binds to IgE and prevents binding of IgE to FcεRI (high-affinity IgE receptor) on basophils and mast cells, thereby reducing the amount of free IgE that is available to trigger the allergic cascade. Treatment of atopic subjects with omalizumab resulted in a marked down-regulation of FcεRI receptors on basophils.

### Pharmacodynamic effects

The *in vitro* histamine release from basophils isolated from Xolair-treated subjects was reduced by approximately 90% following stimulation with an allergen compared to pre-treatment values.

In clinical studies in allergic asthma patients, serum free IgE levels were reduced in a dose-dependent manner within one hour following the first dose and maintained between doses. One year after discontinuation of Xolair dosing, the IgE levels had returned to pre-treatment levels with no observed rebound in IgE levels after washout of the medicinal product.

## Chronic spontaneous urticaria (CSU)

### Mechanism of action

Omalizumab binds to IgE and lowers free IgE levels. Subsequently, IgE receptors (FcεRI) on cells down-regulate. It is not entirely understood how this results in an improvement of CSU symptoms.

### Pharmacodynamic effects

In clinical studies in CSU patients, maximum suppression of free IgE was observed 3 days after the first subcutaneous dose. After repeated dosing once every 4 weeks, pre-dose serum free IgE levels remained stable between 12 and 24 weeks of treatment. After discontinuation of Xolair, free IgE levels increased towards pre-treatment levels over a 16-week treatment-free follow-up period.

## Clinical efficacy and safety in allergic asthma

### Adults and adolescents ≥12 years of age

The efficacy and safety of Xolair were demonstrated in a 28-week double-blind placebo-controlled study (study 1) involving 419 severe allergic asthmatics, ages 12-79 years, who had reduced lung function (FEV<sub>1</sub> 40-80% predicted) and poor asthma symptom control despite receiving high dose inhaled corticosteroids and a long-acting beta2-agonist. Eligible patients had experienced multiple asthma exacerbations requiring systemic corticosteroid treatment or had been hospitalised or attended an emergency room due to a severe asthma exacerbation in the past year despite continuous treatment with high-dose inhaled corticosteroids and a long-acting beta2-agonist. Subcutaneous Xolair or placebo were administered as add-on therapy to >1,000 micrograms beclomethasone dipropionate (or equivalent) plus a long-acting beta2-agonist. Oral corticosteroid, theophylline and leukotriene-modifier maintenance therapies were allowed (22%, 27%, and 35% of patients, respectively).

The rate of asthma exacerbations requiring treatment with bursts of systemic corticosteroids was the primary endpoint. Omalizumab reduced the rate of asthma exacerbations by 19% ( $p = 0.153$ ). Further evaluations which did show statistical significance ( $p < 0.05$ ) in favour of Xolair included reductions in severe exacerbations (where patient's lung function was reduced to below 60% of personal best and requiring systemic corticosteroids) and asthma-related emergency visits (comprised of hospitalisations, emergency room, and unscheduled doctor visits), and improvements in Physician's overall assessment of treatment effectiveness, Asthma-related Quality of Life (AQL), asthma symptoms and lung function.

In a subgroup analysis, patients with pre-treatment total IgE  $\geq 76$  IU/ml were more likely to experience clinically meaningful benefit to Xolair. In these patients in study 1 Xolair reduced the rate of asthma exacerbations by 40% ( $p = 0.002$ ). In addition more patients had clinically meaningful responses in the total IgE  $\geq 76$  IU/ml population across the Xolair severe asthma programme. Table 6 includes results in the study 1 population.

**Table 6: Results of study 1**

|                                       | Whole study 1 population |                  |
|---------------------------------------|--------------------------|------------------|
|                                       | Xolair<br>N=209          | Placebo<br>N=210 |
| <b>Asthma exacerbations</b>           |                          |                  |
| Rate per 28-week period               | 0.74                     | 0.92             |
| % reduction, p-value for rate ratio   | 19.4%, $p = 0.153$       |                  |
| <b>Severe asthma exacerbations</b>    |                          |                  |
| Rate per 28-week period               | 0.24                     | 0.48             |
| % reduction, p-value for rate ratio   | 50.1%, $p = 0.002$       |                  |
| <b>Emergency visits</b>               |                          |                  |
| Rate per 28-week period               | 0.24                     | 0.43             |
| % reduction, p-value for rate ratio   | 43.9%, $p = 0.038$       |                  |
| <b>Physician's overall assessment</b> |                          |                  |
| % responders*                         | 60.5%                    | 42.8%            |
| p-value**                             | $<0.001$                 |                  |
| <b>AQL improvement</b>                |                          |                  |
| % of patients $\geq 0.5$ improvement  | 60.8%                    | 47.8%            |
| p-value                               | 0.008                    |                  |

\* marked improvement or complete control

\*\* p-value for overall distribution of assessment

Study 2 assessed the efficacy and safety of Xolair in a population of 312 severe allergic asthmatics which matched the population in study 1. Treatment with Xolair in this open label study led to a 61% reduction in clinically significant asthma exacerbation rate compared to current asthma therapy alone.

Four additional large placebo-controlled supportive studies of 28 to 52 weeks duration in 1,722 adults and adolescents (studies 3, 4, 5, 6) assessed the efficacy and safety of Xolair in patients with severe persistent asthma. Most patients were inadequately controlled but were receiving less concomitant asthma therapy than patients in studies 1 or 2. Studies 3-5 used exacerbation as primary endpoint, whereas study 6 primarily evaluated inhaled corticosteroid sparing.

In studies 3, 4 and 5 patients treated with Xolair had respective reductions in asthma exacerbation rates of 37.5% ( $p = 0.027$ ), 40.3% ( $p < 0.001$ ) and 57.6% ( $p < 0.001$ ) compared to placebo.

In study 6, significantly more severe allergic asthma patients on Xolair were able to reduce their fluticasone dose to  $\leq 500$  micrograms/day without deterioration of asthma control (60.3%) compared to the placebo group (45.8%,  $p < 0.05$ ).

Quality of life scores were measured using the Juniper Asthma-related Quality of Life Questionnaire. For all six studies there was a statistically significant improvement from baseline in quality of life scores for Xolair patients versus the placebo or control group.

Physician's overall assessment of treatment effectiveness:

Physician's overall assessment was performed in five of the above studies as a broad measure of asthma control performed by the treating physician. The physician was able to take into account PEF (peak expiratory flow), day and night time symptoms, rescue medication use, spirometry and exacerbations. In all five studies a significantly greater proportion of Xolair treated patients were

judged to have achieved either a marked improvement or complete control of their asthma compared to placebo patients.

#### Children 6 to <12 years of age

The primary support for safety and efficacy of Xolair in the group aged 6 to <12 years comes from one randomised, double-blind, placebo-controlled, multi-centre trial (study 7).

Study 7 was a placebo-controlled trial which included a specific subgroup (n=235) of patients as defined in the present indication, who were treated with high-dose inhaled corticosteroids ( $\geq 500$   $\mu\text{g}/\text{day}$  fluticasone equivalent) plus long-acting beta agonist.

A clinically significant exacerbation was defined as a worsening of asthma symptoms as judged clinically by the investigator, requiring doubling of the baseline inhaled corticosteroid dose for at least 3 days and/or treatment with rescue systemic (oral or intravenous) corticosteroids for at least 3 days.

In the specific subgroup of patients on high dose inhaled corticosteroids, the omalizumab group had a statistically significantly lower rate of clinically significant asthma exacerbations than the placebo group. At 24 weeks, the difference in rates between treatment groups represented a 34% (rate ratio 0.662,  $p = 0.047$ ) decrease relative to placebo for omalizumab patients. In the second double-blind 28-week treatment period the difference in rates between treatment groups represented a 63% (rate ratio 0.37,  $p < 0.001$ ) decrease relative to placebo for omalizumab patients.

During the 52-week double-blind treatment period (including the 24-week fixed-dose steroid phase and the 28-week steroid adjustment phase) the difference in rates between treatment groups represented a 50% (rate ratio 0.504,  $p < 0.001$ ) relative decrease in exacerbations for omalizumab patients.

The omalizumab group showed greater decreases in beta-agonist rescue medication use than the placebo group at the end of the 52-week treatment period, although the difference between treatment groups was not statistically significant. For the global evaluation of treatment effectiveness at the end of the 52-week double-blind treatment period in the subgroup of severe patients on high-dose inhaled corticosteroids plus long-acting beta agonists, the proportion of patients rated as having 'excellent' treatment effectiveness was higher, and the proportions having 'moderate' or 'poor' treatment effectiveness lower in the omalizumab group compared to the placebo group; the difference between groups was statistically significant ( $p < 0.001$ ), while there were no differences between the omalizumab and placebo groups for patients' subjective Quality of Life ratings.

#### Clinical efficacy and safety in chronic spontaneous urticaria (CSU)

The efficacy and safety of Xolair were demonstrated in two randomised, placebo-controlled phase III studies (study 1 and 2) in patients with CSU who remained symptomatic despite H1 antihistamine therapy at the approved dose. A third study (study 3) primarily evaluated the safety of Xolair in patients with CSU who remained symptomatic despite treatment with H1 antihistamines at up to four times the approved dose and H2 antihistamine and/or LTRA treatment. The three studies enrolled 975 patients aged between 12 and 75 years (mean age 42.3 years; 39 patients 12-17 years, 54 patients  $\geq 65$  years; 259 males and 716 females). All patients were required to have inadequate symptom control, as assessed by a weekly urticaria activity score (UAS7, range 0-42) of  $\geq 16$ , and a weekly itch severity score (which is a component of the UAS7; range 0-21) of  $\geq 8$  for the 7 days prior to randomisation, despite having used an antihistamine for at least 2 weeks beforehand.

In studies 1 and 2, patients had a mean weekly itch severity score of between 13.7 and 14.5 at baseline and a mean UAS7 score of 29.5 and 31.7 respectively. Patients in safety study 3 had a mean weekly itch severity score of 13.8 and a mean UAS7 score of 31.2 at baseline. Across all three studies, patients reported receiving on average 4 to 6 medications (including H1 antihistamines) for CSU symptoms prior to study enrollment. Patients received Xolair at 75 mg, 150 mg or 300 mg or placebo by subcutaneous injection every 4 weeks for 24 and 12 weeks in studies 1 and 2, respectively, and



300 mg or placebo by subcutaneous injection every 4 weeks for 24 weeks in study 3. All studies had a 16-week treatment-free follow-up period.

The primary endpoint was the change from baseline to week 12 in weekly itch severity score. Omalizumab at 300 mg reduced the weekly itch severity score by 8.55 to 9.77 ( $p < 0.0001$ ) compared to a reduction of 3.63 to 5.14 for placebo (see Table 7). Statistically significant results were further observed in the responder rates for  $UAS7 \leq 6$  (at week 12) which were higher for the 300 mg treatment groups, ranging from 52-66% ( $p < 0.0001$ ) compared to 11-19% for the placebo groups, and complete response ( $UAS7 = 0$ ) was achieved by 34-44% ( $p < 0.0001$ ) of patients treated with 300 mg compared to 5-9% of patients in the placebo groups. Patients in the 300 mg treatment groups achieved the highest mean proportion of angioedema-free days from week 4 to week 12, (91.0-96.1%;  $p < 0.001$ ) compared to the placebo groups (88.1-89.2%). Mean change from baseline to week 12 in the overall DLQI for the 300 mg treatment groups was greater ( $p < 0.001$ ) than for placebo showing an improvement ranging from 9.7-10.3 points compared to 5.1-6.1 points for the corresponding placebo groups.

**Table 7: Change from baseline to week 12 in weekly itch severity score, studies 1, 2 and 3 (mITT population\*)**

|   | Placebo      | Omalizumab<br>300 mg |
|---|--------------|----------------------|
| <b>Study 1</b>                                  |              |                      |
| N   | 80           | 81                   |
| Mean (SD)                                       | -3.63 (5.22) | -9.40 (5.73)         |
| Difference in LS means vs. placebo <sup>1</sup> | -            | -5.80                |
| 95% CI for difference                           | -            | -7.49, -4.10         |
| P-value vs. placebo <sup>2</sup>                | -            | <0.0001              |
| <b>Study 2</b>                                  |              |                      |
| N   | 79           | 79                   |
| Mean (SD)                                       | -5.14 (5.58) | -9.77 (5.95)         |
| Difference in LS means vs. placebo <sup>1</sup> | -            | -4.81                |
| 95% CI for difference                           | -            | -6.49, -3.13         |
| P-value vs. placebo <sup>2</sup>                | -            | <0.0001              |
| <b>Study 3</b>                                  |              |                      |
| N   | 83           | 252                  |
| Mean (SD)                                       | -4.01 (5.87) | -8.55 (6.01)         |
| Difference in LS means vs. placebo <sup>1</sup> | -            | -4.52                |
| 95% CI for difference                           | -            | -5.97, -3.08         |
| P-value vs. placebo <sup>2</sup>                | -            | <0.0001              |

\*Modified intent-to-treat (mITT) population: included all patients who were randomised and received at least one dose of study medication.

BOCF (Baseline Observation Carried Forward) was used to impute missing data.

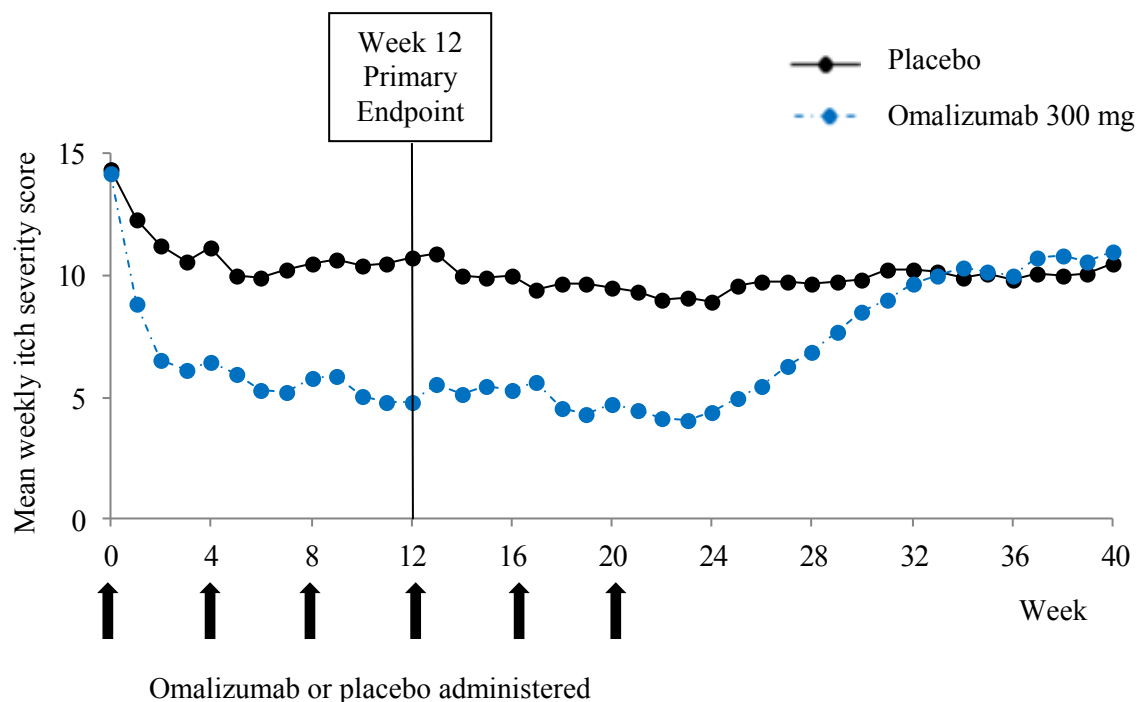
<sup>1</sup> The LS mean was estimated using an ANCOVA model. The strata were baseline weekly itch severity score (<13 vs. ≥13) and baseline weight (<80 kg vs. ≥80 kg).

<sup>2</sup> p-value is derived from ANCOVA t-test.

Figure 1 shows the mean weekly itch severity score over time in study 1. The mean weekly itch severity scores significantly decreased with a maximum effect around week 12 that was sustained over the 24-week treatment period. The results were similar in study 3.

In all three studies the mean weekly itch severity score increased gradually during the 16-week treatment-free follow-up period, consistent with symptom re-occurrence. Mean values at the end of the follow-up period were similar to the placebo group, but lower than respective mean baseline values.

**Figure 1: Mean weekly itch severity score over time, study 1 (mITT population)**



BOCF=baseline observation carried forward; mITT=modified intention-to-treat population

Efficacy after 24 weeks of treatment

The magnitude of the efficacy outcomes observed at week 24 of treatment was comparable to that observed at week 12:

For 300 mg, in studies 1 and 3, the mean decrease from baseline in weekly itch severity score was 9.8 and 8.6, the proportion of patients with UAS7≤6 was 61.7% and 55.6%, and the proportion of patients with complete response (UAS7=0) was 48.1% and 42.5%, respectively, (all p<0.0001, when compared to placebo).

There is limited clinical experience in re-treatment of patients with omalizumab.

Clinical trial data on adolescents (12 to 17 years) included a total of 39 patients, of whom 11 received the 300 mg dose. Results for the 300 mg are available for 9 patients at week 12 and 6 patients at week 24, and show a similar magnitude of response to omalizumab treatment compared to the adult population. Mean change from baseline in weekly itch severity score showed a reduction of 8.25 at week 12 and of 8.95 at week 24. The responder rates were: 33% at week 12 and 67% at week 24 for UAS7=0, and 56% at week 12 and 67% at week 24 for UAS7≤6.

## 5.2 Pharmacokinetic properties

The pharmacokinetics of omalizumab have been studied in adult and adolescent patients with allergic asthma as well as in adult and adolescent patients with CSU. The general pharmacokinetic characteristics of omalizumab are similar in these populations.

### Absorption

After subcutaneous administration, omalizumab is absorbed with an average absolute bioavailability of 62%. Following a single subcutaneous dose in adult and adolescent patients with asthma or CSU, omalizumab was absorbed slowly, reaching peak serum concentrations after an average of 6-8 days. In patients with asthma, following multiple doses of omalizumab, areas under the serum concentration-time curve from Day 0 to Day 14 at steady state were up to 6-fold of those after the first dose.

The pharmacokinetics of omalizumab are linear at doses greater than 0.5 mg/kg. Following doses of 75 mg, 150 mg or 300 mg every 4 weeks in patients with CSU, trough serum concentrations of omalizumab increased proportionally with the dose level.

Administration of Xolair manufactured as a lyophilised or liquid formulation resulted in similar serum concentration-time profiles of omalizumab.

### Distribution

*In vitro*, omalizumab forms complexes of limited size with IgE. Precipitating complexes and complexes larger than one million Daltons in molecular weight are not observed *in vitro* or *in vivo*. Based on population pharmacokinetics, distribution of omalizumab was similar in patients with allergic asthma and patients with CSU. The apparent volume of distribution in patients with asthma following subcutaneous administration was  $78 \pm 32$  ml/kg.

### Elimination

Clearance of omalizumab involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG includes degradation in the reticuloendothelial system and endothelial cells. Intact IgG is also excreted in bile. In asthma patients the omalizumab serum elimination half-life averaged 26 days, with apparent clearance averaging  $2.4 \pm 1.1$  ml/kg/day. Doubling of body weight approximately doubled apparent clearance. In CSU patients, based on population pharmacokinetic simulations, omalizumab serum elimination half-life at steady state averaged 24 days and apparent clearance at steady state for a patient of 80 kg weight was 3.0 ml/kg/day.

### Characteristics in patient populations

*Patients with asthma:* The population pharmacokinetics of omalizumab were analysed to evaluate the effects of demographic characteristics. Analyses of these limited data suggest that no dose adjustments are necessary in patients with asthma for age (6-76 years), race/ethnicity, gender or body mass index (see section 4.2).

*Patients with CSU:* The effects of demographic characteristics and other factors on omalizumab exposure were evaluated based on population pharmacokinetics. In addition, covariate effects were evaluated by analysing the relationship between omalizumab concentrations and clinical responses. These analyses suggest that no dose adjustments are necessary in patients with CSU for age (12-75 years), race/ethnicity, gender, body weight, body mass index, baseline IgE, anti-FcεRI autoantibodies or concomitant use of H2 antihistamines or LTRAs.

### Renal and hepatic impairment

There are no pharmacokinetic or pharmacodynamic data in allergic asthma or CSU patients with renal or hepatic impairment (see sections 4.2 and 4.4).

### **5.3 Preclinical safety data**

The safety of omalizumab has been studied in the cynomolgus monkey, since omalizumab binds to cynomolgus and human IgE with similar affinity. Antibodies to omalizumab were detected in some monkeys following repeated subcutaneous or intravenous administration. However, no apparent toxicity, such as immune complex-mediated disease or complement-dependent cytotoxicity, was seen. There was no evidence of an anaphylactic response due to mast-cell degranulation in cynomolgus monkeys.

Chronic administration of omalizumab at dose levels of up to 250 mg/kg (at least 14 times the highest recommended clinical dose in mg/kg according to the recommended dosing table) was well tolerated in non-human primates (both adult and juvenile animals), with the exception of a dose-related and age-dependent decrease in blood platelets, with a greater sensitivity in juvenile animals. The serum concentration required to attain a 50% drop in platelets from baseline in adult cynomolgus monkeys was roughly 4- to 20-fold higher than anticipated maximum clinical serum concentrations. In addition, acute haemorrhage and inflammation were observed at injection sites in cynomolgus monkeys.

Formal carcinogenicity studies have not been conducted with omalizumab.

In reproduction studies in cynomolgus monkeys, subcutaneous doses up to 75 mg/kg per week (at least 8 times the highest recommended clinical dose in mg/kg over a 4-week period) did not elicit maternal toxicity, embryotoxicity or teratogenicity when administered throughout organogenesis and did not elicit adverse effects on foetal or neonatal growth when administered throughout late gestation, delivery and nursing.

Omalizumab is excreted in breast milk in cynomolgus monkeys. Milk levels of omalizumab were 0.15% of the maternal serum concentration.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

L-arginine hydrochloride  
L-histidine hydrochloride  
L-histidine  
Polysorbate 20  
Water for injections

### **6.2 Incompatibilities**

This medicinal product must not be mixed with other medicinal products.

### **6.3 Shelf life**

15 months.

The shelf life includes potential temperature excursions. The product may be kept for a total of 4 hours at 25°C. If necessary, the product may be returned to the refrigerator for later use, but this must not be done more than once.

#### **6.4 Special precautions for storage**

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Store in the original package in order to protect from light.

#### **6.5 Nature and contents of container**

1 ml solution in a pre-filled syringe barrel (type I glass) with staked needle (stainless steel), (type I) plunger stopper and needle cap.

Pack containing 1 pre-filled syringe, and multipacks containing 4 (4 packs of 1) or 10 (10 packs of 1) pre-filled syringes.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal and other handling**

Prior to completion of the injection, avoid contact with the device activation clips to keep from prematurely covering the needle with the needle guard.

##### Using the syringe

1. Holding the syringe with the needle pointing upwards, carefully pull off the needle cap from the syringe and discard it. Do not touch the exposed needle. Then, gently tap the syringe with your finger until the air bubble rises to the top of the syringe. Slowly push the plunger up to force the air bubble out of the syringe without inadvertently expelling solution.
2. Gently pinch the skin at the injection site and insert the needle.
3. Holding onto the finger flange, slowly depress the plunger as far as it will go. If any solution leaks from the injection site, insert the needle further.
4. Keeping the plunger fully depressed, carefully lift the needle straight out from the injection site.
5. Slowly release the plunger and allow the needle guard to automatically cover the exposed needle.

##### Disposal instructions

Dispose of the used syringe immediately in a sharps container.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Frimley Business Park  
Camberley GU16 7SR  
United Kingdom

**8.     MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/008

EU/1/05/319/009

EU/1/05/319/010

**9.     DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 25 October 2005

Date of latest renewal: 22 June 2015

**10.    DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

## **ANNEX II**

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE  
SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR  
BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY  
AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE  
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO  
THE SAFE AND EFFECTIVE USE OF THE MEDICINAL  
PRODUCT**

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE  
AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer of the biological active substance

Novartis Pharma S.A.S.  
Centre de Biotechnologie  
8, rue de l'Industrie  
F-68330 Huningue  
France

Name and address of the manufacturer responsible for batch release

Novartis Pharma GmbH  
Roonstrasse 25  
D-90429 Nuremberg  
Germany

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING  
AUTHORISATION**

• **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND  
EFFECTIVE USE OF THE MEDICINAL PRODUCT**

• **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.



**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Xolair 75 mg powder and solvent for solution for injection  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial contains 75 mg omalizumab.

**3. LIST OF EXCIPIENTS**

Powder: sucrose, L-histidine, L-histidine hydrochloride monohydrate and polysorbate 20.  
Solvent: water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder and solvent for solution for injection

1 x 75 mg vial  
1 x 2 ml solvent ampoule

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Use only as directed by a doctor.  
Read the package leaflet before use.  
Subcutaneous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator (2°C - 8°C).

Use immediately after reconstitution (may be stored at 2°C - 8°C for up to 8 hours or at 25°C for 2 hours).

Do not freeze.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Frimley Business Park  
Camberley GU16 7SR  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 75 mg

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Xolair 75 mg powder for solution for injection  
omalizumab  
Subcutaneous use

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

75 mg

**6. OTHER**

Store in a refrigerator (2°C - 8°C).

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**  
**AMPOULE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Solvent for Xolair  
Water for injections

**2. METHOD OF ADMINISTRATION**

Use 0.9 ml and discard the rest.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

2 ml

**6. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON CONTAINING 1 VIAL AND 1 AMPOULE AS UNIT PACK (INCLUDING BLUE BOX)**

**1. NAME OF THE MEDICINAL PRODUCT**

Xolair 150 mg powder and solvent for solution for injection  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial contains 150 mg omalizumab.

**3. LIST OF EXCIPIENTS**

Powder: sucrose, L-histidine, L-histidine hydrochloride monohydrate and polysorbate 20.  
Solvent: water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder and solvent for solution for injection

1 x 150 mg vial  
1 x 2 ml solvent ampoule

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Use only as directed by a doctor.  
Read the package leaflet before use.  
Subcutaneous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator (2°C - 8°C).

Use immediately after reconstitution (may be stored at 2°C - 8°C for up to 8 hours or at 25°C for 2 hours).

Do not freeze.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Frimley Business Park  
Camberley GU16 7SR  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/002

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 150 mg



**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON FOR INTERMEDIATE PACK (WITHOUT BLUE BOX) OF MULTIPACKS**

**1. NAME OF THE MEDICINAL PRODUCT**

Xolair 150 mg powder and solvent for solution for injection  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial contains 150 mg omalizumab.

**3. LIST OF EXCIPIENTS**

Powder: sucrose, L-histidine, L-histidine hydrochloride monohydrate and polysorbate 20.  
Solvent: water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder and solvent for solution for injection

1 x 150 mg vial  
1 x 2 ml solvent ampoule  
1 vial and 1 ampoule. Component of a multipack. Not to be sold separately.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Use only as directed by a doctor.  
Read the package leaflet before use.  
Subcutaneous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator (2°C - 8°C).

Use immediately after reconstitution (may be stored at 2°C - 8°C for up to 8 hours or at 25°C for 2 hours).

Do not freeze.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Frimley Business Park  
Camberley GU16 7SR  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/003      Multipack comprising 4 packs  
EU/1/05/319/004      Multipack comprising 10 packs

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 150 mg

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**WRAPPER LABEL ON MULTIPACKS WRAPPED IN FOIL (INCLUDING BLUE BOX)**

**1. NAME OF THE MEDICINAL PRODUCT**

Xolair 150 mg powder and solvent for solution for injection  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial contains 150 mg omalizumab.

**3. LIST OF EXCIPIENTS**

Powder: sucrose, L-histidine, L-histidine hydrochloride monohydrate and polysorbate 20.  
Solvent: water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder and solvent for solution for injection

Multipack: 4 packs, each containing 1 vial (150 mg) and 1 solvent ampoule (2 ml).

Multipack: 10 packs, each containing 1 vial (150 mg) and 1 solvent ampoule (2 ml).

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Use only as directed by a doctor.  
Read the package leaflet before use.  
Subcutaneous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator (2°C - 8°C).

Use immediately after reconstitution (may be stored at 2°C - 8°C for up to 8 hours or at 25°C for 2 hours).

Do not freeze.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Frimley Business Park  
Camberley GU16 7SR  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/003      Multipack comprising 4 packs  
EU/1/05/319/004      Multipack comprising 10 packs

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 150 mg

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Xolair 150 mg powder for solution for injection  
omalizumab  
Subcutaneous use

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

150 mg

**6. OTHER**

Store in a refrigerator (2°C - 8°C).

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**AMPOULE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Solvent for Xolair  
Water for injections

**2. METHOD OF ADMINISTRATION**

Use 1.4 ml and discard the rest.

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

2 ml

**6. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON FOR UNIT PACK**

**1. NAME OF THE MEDICINAL PRODUCT**

Xolair 75 mg solution for injection  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pre-filled syringe of 0.5 ml solution contains 75 mg of omalizumab.

**3. LIST OF EXCIPIENTS**

Also contains: L-arginine hydrochloride, L-histidine hydrochloride, L-histidine, polysorbate 20, water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection

1 x 0.5 ml

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Use only as directed by a doctor.  
Read the package leaflet before use.  
Subcutaneous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator (2°C – 8°C).  
Do not freeze.  
Store in the original package in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Dispose the used syringe immediately in a sharps container.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Frimley Business Park  
Camberley GU16 7SR  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/005      75 mg solution for injection

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Xolair 75 mg



**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX)**

**1. NAME OF THE MEDICINAL PRODUCT**

Xolair 75 mg solution for injection  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pre-filled syringe of 0.5 ml solution contains 75 mg of omalizumab.

**3. LIST OF EXCIPIENTS**

Also contains: L-arginine hydrochloride, L-histidine hydrochloride, L-histidine, polysorbate 20, water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection

Multipack: 4 packs, each containing 1 x 0.5 ml.

Multipack: 10 packs, each containing 1 x 0.5 ml.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Use only as directed by a doctor.  
Read the package leaflet before use.  
Subcutaneous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator (2°C – 8°C).  
Do not freeze.  
Store in the original package in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Dispose the used syringe immediately in a sharps container.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Frimley Business Park  
Camberley GU16 7SR  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/006 75 mg solution for injection (4)  
EU/1/05/319/007 75 mg solution for injection (10)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 75 mg

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX)**

**1. NAME OF THE MEDICINAL PRODUCT**

Xolair 75 mg solution for injection  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pre-filled syringe of 0.5 ml solution contains 75 mg of omalizumab.

**3. LIST OF EXCIPIENTS**

Also contains: L-arginine hydrochloride, L-histidine hydrochloride, L-histidine, polysorbate 20, water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection

1 x 0.5 ml. Component of a multipack. Not to be sold separately.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Use only as directed by a doctor.  
Read the package leaflet before use.  
Subcutaneous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Store in the original package in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Dispose the used syringe immediately in a sharps container.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR

United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/006 75 mg solution for injection (4)

EU/1/05/319/007 75 mg solution for injection (10)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 75 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER OF PRE-FILLED SYRINGE**

**1. NAME OF THE MEDICINAL PRODUCT**

Xolair 75 mg solution for injection  
omalizumab  
Subcutaneous use.

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS  
PRE-FILLED SYRINGE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Xolair 75 mg solution for injection  
omalizumab  
SC use

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

0.5 ml

**6. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON FOR UNIT PACK**

**1. NAME OF THE MEDICINAL PRODUCT**

Xolair 150 mg solution for injection  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pre-filled syringe of 1 ml solution contains 150 mg of omalizumab.

**3. LIST OF EXCIPIENTS**

Also contains: L-arginine hydrochloride, L-histidine hydrochloride, L-histidine, polysorbate 20, water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection

1 x 1 ml

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Use only as directed by a doctor.  
Read the package leaflet before use.  
Subcutaneous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator (2°C – 8°C).  
Do not freeze.  
Store in the original package in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Dispose the used syringe immediately in a sharps container.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Frimley Business Park  
Camberley GU16 7SR  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/008      150 mg solution for injection

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 150 mg



**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX)**

**1. NAME OF THE MEDICINAL PRODUCT**

Xolair 150 mg solution for injection  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pre-filled syringe of 1 ml solution contains 150 mg of omalizumab.

**3. LIST OF EXCIPIENTS**

Also contains: L-arginine hydrochloride, L-histidine hydrochloride, L-histidine, polysorbate 20, water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection

Multipack: 4 packs, each containing 1 x 1 ml.

Multipack: 10 packs, each containing 1 x 1 ml.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Use only as directed by a doctor.  
Read the package leaflet before use.  
Subcutaneous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Store in the original package in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Dispose the used syringe immediately in a sharps container.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR

United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/009 150 mg solution for injection (4)

EU/1/05/319/010 150 mg solution for injection (10)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 150 mg

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX)**

**1. NAME OF THE MEDICINAL PRODUCT**

Xolair 150 mg solution for injection  
omalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pre-filled syringe of 1 ml solution contains 150 mg of omalizumab.

**3. LIST OF EXCIPIENTS**

Also contains: L-arginine hydrochloride, L-histidine hydrochloride, L-histidine, polysorbate 20, water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection

1 x 1 ml. Component of a multipack. Not to be sold separately.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Use only as directed by a doctor.  
Read the package leaflet before use.  
Subcutaneous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Store in the original package in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Dispose the used syringe immediately in a sharps container.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR

United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/05/319/009 150 mg solution for injection (4)

EU/1/05/319/010 150 mg solution for injection (10)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xolair 150 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER OF PRE-FILLED SYRINGE**

**1. NAME OF THE MEDICINAL PRODUCT**

Xolair 150 mg solution for injection  
omalizumab  
Subcutaneous use.

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS  
PRE-FILLED SYRINGE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Xolair 150 mg solution for injection  
omalizumab  
SC use

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

1 ml

**6. OTHER**

**B. PACKAGE LEAFLET**

## **Package leaflet: Information for the user**

### **Xolair 75 mg powder and solvent for solution for injection** omalizumab

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Xolair is and what it is used for
2. What you need to know before you are given Xolair
3. How Xolair is given
4. Possible side effects
5. How to store Xolair
6. Contents of the pack and other information

#### **1. What Xolair is and what it is used for**

The active substance of Xolair is omalizumab. Omalizumab is a man-made protein that is similar to natural proteins produced by the body; it belongs to a class of medicines called monoclonal antibodies. It is used to prevent asthma from getting worse by controlling symptoms of severe allergic asthma in adults and adolescents (12 years of age and older) and children (6 to less than 12 years of age) who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high-dose steroid inhalers or beta-agonist inhalers.

Xolair works by blocking a substance called immunoglobulin E (IgE), which is produced by the body. IgE plays a key role in causing allergic asthma.

#### **2. What you need to know before you are given Xolair**

##### **You should not be given Xolair**

- if you are allergic to omalizumab or any of the other ingredients of this medicine (listed in section 6).

If you think you may be allergic to any of the ingredients, tell your doctor as you should not be given Xolair.

##### **Warnings and precautions**

Xolair contains a protein, and proteins can cause serious allergic reactions in some people. Signs include rash, difficulty in breathing, swelling or feeling faint. If you have an allergic reaction after taking Xolair, contact a doctor as soon as you can.

A certain type of allergic reaction called serum sickness has been observed in patients treated with Xolair. The symptoms of serum sickness can be one or more of the following symptoms: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain. If you experience any of these symptoms, or in particular if you experience a combination of such symptoms, contact your doctor immediately.



Churg-Strauss and Hypereosinophilic syndrome have been observed in patients treated with Xolair. The symptoms may include one or more of the following: swelling, pain or rash around blood or lymph vessels, high level of a specific type of white blood cells (marked eosinophilia), worsening problems with breathing, nasal congestion, heart problems, pain, numbness, tingling in the arm and legs. If you experience any of these symptoms, or in particular if you experience a combination of such symptoms, contact your doctor immediately.

Talk to your doctor before you are given Xolair:

- if you have kidney or liver problems.
- if you have a disorder where your own immune system attacks parts of your own body (autoimmune disease).
- if you live in a region where infections caused by parasites are common or if you are travelling to such a region as Xolair may weaken your resistance to such infections.

Xolair does not treat acute asthma symptoms, such as a sudden asthma attack. Therefore Xolair should not be used to treat such symptoms.

Xolair is not meant to prevent or treat other allergy-type conditions, such as sudden allergic reactions, hyperimmunoglobulin E syndrome (an inherited immune disorder), aspergillosis (a fungus-related lung disease), food allergy, eczema or hay fever because Xolair has not been studied in these conditions.

### **Children (under 6 years of age)**

Xolair should not be given to children under 6 years of age. There are not enough data in this group.

### **Other medicines and Xolair**

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

This is especially important if you are taking:

- medicines to treat an infection caused by a parasite, as Xolair may reduce the effect of your medicines,
- inhaled corticosteroids and other medicines for allergic asthma.

### **Pregnancy and breast-feeding**

You should not be given Xolair when you are pregnant, unless this is considered necessary by your doctor.

If you plan to become pregnant, tell your doctor before starting treatment with Xolair. Your doctor will discuss with you the benefits and potential risks of being given this medicine during pregnancy.

If you become pregnant while being treated with Xolair, tell your doctor immediately.

You should not be given Xolair when you are breast-feeding.

### **Driving and using machines**

It is unlikely that Xolair will affect your ability to drive and use machines.

### **3. How Xolair is given**

Instructions on how to use Xolair are given in the section “Information for the healthcare professional”.

Your doctor will work out how much Xolair you need and how often you will be given it. This depends on your body weight and the results of a blood test carried out before the start of the treatment to measure the amount of IgE in your blood.

Xolair is given to you by a doctor or nurse as an injection just under the skin (subcutaneously).

Follow carefully all instructions given by your doctor or nurse.

#### **How much you will be given**

You will be given 1 to 4 injections at a time, either every two weeks, or every four weeks.

Carry on taking your current asthma medicine during Xolair treatment. Do not stop taking any asthma medicines without talking to your doctor.

You may not see an immediate improvement in your asthma after beginning Xolair therapy. It usually takes between 12 and 16 weeks to have the full effect.

#### **Use in children and adolescents**

Xolair can be given to children and adolescents aged 6 years or older, who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high dose steroid inhalers or beta-agonist inhalers. Your doctor will work out how much Xolair your child needs and how often it needs to be given. This will depend on your child’s weight and the results of a blood test carried out before the start of the treatment to measure the amount of IgE in his/her blood.

#### **If a dose of Xolair is missed**

Contact your doctor or hospital as soon as possible to re-schedule your appointment.

#### **If you stop treatment with Xolair**

Do not stop treatment with Xolair unless your doctor tells you to. Interrupting or stopping the treatment with Xolair may cause your asthma symptoms to come back.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

### **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them. The side effects caused by Xolair are usually mild to moderate but can occasionally be serious.

#### Serious side effects include:

Rare side effects (may affect up to 1 in 1,000 people)

- Sudden severe allergic reactions: if you notice any serious sudden signs of allergy or combination of signs such as rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heart beat, dizziness and light-headedness, shortness of breath, wheezing or trouble breathing, or any other new symptoms, tell your doctor or nurse immediately. If you have a history of severe allergic reactions (anaphylaxis) unrelated to Xolair you may be more at risk of developing a severe allergic reaction following use of Xolair.
- Systemic lupus erythematosus (SLE). Symptoms may include muscle pain, joint pain and swelling, and rash. You may also experience other signs such as fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)

- Development of one or more of the following symptoms: swelling, pain or rash around blood or lymph vessels, high level of a specific type of white blood cells (marked eosinophilia), worsening problems with breathing, nasal congestion, heart problems, pain, numbness, tingling in the arms and legs (signs of so-called “Churg-Strauss syndrome or hypereosinophilic syndrome”).
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Development of any of the following symptoms, especially if in combination: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain (signs of serum sickness).

If you experience any of these, tell your doctor or nurse straight away.

Other side effects include:

Very common side effects (may affect more than 1 in 10 people)

- fever (in children)

Common side effects (may affect up to 1 in 10 people)

- reactions at the injection site including pain, swelling, itching and redness
- pain in the upper part of the tummy (in children)
- headache (very common in children)

Uncommon side effects (may affect up to 1 in 100 people)

- feeling dizzy, sleepy or tired
- tingling or numbness of the hands or feet
- fainting, low blood pressure while sitting or standing (postural hypotension), flushing
- sore throat, coughing, acute breathing problems
- feeling sick (nausea), diarrhoea, indigestion
- itching, hives, rash, increased sensitivity of the skin to sun
- weight increase
- flu-like symptoms
- swelling arms

Rare side effects (may affect up to 1 in 1,000 people)

- parasitic infection

Not known (frequency cannot be estimated from the available data)

- joint pain, muscle pain and joint swelling
- hair loss

### **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Xolair**

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C). Do not freeze.

## 6. Contents of the pack and other information

### What Xolair contains

- The active substance is omalizumab. One vial contains 75 mg of omalizumab. After reconstitution one vial contains 125 mg/ml of omalizumab (75 mg in 0.6 ml).
- The other ingredients are sucrose, L-histidine, L-histidine hydrochloride monohydrate and polysorbate 20.

### What Xolair looks like and contents of the pack

Xolair 75 mg powder and solvent for solution for injection is supplied as a white to off-white powder in a small glass vial together with an ampoule containing 2 ml of water for injections. The powder is reconstituted in the water before it is injected by a doctor or nurse.

Xolair is available in packs containing one vial of powder for solution for injection and one ampoule of 2 ml water for injections.

Xolair is also available in vials with 150 mg omalizumab.

### Marketing Authorisation Holder

Novartis Europharm Limited  
Frimley Business Park  
Camberley GU16 7SR  
United Kingdom

### Manufacturer

Novartis Pharma GmbH  
Roonstrasse 25  
D-90429 Nuremberg  
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Novartis Pharma N.V.  
Tél/Tel: +32 2 246 16 11

#### **Lietuva**

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#### **България**

Novartis Pharma Services Inc.  
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**Slovenská republika**

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**Suomi/Finland**

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Puh/Tel: +358 (0)10 6133 200

**Sverige**

Novartis Sverige AB  
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**United Kingdom**

Novartis Pharmaceuticals UK Ltd.  
Tel: +44 1276 698370

**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>

## INFORMATION FOR THE HEALTHCARE PROFESSIONAL

The following information is intended for healthcare professionals only:

The lyophilised medicinal product takes 15-20 minutes to dissolve, although in some cases it may take longer. The fully reconstituted medicinal product will appear clear to slightly opalescent, colourless to pale brownish-yellow and may have a few small bubbles or foam around the edge of the vial. Because of the viscosity of the reconstituted medicinal product care must be taken to withdraw all of the medicinal product from the vial before expelling any air or excess solution from the syringe in order to obtain the 0.6 ml.

To prepare Xolair 75 mg vials for subcutaneous administration, please adhere to the following instructions:

1. Draw 0.9 ml of water for injections from the ampoule into a syringe equipped with a large-bore 18-gauge needle.
2. With the vial placed upright on a flat surface, insert the needle and transfer the water for injections into the vial containing the lyophilised powder using standard aseptic techniques, directing the water for injections directly onto the powder.
3. Keeping the vial in an upright position, vigorously swirl it (do not shake) for approximately 1 minute to evenly wet the powder.
4. To aid in dissolution after completing step 3, gently swirl the vial for 5-10 seconds approximately every 5 minutes in order to dissolve any remaining solids.

Note that in some cases it may take longer than 20 minutes for the powder to dissolve completely. If this is the case, repeat step 4 until there are no visible gel-like particles in the solution.

When the medicinal product is fully dissolved, there should be no visible gel-like particles in the solution. Small bubbles or foam around the edge of the vial are common. The reconstituted medicinal product will appear clear to slightly opalescent, colourless to pale brownish-yellow. Do not use if solid particles are present.

5. Invert the vial for at least 15 seconds in order to allow the solution to drain towards the stopper. Using a new 3-ml syringe equipped with a large-bore, 18-gauge needle, insert the needle into the inverted vial. Keeping the vial inverted position the needle tip at the very bottom of the solution in the vial when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove all of the solution from the inverted vial.
6. Replace the 18-gauge needle with a 25-gauge needle for subcutaneous injection.
7. Expel air, large bubbles, and any excess solution in order to obtain the required 0.6 ml dose. A thin layer of small bubbles may remain at the top of the solution in the syringe. Because the solution is slightly viscous, it may take 5-10 seconds to administer the solution by subcutaneous injection.

The vial delivers 0.6 ml (75 mg) of Xolair.

8. The injections are administered subcutaneously in the deltoid region of the arm or the thigh.

## Package leaflet: Information for the user

### **Xolair 150 mg powder and solvent for solution for injection** omalizumab

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Xolair is and what it is used for
2. What you need to know before you are given Xolair
3. How Xolair is given
4. Possible side effects
5. How to store Xolair
6. Contents of the pack and other information

#### **1. What Xolair is and what it is used for**

Xolair is used for the treatment of allergic asthma and chronic spontaneous urticaria (CSU). The active substance of Xolair is omalizumab. Omalizumab is a man-made protein that is similar to natural proteins produced by the body; it belongs to a class of medicines called monoclonal antibodies. Xolair works by blocking a substance called immunoglobulin E (IgE), which is produced by the body. IgE plays a key role in causing allergic asthma or CSU.

##### Allergic asthma

This medicine is used to prevent asthma from getting worse by controlling symptoms of severe allergic asthma in adults and adolescents (12 years of age and older) and children (6 to less than 12 years of age) who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high-dose steroid inhalers or beta-agonist inhalers.

##### Chronic spontaneous urticaria (CSU)

This medicine is used to treat chronic spontaneous urticaria in adults and adolescents (12 years of age or older) who are already receiving antihistamines but whose CSU symptoms are not well controlled by these medicines.

#### **2. What you need to know before you are given Xolair**

##### **You should not be given Xolair**

- if you are allergic to omalizumab or any of the other ingredients of this medicine (listed in section 6).

If you think you may be allergic to any of the ingredients, tell your doctor as you should not be given Xolair.

##### **Warnings and precautions**

Xolair contains a protein, and proteins can cause serious allergic reactions in some people. Signs include rash, difficulty in breathing, swelling or feeling faint. If you have an allergic reaction after taking Xolair, contact a doctor as soon as you can.

A certain type of allergic reaction called serum sickness has been observed in patients treated with Xolair. The symptoms of serum sickness can be one or more of the following symptoms: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain. If you experience any of these symptoms, or in particular if you experience a combination of such symptoms, contact your doctor immediately.

Churg-Strauss and Hypereosinophilic syndrome have been observed in allergic asthma patients treated with Xolair. The symptoms may include one or more of the following: swelling, pain or rash around blood or lymph vessels, high level of a specific type of white blood cells (marked eosinophilia), worsening problems with breathing, nasal congestion, heart problems, pain, numbness, tingling in the arm and legs. If you experience any of these symptoms, or in particular if you experience a combination of such symptoms, contact your doctor immediately.

Talk to your doctor before you are given Xolair:

- if you have kidney or liver problems.
- if you have a disorder where your own immune system attacks parts of your own body (autoimmune disease).
- if you live in a region where infections caused by parasites are common or if you are travelling to such a region as Xolair may weaken your resistance to such infections.

Xolair does not treat acute asthma symptoms, such as a sudden asthma attack. Therefore Xolair should not be used to treat such symptoms.

Xolair is not meant to prevent or treat other allergy-type conditions, such as sudden allergic reactions, hyperimmunoglobulin E syndrome (an inherited immune disorder), aspergillosis (a fungus-related lung disease), food allergy, eczema or hay fever because Xolair has not been studied in these conditions.

### **Children and adolescents**

#### Allergic asthma

Xolair is not recommended for children under 6 years of age.

#### Chronic spontaneous urticaria (CSU)

Do not give Xolair to children under 12 years of age. Its use in children under 12 has not been studied.

### **Other medicines and Xolair**

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

This is especially important if you are taking:

- medicines to treat an infection caused by a parasite, as Xolair may reduce the effect of your medicines,
- inhaled corticosteroids and other medicines for allergic asthma.

### **Pregnancy and breast-feeding**

You should not be given Xolair when you are pregnant, unless this is considered necessary by your doctor.

If you plan to become pregnant, tell your doctor before starting treatment with Xolair. Your doctor will discuss with you the benefits and potential risks of being given this medicine during pregnancy.

If you become pregnant while being treated with Xolair, tell your doctor immediately.

You should not be given Xolair when you are breast-feeding.



### **Driving and using machines**

It is unlikely that Xolair will affect your ability to drive and use machines.

### **3. How Xolair is given**

Instructions on how to use Xolair are given in the section “Information for the healthcare professional”.

Xolair is given to you by a doctor or nurse as an injection just under the skin (subcutaneously).

Follow carefully all instructions given by your doctor or nurse.

#### **How much you will be given**

##### Allergic asthma

Your doctor will work out how much Xolair you need and how often you will be given it. This depends on your body weight and the results of a blood test carried out before the start of the treatment to measure the amount of IgE in your blood.

You will be given 1 to 4 injections at a time, either every two weeks, or every four weeks.

Carry on taking your current asthma medicine during Xolair treatment. Do not stop taking any asthma medicines without talking to your doctor.

You may not see an immediate improvement in your asthma after beginning Xolair therapy. It usually takes between 12 and 16 weeks to have the full effect.

##### Chronic spontaneous urticaria (CSU)

You will be given two 150 mg injections at a time every four weeks.

Continue taking your current medicine for CSU during Xolair treatment. Do not stop taking any medicine without talking to your doctor first.

#### **Use in children and adolescents**

##### Allergic asthma

Xolair can be given to children and adolescents aged 6 years or older, who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high dose steroid inhalers or beta-agonist inhalers. Your doctor will work out how much Xolair your child needs and how often it needs to be given. This will depend on your child’s weight and the results of a blood test carried out before the start of the treatment to measure the amount of IgE in his/her blood.

##### Chronic spontaneous urticaria (CSU)

Xolair can be given to adolescents aged 12 years or older, who are already receiving antihistamines but whose CSU symptoms are not well controlled by these medicines.

#### **If a dose of Xolair is missed**

Contact your doctor or hospital as soon as possible to re-schedule your appointment.

#### **If you stop treatment with Xolair**

Do not stop treatment with Xolair unless your doctor tells you to. Interrupting or stopping the treatment with Xolair may cause your asthma or CSU symptoms to come back.

However, if you are being treated for CSU, your doctor may stop Xolair treatment from time to time so that your symptoms can be assessed. Follow your doctor’s instructions.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

#### 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The side effects caused by Xolair are usually mild to moderate but can occasionally be serious.

##### Serious side effects include:

Rare side effects (may affect up to 1 in 1,000 people)

- Sudden severe allergic reactions: if you notice any serious sudden signs of allergy or combination of signs such as rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heart beat, dizziness and light-headedness, shortness of breath, wheezing or trouble breathing, or any other new symptoms, tell your doctor or nurse immediately. If you have a history of severe allergic reactions (anaphylaxis) unrelated to Xolair you may be more at risk of developing a severe allergic reaction following use of Xolair.
- Systemic lupus erythematosus (SLE). Symptoms may include muscle pain, joint pain and swelling, and rash. You may also experience other signs such as fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)

- Development of one or more of the following symptoms: swelling, pain or rash around blood or lymph vessels, high level of a specific type of white blood cells (marked eosinophilia), worsening problems with breathing, nasal congestion, heart problems, pain, numbness, tingling in the arms and legs (signs of so-called “Churg-Strauss syndrome or hypereosinophilic syndrome”).
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Development of any of the following symptoms, especially if in combination: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain (signs of serum sickness).

If you experience any of these, tell your doctor or nurse straight away.

##### Other side effects include:

Very common side effects (may affect more than 1 in 10 people)

- fever (in children)

Common side effects (may affect up to 1 in 10 people)

- reactions at the injection site including pain, swelling, itching and redness
- pain in the upper part of the tummy (in children)
- headache (very common in children)
- upper respiratory tract infection, such as inflammation of the pharynx and common cold
- feeling of pressure or pain in the cheeks and forehead (sinusitis, sinus headache)
- pain in joints (arthralgia)

Uncommon side effects (may affect up to 1 in 100 people)

- feeling dizzy, sleepy or tired
- tingling or numbness of the hands or feet
- fainting, low blood pressure while sitting or standing (postural hypotension), flushing
- sore throat, coughing, acute breathing problems
- feeling sick (nausea), diarrhoea, indigestion
- itching, hives, rash, increased sensitivity of the skin to sun
- weight increase
- flu-like symptoms
- swelling arms

Rare side effects (may affect up to 1 in 1,000 people)

- parasitic infection

Not known (frequency cannot be estimated from the available data)

- muscle pain and joint swelling
- hair loss

### **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Xolair**

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C). Do not freeze.

## **6. Contents of the pack and other information**

### **What Xolair contains**

- The active substance is omalizumab. One vial contains 150 mg of omalizumab. After reconstitution one vial contains 125 mg/ml of omalizumab (150 mg in 1.2 ml).
- The other ingredients are sucrose, L-histidine, L-histidine hydrochloride monohydrate and polysorbate 20.

### **What Xolair looks like and contents of the pack**

Xolair 150 mg powder and solvent for solution for injection is supplied as a white to off-white powder in a small glass vial together with an ampoule containing 2 ml of water for injections. The powder is reconstituted in the water before it is injected by a doctor or nurse.

Xolair 150 mg powder and solvent for solution for injection is available in packs containing one vial of powder for solution for injection and one ampoule of 2 ml water for injections, and in multipacks containing four or ten intermediate packs, each with one vial of powder for solution for injection and one ampoule of 2 ml water for injections. Not all pack sizes may be marketed.

Xolair is also available in vials with 75 mg omalizumab.

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**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>

## INFORMATION FOR THE HEALTHCARE PROFESSIONAL

The following information is intended for healthcare professionals only:

The lyophilised medicinal product takes 15-20 minutes to dissolve, although in some cases it may take longer. The fully reconstituted medicinal product will appear clear to slightly opalescent, colourless to pale brownish-yellow and may have a few small bubbles or foam around the edge of the vial. Because of the viscosity of the reconstituted medicinal product care must be taken to withdraw all of the medicinal product from the vial before expelling any air or excess solution from the syringe in order to obtain the 1.2 ml.

To prepare Xolair 150 mg vials for subcutaneous administration, please adhere to the following instructions:

1. Draw 1.4 ml of water for injections from the ampoule into a syringe equipped with a large-bore 18-gauge needle.
2. With the vial placed upright on a flat surface, insert the needle and transfer the water for injections into the vial containing the lyophilised powder using standard aseptic techniques, directing the water for injections directly onto the powder.
3. Keeping the vial in an upright position, vigorously swirl it (do not shake) for approximately 1 minute to evenly wet the powder.
4. To aid in dissolution after completing step 3, gently swirl the vial for 5-10 seconds approximately every 5 minutes in order to dissolve any remaining solids.

Note that in some cases it may take longer than 20 minutes for the powder to dissolve completely. If this is the case, repeat step 4 until there are no visible gel-like particles in the solution.

When the medicinal product is fully dissolved, there should be no visible gel-like particles in the solution. Small bubbles or foam around the edge of the vial are common. The reconstituted medicinal product will appear clear to slightly opalescent, colourless to pale brownish-yellow. Do not use if solid particles are present.

5. Invert the vial for at least 15 seconds in order to allow the solution to drain towards the stopper. Using a new 3-ml syringe equipped with a large-bore, 18-gauge needle, insert the needle into the inverted vial. Keeping the vial inverted position the needle tip at the very bottom of the solution in the vial when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove all of the solution from the inverted vial.
6. Replace the 18-gauge needle with a 25-gauge needle for subcutaneous injection.
7. Expel air, large bubbles, and any excess solution in order to obtain the required 1.2 ml dose. A thin layer of small bubbles may remain at the top of the solution in the syringe. Because the solution is slightly viscous, it may take 5-10 seconds to administer the solution by subcutaneous injection.

The vial delivers 1.2 ml (150 mg) of Xolair. For a 75 mg dose, draw up 0.6 ml into the syringe and discard the remaining solution.

8. The injections are administered subcutaneously in the deltoid region of the arm or the thigh.

## **Package leaflet: Information for the user**

### **Xolair 75 mg solution for injection** omalizumab

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Xolair is and what it is used for
2. What you need to know before you are given Xolair
3. How Xolair is given
4. Possible side effects
5. How to store Xolair
6. Contents of the pack and other information

#### **1. What Xolair is and what it is used for**

The active substance of Xolair is omalizumab. Omalizumab is a man-made protein that is similar to natural proteins produced by the body; it belongs to a class of medicines called monoclonal antibodies. It is used to prevent asthma from getting worse by controlling symptoms of severe allergic asthma in adults and adolescents (12 years of age and older) and children (6 to less than 12 years of age) who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high-dose steroid inhalers or beta-agonist inhalers.

Xolair works by blocking a substance called immunoglobulin E (IgE), which is produced by the body. IgE plays a key role in causing allergic asthma.

#### **2. What you need to know before you are given Xolair**

##### **You should not be given Xolair**

- if you are allergic to omalizumab or any of the other ingredients of this medicine (listed in section 6).

If you think you may be allergic to any of the ingredients, tell your doctor as you should not be given Xolair.

##### **Warnings and precautions**

Xolair contains a protein, and proteins can cause serious allergic reactions in some people. Signs include rash, difficulty in breathing, swelling or feeling faint. If you have an allergic reaction after taking Xolair, contact a doctor as soon as you can.

A certain type of allergic reaction called serum sickness has been observed in patients treated with Xolair. The symptoms of serum sickness can be one or more of the following symptoms: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain. If you experience any of these symptoms, or in particular if you experience a combination of such symptoms, contact your doctor immediately.

Take special care with Xolair if you have ever had an allergic reaction to latex (the needle cap of the syringe may contain dry rubber (latex)).

Churg-Strauss and Hypereosinophilic syndrome have been observed in patients treated with Xolair. The symptoms may include one or more of the following: swelling, pain or rash around blood or lymph vessels, high level of a specific type of white blood cells (marked eosinophilia), worsening problems with breathing, nasal congestion, heart problems, pain, numbness, tingling in the arm and legs. If you experience any of these symptoms, or in particular if you experience a combination of such symptoms, contact your doctor immediately.

Talk to your doctor before you are given Xolair:

- If you have kidney or liver problems.
- If you have a disorder where your own immune system attacks parts of your own body (autoimmune disease).
- If you live in a region where infections caused by parasites are common or if you are travelling to such a region as Xolair may weaken your resistance to such infections.

Xolair does not treat acute asthma symptoms, such as a sudden asthma attack. Therefore Xolair should not be used to treat such symptoms.

Xolair is not meant to prevent or treat other allergy-type conditions, such as sudden allergic reactions, hyperimmunoglobulin E syndrome (an inherited immune disorder), aspergillosis (a fungus-related lung disease), food allergy, eczema or hay fever because Xolair has not been studied in these conditions.

### **Children (under 6 years of age)**

Xolair should not be given to children under 6 years of age. There are not enough data in this group.

### **Other medicines and Xolair**

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

This is especially important if you are taking:

- medicines to treat an infection caused by a parasite, as Xolair may reduce the effect of your medicines,
- inhaled corticosteroids and other medicines for allergic asthma.

### **Pregnancy and breast-feeding**

You should not be given Xolair when you are pregnant, unless this is considered necessary by your doctor.

If you plan to become pregnant, tell your doctor before starting treatment with Xolair. Your doctor will discuss with you the benefits and potential risks of being given this medicine during pregnancy.

If you become pregnant while being treated with Xolair, tell your doctor immediately.

You should not be given Xolair when you are breast-feeding.

### **Driving and using machines**

It is unlikely that Xolair will affect your ability to drive and use machines.



### **3. How Xolair is given**

Instructions on how to use Xolair are given in the section “Information for the healthcare professional”.

Your doctor will work out how much Xolair you need, and how often you will be given it. This depends on your body weight and the results of a blood test carried out before the start of the treatment to measure the amount of IgE in your blood.

Xolair is given to you by a doctor or nurse as an injection just under the skin (subcutaneously).

Follow carefully all instructions given by your doctor or nurse.

#### **How much you will be given**

You will be given 1 to 4 injections at a time, either every two weeks, or every four weeks.

Carry on taking your current asthma medicine during Xolair treatment. Do not stop taking any asthma medicines without talking to your doctor.

You may not see an immediate improvement in your asthma after beginning Xolair therapy. It usually takes between 12 and 16 weeks to have the full effect.

#### **Use in children and adolescents**

Xolair can be given to children and adolescents aged 6 years or older, who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high dose steroid inhalers or beta-agonist inhalers. Your doctor will work out how much Xolair your child needs and how often it needs to be given. This will depend on your child’s weight and the results of a blood test carried out before the start of the treatment to measure the amount of IgE in his/her blood.

#### **If a dose of Xolair is missed**

Contact your doctor or hospital as soon as possible to re-schedule your appointment.

#### **If you stop treatment with Xolair**

Do not stop treatment with Xolair unless your doctor tells you to. Interrupting or stopping the treatment with Xolair may cause your asthma symptoms to come back.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

### **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them. The side effects caused by Xolair are usually mild to moderate but can occasionally be serious.

#### Serious side effects include:

Rare side effects (may affect up to 1 in 1,000 people)

- Sudden severe allergic reactions: if you notice any serious sudden signs of allergy or combination of signs such as rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heart beat, dizziness and light-headedness, shortness of breath, wheezing or trouble breathing, or any other new symptoms, tell your doctor or nurse immediately. If you have a history of severe allergic reactions (anaphylaxis) unrelated to Xolair you may be more at risk of developing a severe allergic reaction following use of Xolair.
- Systemic lupus erythematosus (SLE). Symptoms may include muscle pain, joint pain and swelling, and rash. You may also experience other signs such as fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)

- Development of one or more of the following symptoms: swelling, pain or rash around blood or lymph vessels, high level of a specific type of white blood cells (marked eosinophilia), worsening problems with breathing, nasal congestion, heart problems, pain, numbness, tingling in the arms and legs (signs of so-called “Churg-Strauss syndrome or hypereosinophilic syndrome”).
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Development of any of the following symptoms, especially if in combination: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain (signs of serum sickness).

If you experience any of these, tell your doctor or nurse straight away.

#### Other side effects include:

Very common side effects (may affect more than 1 in 10 people)

- fever (in children)

Common side effects (may affect up to 1 in 10 people)

- reactions at the injection site including pain, swelling, itching and redness
- pain in the upper part of the tummy (in children)
- headache (very common in children)

Uncommon side effects (may affect up to 1 in 100 people)

- feeling dizzy, sleepy or tired
- tingling or numbness of the hands or feet
- fainting, low blood pressure while sitting or standing (postural hypotension), flushing
- sore throat, coughing, acute breathing problems
- feeling sick (nausea), diarrhoea, indigestion
- itching, hives, rash, increased sensitivity of the skin to sun
- weight increase
- flu-like symptoms
- swelling arms

Rare side effects (may affect up to 1 in 1,000 people)

- parasitic infection

Not known (frequency cannot be estimated from the available data)

- joint pain, muscle pain and joint swelling
- hair loss

#### **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

#### **5. How to store Xolair**

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.
- Store in the original package in order to protect from light.
- Store in a refrigerator (2°C – 8°C). Do not freeze.
- Do not use any pack that is damaged or shows signs of tampering.

## 6. Contents of the pack and other information

### What Xolair contains

- The active substance is omalizumab. One syringe of 0.5 ml solution contains 75 mg omalizumab.
- The other ingredients are L-arginine hydrochloride, L-histidine hydrochloride, L-histidine, Polysorbate 20 and water for injections.
- The needle cap of the syringe may contain dry rubber (latex).

### What Xolair looks like and contents of the pack

Xolair solution for injection is supplied as a clear to slightly opalescent, colourless to pale brownish-yellow solution in a pre-filled syringe.

Xolair 75 mg solution for injection is available in packs containing 1 pre-filled syringe and in multipacks comprising 4 or 10 intermediate packs, each containing 1 pre-filled syringe.

Not all pack sizes may be marketed in your country.

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**Sverige**

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**United Kingdom**

Novartis Pharmaceuticals UK Ltd.  
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**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>

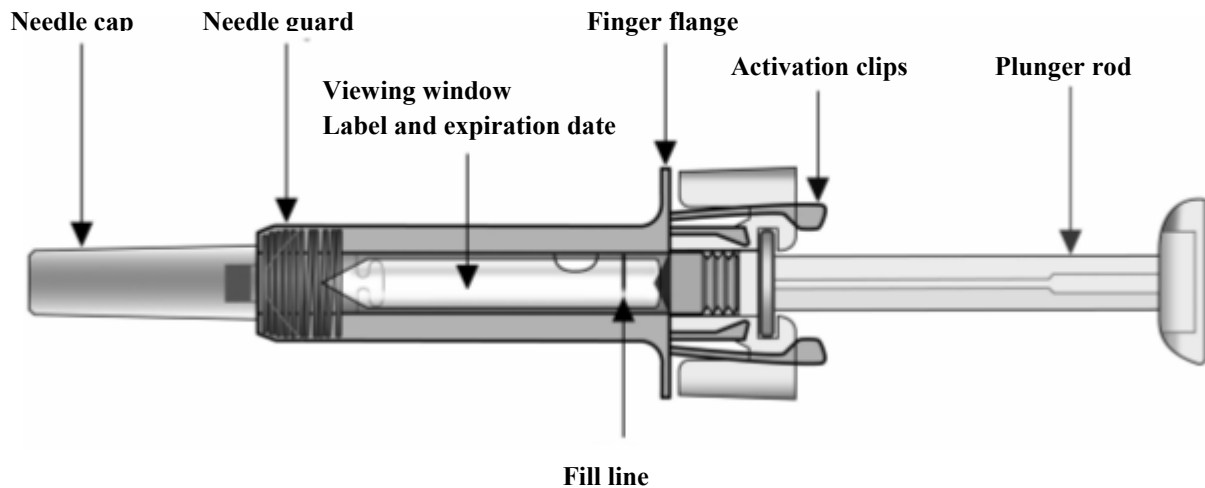
## INFORMATION FOR THE HEALTHCARE PROFESSIONAL

The following information is intended for healthcare professionals only:

Before using the syringe, please read the following information carefully.

Each Xolair pack contains a pre-filled syringe individually sealed in a plastic wrapper.

### Parts of the pre-filled syringe



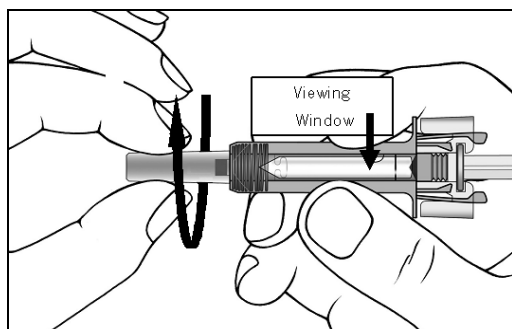
**Xolair syringes are intended to be used by a healthcare professional only.**

The needle cap of the syringe may contain dry rubber (latex), which should not be handled by persons sensitive to this substance.

### Preparing the syringe for use

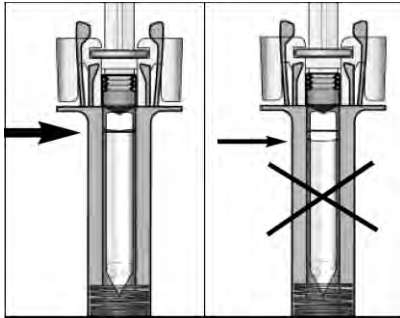
Prior to completion of the injection, avoid contact with the device activation clips (see first illustration) to keep from prematurely covering the needle with the needle guard.

1. Take the box containing the syringe out of the refrigerator and leave it for about 20 minutes so that it reaches room temperature (leave the syringe in the box to protect it from light).
2. If necessary, the syringe can be returned to the refrigerator for use at a later time, but this must not be done more than once. The cumulative time during which the syringe is kept at room temperature (25°C) must not exceed 4 hours.
3. When you are ready to use the syringe, wash your hands thoroughly with soap and water.
4. Clean the injection site.
5. Remove the plastic tray from the box, peel back the paper cover, and remove the syringe.
6. Inspect the syringe. **DO NOT USE** if it is broken or if the liquid looks cloudy or contains particles. In all these cases, return the entire pack to the pharmacy.
7. Holding the syringe horizontally (as shown below), look into the viewing window to check the dose (75 mg) of medicine and the expiry date printed on the label. Note: Rotate the inner part of the syringe assembly as shown below so that the label can be read in the viewing window.



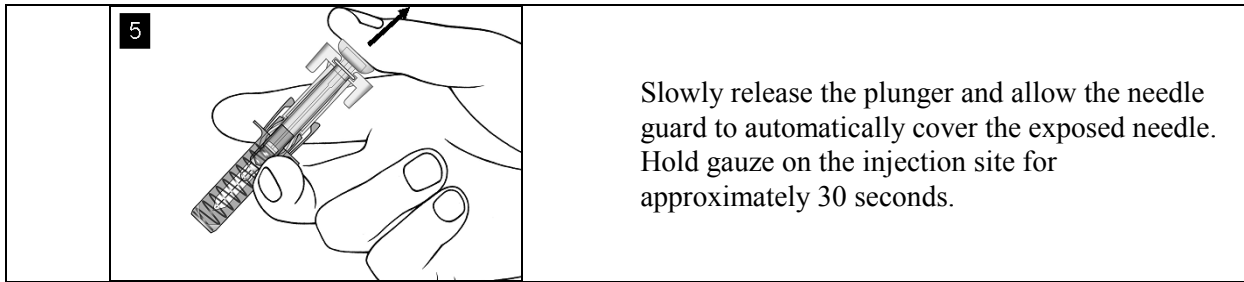
**DO NOT USE** if the product has expired or if the dose is incorrect. In both these cases, return the entire pack to the pharmacy.

8. Hold the syringe vertically with the plunger uppermost and tap the side of the syringe against your finger to allow the air bubble to rise.
9. Check to see if the liquid level is at or above the minimum fill line. If the liquid is below the fill line, return the entire pack to the pharmacy.



### Using the syringe

|  |  |
|--|--|
|  | <p>Holding the syringe with the needle pointing upwards, carefully pull off the needle cap from the syringe and discard it. Do not touch the exposed needle. Then, gently tap the syringe with your finger until the air bubble rises to the top of the syringe. Slowly push the plunger up to force the air bubble out of the syringe without inadvertently expelling solution.</p> |
|  | <p>Gently pinch the skin at the injection site and insert the needle.</p>  |
|  | <p>Holding onto the finger flange, slowly depress the plunger as far as it will go. If any solution leaks from the injection site, insert the needle further.</p>  |
|  | <p>Keeping the plunger fully depressed, carefully lift the needle straight out from the injection site.</p>  |



**Disposal instructions**

Dispose of the used syringe immediately in a sharps container. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## Package leaflet: Information for the user

### Xolair 150 mg solution for injection omalizumab

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Xolair is and what it is used for
2. What you need to know before you are given Xolair
3. How Xolair is given
4. Possible side effects
5. How to store Xolair
6. Contents of the pack and other information

#### **1. What Xolair is and what it is used for**

Xolair is used for the treatment of allergic asthma and chronic spontaneous urticaria (CSU). The active substance of Xolair is omalizumab. Omalizumab is a man-made protein that is similar to natural proteins produced by the body; it belongs to a class of medicines called monoclonal antibodies. Xolair works by blocking a substance called immunoglobulin E (IgE), which is produced by the body. IgE plays a key role in causing allergic asthma or CSU.

##### Allergic asthma

This medicine is used to prevent asthma from getting worse by controlling symptoms of severe allergic asthma in adults and adolescents (12 years of age and older) and children (6 to less than 12 years of age) who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high-dose steroid inhalers or beta-agonist inhalers.

##### Chronic spontaneous urticaria (CSU)

This medicine is used to treat chronic spontaneous urticaria in adults and adolescents (12 years of age or older) who are already receiving antihistamines but whose CSU symptoms are not well controlled by these medicines.

#### **2. What you need to know before you are given Xolair**

##### **You should not be given Xolair**

- if you are allergic to omalizumab or any of the other ingredients of this medicine (listed in section 6).

If you think you may be allergic to any of the ingredients, tell your doctor as you should not be given Xolair.

##### **Warnings and precautions**

Xolair contains a protein, and proteins can cause serious allergic reactions in some people. Signs include rash, difficulty in breathing, swelling or feeling faint. If you have an allergic reaction after taking Xolair, contact a doctor as soon as you can.



A certain type of allergic reaction called serum sickness has been observed in patients treated with Xolair. The symptoms of serum sickness can be one or more of the following symptoms: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain. If you experience any of these symptoms, or in particular if you experience a combination of such symptoms, contact your doctor immediately.

Take special care with Xolair if you have ever had an allergic reaction to latex (the needle cap of the syringe may contain dry rubber (latex)).

Churg-Strauss and Hypereosinophilic syndrome have been observed in allergic asthma patients treated with Xolair. The symptoms may include one or more of the following: swelling, pain or rash around blood or lymph vessels, high level of a specific type of white blood cells (marked eosinophilia), worsening problems with breathing, nasal congestion, heart problems, pain, numbness, tingling in the arm and legs. If you experience any of these symptoms, or in particular if you experience a combination of such symptoms, contact your doctor immediately.

Talk to your doctor before you are given Xolair:

- If you have kidney or liver problems.
- If you have a disorder where your own immune system attacks parts of your own body (autoimmune disease).
- If you live in a region where infections caused by parasites are common or if you are travelling to such a region as Xolair may weaken your resistance to such infections.

Xolair does not treat acute asthma symptoms, such as a sudden asthma attack. Therefore Xolair should not be used to treat such symptoms.

Xolair is not meant to prevent or treat other allergy-type conditions, such as sudden allergic reactions, hyperimmunoglobulin E syndrome (an inherited immune disorder), aspergillosis (a fungus-related lung disease), food allergy, eczema or hay fever because Xolair has not been studied in these conditions.

### **Children and adolescents**

#### Allergic asthma

Xolair is not recommended for children under 6 years of age.

#### Chronic spontaneous urticaria (CSU)

Do not give Xolair to children under 12 years of age. Its use in children under 12 has not been studied.

### **Other medicines and Xolair**

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

This is especially important if you are taking:

- medicines to treat an infection caused by a parasite, as Xolair may reduce the effect of your medicines,
- inhaled corticosteroids and other medicines for allergic asthma.

### **Pregnancy and breast-feeding**

You should not be given Xolair when you are pregnant, unless this is considered necessary by your doctor.

If you plan to become pregnant, tell your doctor before starting treatment with Xolair. Your doctor will discuss with you the benefits and potential risks of being given this medicine during pregnancy.

If you become pregnant while being treated with Xolair, tell your doctor immediately.

You should not be given Xolair when you are breast-feeding.

### **Driving and using machines**

It is unlikely that Xolair will affect your ability to drive and use machines.

## **3. How Xolair is given**

Instructions on how to use Xolair are given in the section “Information for the healthcare professional”.

Xolair is given to you by a doctor or nurse as an injection just under the skin (subcutaneously).

Follow carefully all instructions given by your doctor or nurse.

### **How much you will be given**

#### Allergic asthma

Your doctor will work out how much Xolair you need and how often you will be given it. This depends on your body weight and the results of a blood test carried out before the start of the treatment to measure the amount of IgE in your blood.

You will be given 1 to 4 injections at a time, either every two weeks, or every four weeks.

Carry on taking your current asthma medicine during Xolair treatment. Do not stop taking any asthma medicines without talking to your doctor.

You may not see an immediate improvement in your asthma after beginning Xolair therapy. It usually takes between 12 and 16 weeks to have the full effect.

#### Chronic spontaneous urticaria (CSU)

You will be given two 150 mg injections at a time every four weeks.

Continue taking your current medicine for CSU during Xolair treatment. Do not stop taking any medicine without talking to your doctor first.

### **Use in children and adolescents**

#### Allergic asthma

Xolair can be given to children and adolescents aged 6 years or older, who are already receiving asthma medicine, but whose asthma symptoms are not well controlled by medicines such as high dose steroid inhalers or beta-agonist inhalers. Your doctor will work out how much Xolair your child needs and how often it needs to be given. This will depend on your child’s weight and the results of a blood test carried out before the start of the treatment to measure the amount of IgE in his/her blood.

#### Chronic spontaneous urticaria (CSU)

Xolair can be given to adolescents aged 12 years or older, who are already receiving antihistamines but whose CSU symptoms are not well controlled by these medicines.

**If a dose of Xolair is missed**

Contact your doctor or hospital as soon as possible to re-schedule your appointment.

**If you stop treatment with Xolair**

Do not stop treatment with Xolair unless your doctor tells you to. Interrupting or stopping the treatment with Xolair may cause your asthma or CSU symptoms to come back.

However, if you are being treated for CSU, your doctor may stop Xolair treatment from time to time so that your symptoms can be assessed. Follow your doctor's instructions.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

**4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them. The side effects caused by Xolair are usually mild to moderate but can occasionally be serious.

Serious side effects include:

Rare side effects (may affect up to 1 in 1,000 people)

- Sudden severe allergic reactions: if you notice any serious sudden signs of allergy or combination of signs such as rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heart beat, dizziness and light-headedness, shortness of breath, wheezing or trouble breathing, or any other new symptoms, tell your doctor or nurse immediately. If you have a history of severe allergic reactions (anaphylaxis) unrelated to Xolair you may be more at risk of developing a severe allergic reaction following use of Xolair.
- Systemic lupus erythematosus (SLE). Symptoms may include muscle pain, joint pain and swelling, and rash. You may also experience other signs such as fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)

- Development of one or more of the following symptoms: swelling, pain or rash around blood or lymph vessels, high level of a specific type of white blood cells (marked eosinophilia), worsening problems with breathing, nasal congestion, heart problems, pain, numbness, tingling in the arms and legs (signs of so-called "Churg-Strauss syndrome or hypereosinophilic syndrome").
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Development of any of the following symptoms, especially if in combination: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain (signs of serum sickness).

If you experience any of these, tell your doctor or nurse straight away.

Other side effects include:

Very common side effects (may affect more than 1 in 10 people)

- fever (in children)

Common side effects (may affect up to 1 in 10 people)

- reactions at the injection site including pain, swelling, itching and redness
- pain in the upper part of the tummy (in children)
- headache (very common in children)
- upper respiratory tract infection, such as inflammation of the pharynx and common cold
- feeling of pressure or pain in the cheeks and forehead (sinusitis, sinus headache)
- pain in joints (arthralgia)

Uncommon side effects (may affect up to 1 in 100 people)

- feeling dizzy, sleepy or tired
- tingling or numbness of the hands or feet
- fainting, low blood pressure while sitting or standing (postural hypotension), flushing
- sore throat, coughing, acute breathing problems
- feeling sick (nausea), diarrhoea, indigestion
- itching, hives, rash, increased sensitivity of the skin to sun
- weight increase
- flu-like symptoms
- swelling arms

Rare side effects (may affect up to 1 in 1,000 people)

- parasitic infection

Not known (frequency cannot be estimated from the available data)

- muscle pain and joint swelling
- hair loss

### **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Xolair**

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.
- Store in the original package in order to protect from light.
- Store in a refrigerator (2°C – 8°C). Do not freeze.
- Do not use any pack that is damaged or shows signs of tampering.

## **6. Contents of the pack and other information**

### **What Xolair contains**

- The active substance is omalizumab. One syringe of 1 ml solution contains 150 mg omalizumab.
- The other ingredients are L-arginine hydrochloride, L-histidine hydrochloride, L-histidine, Polysorbate 20 and water for injections.
- The needle cap of the syringe may contain dry rubber (latex).

### **What Xolair looks like and contents of the pack**

Xolair solution for injection is supplied as a clear to slightly opalescent, colourless to pale brownish-yellow solution in a pre-filled syringe.

Xolair 150 mg solution for injection is available in packs containing 1 pre-filled syringe and in multipacks comprising 4 or 10 intermediate packs, each containing 1 pre-filled syringe.

Not all pack sizes may be marketed in your country.

**Marketing Authorisation Holder**

Novartis Europharm Limited  
Frimley Business Park  
Camberley GU16 7SR  
United Kingdom

**Manufacturer**

Novartis Pharma GmbH  
Roonstrasse 25  
D-90429 Nuremberg  
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**Other sources of information**

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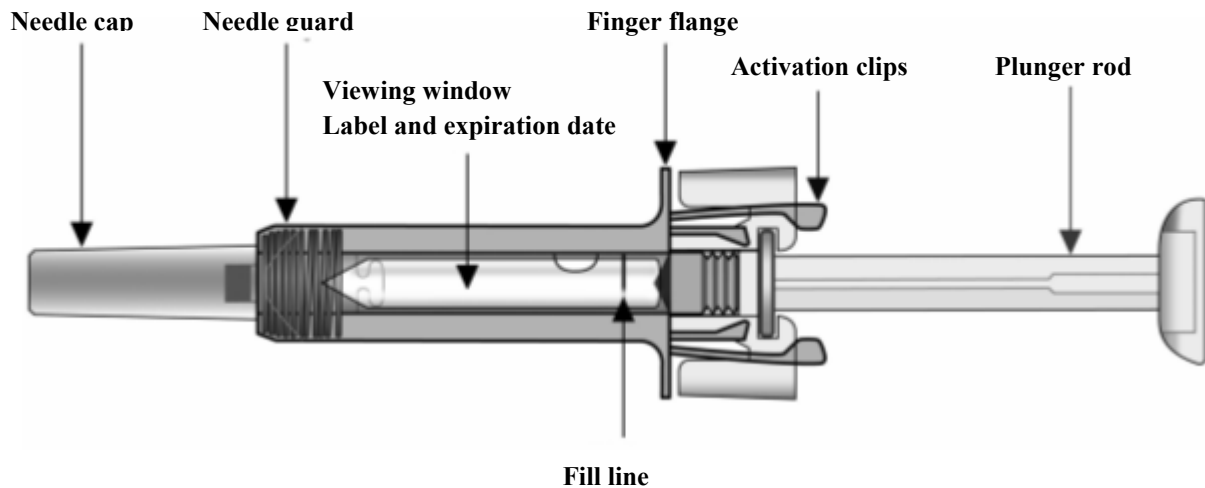
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### Parts of the pre-filled syringe



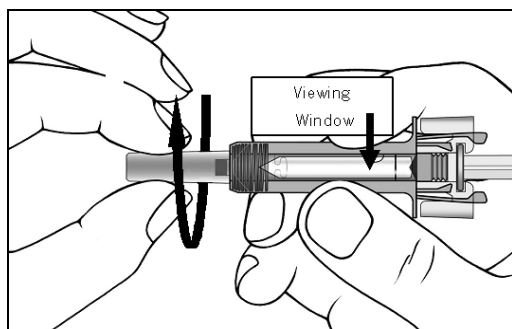
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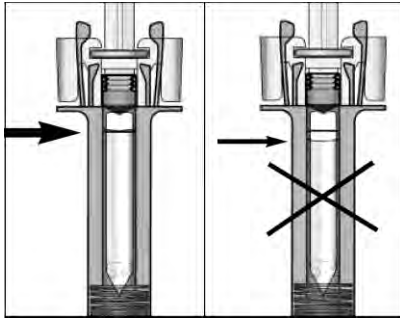
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1. Take the box containing the syringe out of the refrigerator and leave it for about 20 minutes so that it reaches room temperature (leave the syringe in the box to protect it from light).
2. If necessary, the syringe can be returned to the refrigerator for use at a later time, but this must not be done more than once. The cumulative time during which the syringe is kept at room temperature (25°C) must not exceed 4 hours.
3. When you are ready to use the syringe, wash your hands thoroughly with soap and water.
4. Clean the injection site.
5. Remove the plastic tray from the box, peel back the paper cover, and remove the syringe.
6. Inspect the syringe. **DO NOT USE** if it is broken or if the liquid looks cloudy or contains particles. In all these cases, return the entire pack to the pharmacy.
7. Holding the syringe horizontally (as shown below), look into the viewing window to check the dose (150 mg) of medicine and the expiry date printed on the label. Note: Rotate the inner part of the syringe assembly as shown below so that the label can be read in the viewing window.



**DO NOT USE** if the product has expired or if the dose is incorrect. In both these cases, return the entire pack to the pharmacy.

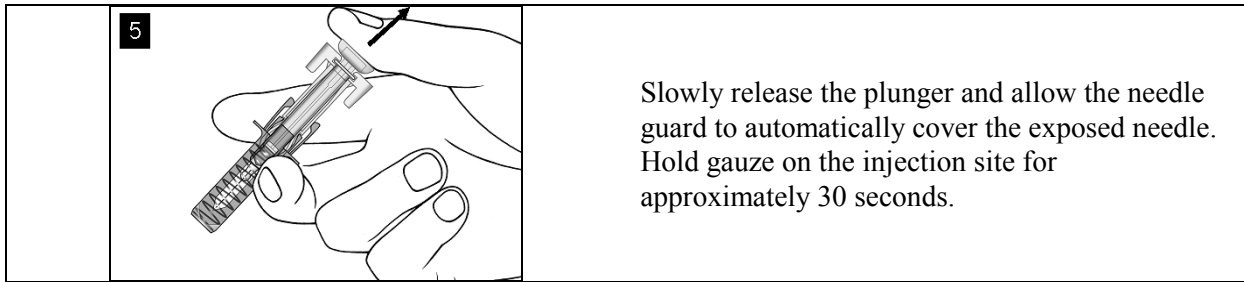
8. Hold the syringe vertically with the plunger uppermost and tap the side of the syringe against your finger to allow the air bubble to rise.
9. Check to see if the liquid level is at or above the minimum fill line. If the liquid is below the fill line, return the entire pack to the pharmacy.



### Using the syringe

|  |  |
|--|--|
|  | <p>Holding the syringe with the needle pointing upwards, carefully pull off the needle cap from the syringe and discard it. Do not touch the exposed needle. Then, gently tap the syringe with your finger until the air bubble rises to the top of the syringe. Slowly push the plunger up to force the air bubble out of the syringe without inadvertently expelling solution.</p> |
|  | <p>Gently pinch the skin at the injection site and insert the needle.</p>  |
|  | <p>Holding onto the finger flange, slowly depress the plunger as far as it will go. If any solution leaks from the injection site, insert the needle further.</p>  |
|  | <p>Keeping the plunger fully depressed, carefully lift the needle straight out from the injection site.</p>  |





**Disposal instructions**

Dispose of the used syringe immediately in a sharps container. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**ANNEX IV**

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS  
OF THE MARKETING AUTHORISATION(S)**

## **Scientific conclusions**

Taking into account the PRAC Assessment Report on the PSUR(s) for omalizumab, the scientific conclusions of CHMP are as follows:

Cases of systemic lupus erythematosus (SLE) in relation to Xolair treatment, including two cases with positive dechallenge and one case with positive dechallenge /rechallenged, were reported. Although in the majority of cases the information was too limited to allow a causality assessment, confounding factors such as pre-existing lupus, including potential incipient SLE, were present in many of the remaining cases and the pathogenesis of SLE/drug-induced lupus is still poorly understood and probably multifactorial, it does not appear unreasonable that Xolair, a drug that forms immune complexes with IgE with the potential to induce immune complex injury and for which events such as serum sickness have been rarely reported, could play a role in the pathogenesis of SLE/drug-induced lupus. After a thorough assessment of the available data, there appears to be reasonable support for the possibility of a causal relationship between Xolair and systemic lupus erythematosus.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to the product information of medicinal products containing omalizumab were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

## **Grounds for the variation to the terms of the marketing authorisation(s)**

On the basis of the scientific conclusions for omalizumab the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing omalizumab is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XOLAIR safely and effectively. See full prescribing information for XOLAIR.

XOLAIR® (omalizumab) for injection, for subcutaneous use  
Initial U.S. Approval: 2003

### WARNING: ANAPHYLAXIS

See full prescribing information for complete boxed warning.

Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of Xolair. Anaphylaxis has occurred after the first dose of Xolair but also has occurred beyond 1 year after beginning treatment. Closely observe patients for an appropriate period of time after Xolair administration and be prepared to manage anaphylaxis that can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and have them seek immediate medical care should symptoms occur. (5.1)

### RECENT MAJOR CHANGES

|                                 |         |
|---------------------------------|---------|
| Indications and Usage (1.1)     | 07/2016 |
| Dosage and Administration (2.1) | 07/2016 |
| Warnings and Precautions (5.1)  | 12/2015 |

### INDICATIONS AND USAGE

Xolair is an anti-IgE antibody indicated for:

- Moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids (1.1)
- Chronic idiopathic urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment (1.2)

Limitations of use:

- Not indicated for other allergic conditions or other forms of urticaria. (1.1, 1.2.)
- Not indicated for acute bronchospasm or status asthmaticus. (1.1, 5.3)

### DOSAGE AND ADMINISTRATION

For subcutaneous (SC) administration only. (2.1, 2.2)

Divide doses of more than 150 mg among more than one injection site to limit injections to not more than 150 mg per site. (2.4)

- Asthma:** Xolair 75 to 375 mg SC every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See the dose determination charts. (2.1)

- Chronic Idiopathic Urticaria:** Xolair 150 or 300 mg SC every 4 weeks. Dosing in CIU is not dependent on serum IgE level or body weight. (2.2)

### DOSAGE FORMS AND STRENGTHS

For injection: Lyophilized, sterile powder in a single-use 5mL vial, 150 mg. (3)

### CONTRAINDICATIONS

Severe hypersensitivity reaction to Xolair or any ingredient of Xolair. (4, 5.1)

### WARNINGS AND PRECAUTIONS

- Anaphylaxis:** Administer only in a healthcare setting prepared to manage anaphylaxis that can be life-threatening and observe patients for an appropriate period of time after administration. (5.1)
- Malignancy:** Malignancies have been observed in clinical studies. (5.2)
- Acute Asthma Symptoms:** Do not use for the treatment of acute bronchospasm or status asthmaticus. (5.3)
- Corticosteroid Reduction:** Do not abruptly discontinue corticosteroids upon initiation of Xolair therapy. (5.4)
- Fever, Arthralgia, and Rash:** Stop Xolair if patients develop signs and symptoms similar to serum sickness. (5.6)
- Eosinophilic Conditions:** Be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy, especially upon reduction of oral corticosteroids. (5.5)

### ADVERSE REACTIONS

- Asthma:** The most common adverse reactions in clinical studies with adult and adolescent patients  $\geq 12$  years of age were arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. In clinical studies with pediatric patients 6 to  $<12$  years of age, the most common adverse reactions were nasopharyngitis, headache, pyrexia, upper abdominal pain, pharyngitis streptococcal, otitis media, viral gastroenteritis, arthropod bites, and epistaxis. (6.1)
- Chronic Idiopathic Urticaria:** The most common adverse reactions ( $\geq 2\%$  Xolair-treated patients and more frequent than in placebo) included the following: nausea, nasopharyngitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection, arthralgia, headache, and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

No formal drug interaction studies have been performed. (7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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## FULL PRESCRIBING INFORMATION

### WARNING: ANAPHYLAXIS

**Anaphylaxis presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of Xolair. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, observe patients closely for an appropriate period of time after Xolair administration. Health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and instruct them to seek immediate medical care should symptoms occur [see *Warnings and Precautions (5.1) and Adverse Reactions (6.1, 6.3)*].**

## 1 INDICATIONS AND USAGE

### 1.1 Asthma

Xolair is indicated for patients 6 years of age and older with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.

Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.

#### Limitations of Use:

- Xolair is not indicated for the relief of acute bronchospasm or status asthmaticus.
- Xolair is not indicated for treatment of other allergic conditions.

### 1.2 Chronic Idiopathic Urticaria (CIU)

Xolair is indicated for the treatment of adults and adolescents 12 years of age and older with chronic idiopathic urticaria who remain symptomatic despite H1 antihistamine treatment.

#### Limitation of Use:

Xolair is not indicated for treatment of other forms of urticaria.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosage for Asthma

Administer Xolair 75 to 375 mg by subcutaneous injection every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL) measured before the start of treatment, and by body weight (kg).

Adjust doses for significant changes in body weight during treatment (see Table 1, 2 and 3).

Total IgE levels are elevated during treatment and remain elevated for up to one year after the discontinuation of treatment. Therefore, re-testing of IgE levels during Xolair treatment cannot be used as a guide for dose determination.

- Interruptions lasting less than one year: Dose based on serum IgE levels obtained at the initial dose determination.
- Interruptions lasting one year or more: Re-test total serum IgE levels for dose determination using Table 1, 2, or 3 based on the patient’s age.

Periodically reassess the need for continued therapy based upon the patient’s disease severity and level of asthma control.

Adult and adolescent patients 12 years of age and older: Initiate dosing according to Table 1 or 2.

**Table 1. Subcutaneous Xolair Doses Every 4 Weeks for Patients 12 Years of Age and Older with Asthma**

| Pre-treatment Serum IgE | Body Weight |            |            |                    |
|-------------------------|-------------|------------|------------|--------------------|
|                         | 30–60 kg    | > 60–70 kg | > 70–90 kg | > 90–150 kg        |
| ≥ 30–100 IU/mL          | 150 mg      | 150 mg     | 150 mg     | 300 mg             |
| > 100–200 IU/mL         | 300 mg      | 300 mg     | 300 mg     | <b>SEE TABLE 2</b> |
| > 200–300 IU/mL         | 300 mg      |            |            |                    |
| > 300–400 IU/mL         |             |            |            |                    |
| > 400–500 IU/mL         |             |            |            |                    |
| > 500–600 IU/mL         |             |            |            |                    |

**Table 2. Subcutaneous Xolair Doses Every 2 Weeks for Patients 12 Years of Age and Older with Asthma**

| Pre-treatment Serum IgE | Body Weight        |            |            |                    |
|-------------------------|--------------------|------------|------------|--------------------|
|                         | 30–60 kg           | > 60–70 kg | > 70–90 kg | > 90–150 kg        |
| ≥ 30–100 IU/mL          | <b>SEE TABLE 1</b> |            |            |                    |
| > 100–200 IU/mL         |                    |            |            | 225 mg             |
| > 200–300 IU/mL         |                    | 225 mg     | 225 mg     | 300 mg             |
| > 300–400 IU/mL         | 225 mg             | 225 mg     | 300 mg     | <b>DO NOT DOSE</b> |
| > 400–500 IU/mL         | 300 mg             | 300 mg     | 375mg      |                    |
| > 500–600 IU/mL         | 300 mg             | 375 mg     |            |                    |
| > 600–700 IU/mL         | 375 mg             |            |            |                    |

Pediatric patients 6 to <12 years of age: Initiate dosing according to Table 3.

**Table 3. Subcutaneous Xolair Doses Every 2 or 4 Weeks\* for Pediatric Patients with Asthma Who Begin Xolair Between the Ages of 6 to <12 Years**

| Pre-treatment Serum IgE (IU/mL) | Dosing Freq.  | Body Weight |           |           |           |           |           |           |           |            |             |
|---------------------------------|---------------|-------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|------------|-------------|
|                                 |               | 20-25 kg    | >25-30 kg | >30-40 kg | >40-50 kg | >50-60 kg | >60-70 kg | >70-80 kg | >80-90 kg | >90-125 kg | >125-150 kg |
|                                 |               | Dose (mg)   |           |           |           |           |           |           |           |            |             |
| 30-100                          | Every 4 weeks | 75          | 75        | 75        | 150       | 150       | 150       | 150       | 150       | 300        | 300         |
| >100-200                        |               | 150         | 150       | 150       | 300       | 300       | 300       | 300       | 300       | 225        | 300         |
| >200-300                        |               | 150         | 150       | 225       | 300       | 300       | 225       | 225       | 225       | 300        | 375         |
| >300-400                        |               | 225         | 225       | 300       | 225       | 225       | 225       | 300       | 300       |            |             |
| >400-500                        |               | 225         | 300       | 225       | 225       | 300       | 300       | 375       | 375       |            |             |
| >500-600                        |               | 300         | 300       | 225       | 300       | 300       | 375       |           |           |            |             |
| >600-700                        |               | 300         | 225       | 225       | 300       | 375       |           |           |           |            |             |
| >700-800                        | Every 2 weeks | 225         | 225       | 300       | 375       |           |           |           |           |            |             |
| >800-900                        |               | 225         | 225       | 300       | 375       |           |           |           |           |            |             |
| >900-1000                       |               | 225         | 300       | 375       |           |           |           |           |           |            |             |
| >1000-1100                      |               | 225         | 300       | 375       |           |           |           |           |           |            |             |
| >1100-1200                      |               | 300         | 300       |           |           |           |           |           |           |            |             |
| >1200-1300                      | 300           | 375         |           |           |           |           |           |           |           |            |             |

\*Dosing frequency:

|                                     |   |
|-------------------------------------|---|
| <input checked="" type="checkbox"/> | Subcutaneous doses to be administered every 4 weeks |
| <input type="checkbox"/>            | Subcutaneous doses to be administered every 2 weeks |

## 2.2 Dosage for Chronic Idiopathic Urticaria

Administer Xolair 150 or 300 mg by subcutaneous injection every 4 weeks.

Dosing of Xolair in CIU patients is not dependent on serum IgE (free or total) level or body weight.

The appropriate duration of therapy for CIU has not been evaluated. Periodically reassess the need for continued therapy.

## 2.3 Reconstitution

The supplied Xolair lyophilized powder must be reconstituted with Sterile Water for Injection (SWFI) USP, using the following instructions:

- 1) Before reconstitution, determine the number of vials that will need to be reconstituted (each vial delivers 150 mg of Xolair in 1.2 mL) (see Table 4).

- 2) Draw 1.4 mL of SWFI, USP, into a 3 mL syringe equipped with a 1 inch, 18-gauge needle.
- 3) Place the vial upright on a flat surface and using standard aseptic technique, insert the needle and inject the SWFI, USP, directly onto the product.
- 4) Keeping the vial upright, gently swirl the upright vial for approximately 1 minute to evenly wet the powder. Do not shake.
- 5) Gently swirl the vial for 5 to 10 seconds approximately every 5 minutes in order to dissolve any remaining solids. **The lyophilized product takes 15 to 20 minutes to dissolve.** If it takes longer than 20 minutes to dissolve completely, gently swirl the vial for 5 to 10 seconds approximately every 5 minutes until there are no visible gel-like particles in the solution. Do not use if the contents of the vial do not dissolve completely by 40 minutes.
- 6) After reconstitution, Xolair solution is somewhat viscous and will appear clear or slightly opalescent. It is acceptable if there are a few small bubbles or foam around the edge of the vial; there should be no visible gel-like particles in the reconstituted solution. Do not use if foreign particles are present.
- 7) Invert the vial for 15 seconds in order to allow the solution to drain toward the stopper.
- 8) **Use the Xolair solution within 8 hours following reconstitution when stored in the vial at 2 to 8°C (36 to 46°F), or within 4 hours of reconstitution when stored at room temperature.** Reconstituted Xolair vials should be protected from sunlight.
- 9) Using a new 3 mL syringe equipped with a 1-inch, 18-gauge needle, insert the needle into the inverted vial. Position the needle tip at the very bottom of the solution in the vial stopper when drawing the solution into the syringe. The reconstituted product is somewhat viscous. **Withdraw all of the product** from the vial before expelling any air or excess solution from the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove all of the solution from the inverted vial.
- 10) Replace the 18-gauge needle with a 25-gauge needle for subcutaneous injection.
- 11) Expel air, large bubbles, and any excess solution in order to obtain a volume of 1.2 mL corresponding to a dose of 150 mg of Xolair. To obtain a volume of 0.6 mL corresponding to a dose of 75 mg of Xolair, expel air, large bubbles and discard 0.6 mL from the syringe. A thin layer of small bubbles may remain at the top of the solution in the syringe.

#### **2.4 Administration**

Administer Xolair by subcutaneous injection. The injection may take 5-10 seconds to administer because the solution is slightly viscous. Do not administer more than 150 mg (contents of one vial) per injection site. Divide doses of more than 150 mg among two or more injection sites (Table 4).



**Table 4. Number of Vials, Injections and Total Injection Volumes**

| Xolair Dose* | Number of vials | Number of Injections | Total Volume Injected |
|--------------|-----------------|----------------------|-----------------------|
| 75 mg        | 1               | 1                    | 0.6 mL                |
| 150 mg       | 1               | 1                    | 1.2 mL                |
| 225 mg       | 2               | 2                    | 1.8 mL                |
| 300 mg       | 2               | 2                    | 2.4 mL                |
| 375mg        | 3               | 3                    | 3.0 mL                |

\*All doses in the table are approved for use in asthma patients. The 150 mg and 300 mg Xolair doses are intended for use in CIU patients.

### **3 DOSAGE FORMS AND STRENGTHS**

For injection: 150 mg of omalizumab as lyophilized, sterile powder in a single-use 5 mL vial.

### **4 CONTRAINDICATIONS**

The use of Xolair is contraindicated in the following:

Severe hypersensitivity reaction to Xolair or any ingredient of Xolair [*see Warnings and Precautions (5.1)*].

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Anaphylaxis**

Anaphylaxis has been reported to occur after administration of Xolair in premarketing clinical trials and in postmarketing spontaneous reports [*see Boxed Warning and Adverse Reactions (6.3)*]. Signs and symptoms in these reported cases have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some of these events have been life-threatening. In premarketing clinical trials in patients with asthma, anaphylaxis was reported in 3 of 3507 (0.1%) patients. Anaphylaxis occurred with the first dose of Xolair in two patients and with the fourth dose in one patient. The time to onset of anaphylaxis was 90 minutes after administration in two patients and 2 hours after administration in one patient.

A case-control study showed that, among Xolair users, patients with a history of anaphylaxis to foods, medications, or other causes were at increased risk of anaphylaxis associated with Xolair, compared to those with no prior history of anaphylaxis [*see Adverse Reactions (6.1)*].

In postmarketing spontaneous reports, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2% of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond one year after beginning regularly scheduled treatment.

Administer Xolair only in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening. Observe patients closely for an appropriate period

of time after administration of Xolair, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials and postmarketing spontaneous reports [see Adverse Reactions (6)]. Inform patients of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs or symptoms occur.

Discontinue Xolair in patients who experience a severe hypersensitivity reaction [see *Contraindications* (4)].

## **5.2 Malignancy**

Malignant neoplasms were observed in 20 of 4127 (0.5%) Xolair-treated patients compared with 5 of 2236 (0.2%) control patients in clinical studies of adults and adolescents  $\geq$  12 years of age with asthma and other allergic disorders. The observed malignancies in Xolair-treated patients were a variety of types, with breast, non-melanoma skin, prostate, melanoma, and parotid occurring more than once, and five other types occurring once each. The majority of patients were observed for less than 1 year. The impact of longer exposure to Xolair or use in patients at higher risk for malignancy (e.g., elderly, current smokers) is not known.

In a subsequent observational study of 5007 Xolair-treated and 2829 non-Xolair-treated adolescent and adult patients with moderate to severe persistent asthma and a positive skin test reaction or in vitro reactivity to a perennial aeroallergen, patients were followed for up to 5 years. In this study, the incidence rates of primary malignancies (per 1000 patient years) were similar among Xolair-treated (12.3) and non-Xolair-treated patients (13.0) [see *Adverse Reactions* (6)]. However, study limitations preclude definitively ruling out a malignancy risk with Xolair. Study limitations include: the observational study design, the bias introduced by allowing enrollment of patients previously exposed to Xolair (88%), enrollment of patients (56%) while a history of cancer or a premalignant condition were study exclusion criteria, and the high study discontinuation rate (44%).

## **5.3 Acute Asthma Symptoms**

Xolair has not been shown to alleviate asthma exacerbations acutely. Do not use Xolair to treat acute bronchospasm or status asthmaticus.

## **5.4 Corticosteroid Reduction**

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of Xolair therapy for asthma. Decrease corticosteroids gradually under the direct supervision of a physician. In CIU patients, the use of Xolair in combination with corticosteroids has not been evaluated.

## **5.5 Eosinophilic Conditions**

In rare cases, patients with asthma on therapy with Xolair may present with serious systemic eosinophilia sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients.

A causal association between Xolair and these underlying conditions has not been established.

### **5.6 Fever, Arthralgia, and Rash**

In post-approval use, some patients have experienced a constellation of signs and symptoms including arthritis/arthralgia, rash, fever and lymphadenopathy with an onset 1 to 5 days after the first or subsequent injections of Xolair. These signs and symptoms have recurred after additional doses in some patients. Although circulating immune complexes or a skin biopsy consistent with a Type III reaction were not seen with these cases, these signs and symptoms are similar to those seen in patients with serum sickness. Physicians should stop Xolair if a patient develops this constellation of signs and symptoms [*see Adverse Reactions (6.3)*].

### **5.7 Parasitic (Helminth) Infection**

Monitor patients at high risk of geohelminth infection while on Xolair therapy. Insufficient data are available to determine the length of monitoring required for geohelminth infections after stopping Xolair treatment.

In a one-year clinical trial conducted in Brazil in adult and adolescent patients at high risk for geohelminthic infections (roundworm, hookworm, whipworm, threadworm), 53% (36/68) of Xolair-treated patients experienced an infection, as diagnosed by standard stool examination, compared to 42% (29/69) of placebo controls. The point estimate of the odds ratio for infection was 1.96, with a 95% confidence interval (0.88, 4.36) indicating that in this study a patient who had an infection was anywhere from 0.88 to 4.36 times as likely to have received Xolair than a patient who did not have an infection. Response to appropriate anti-geohelminth treatment of infection as measured by stool egg counts was not different between treatment groups.

### **5.8 Laboratory Tests**

Serum total IgE levels increase following administration of Xolair due to formation of Xolair:IgE complexes [*see Clinical Pharmacology (12.2)*]. Elevated serum total IgE levels may persist for up to 1 year following discontinuation of Xolair. Do not use serum total IgE levels obtained less than 1 year following discontinuation to reassess the dosing regimen for asthma patients, because these levels may not reflect steady state free IgE levels [*see Dosage and Administration (2.1)*].

## **6 ADVERSE REACTIONS**

Use of Xolair has been associated with:

- Anaphylaxis [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Malignancies [*see Warnings and Precautions (5.2)*]

### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions from Clinical Studies in Adult and Adolescent Patients 12 Years of Age and Older with Asthma

The data described below reflect Xolair exposure for 2076 adult and adolescent patients ages 12 and older, including 1687 patients exposed for six months and 555 exposed for one year or more, in either placebo-controlled or other controlled asthma studies. The mean age of patients receiving Xolair was 42 years, with 134 patients 65 years of age or older; 60% were women, and 85% Caucasian. Patients received Xolair 150 to 375 mg every 2 or 4 weeks or, for patients assigned to control groups, standard therapy with or without a placebo.

The adverse events most frequently resulting in clinical intervention (e.g., discontinuation of Xolair, or the need for concomitant medication to treat an adverse event) were injection site reaction (45%), viral infections (23%), upper respiratory tract infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%). These events were observed at similar rates in Xolair-treated patients and control patients.

Table 5 shows adverse reactions from four placebo-controlled asthma trials that occurred  $\geq 1\%$  and more frequently in adult and adolescent patients 12 years of age and older receiving Xolair than in those receiving placebo. Adverse events were classified using preferred terms from the International Medical Nomenclature (IMN) dictionary. Injection site reactions were recorded separately from the reporting of other adverse events.

**Table 5. Adverse Reactions  $\geq 1\%$  More Frequent in Xolair-Treated Adult or Adolescent Patients 12 years of Age and Older in Four Placebo-controlled Asthma Trials**

| Adverse reaction              | Xolair<br>n=738 | Placebo<br>n=717 |
|-------------------------------|-----------------|------------------|
| <u>Body as a whole</u>        |                 |                  |
| Pain                          | 7%              | 5%               |
| Fatigue                       | 3%              | 2%               |
| <u>Musculoskeletal system</u> |                 |                  |
| Arthralgia                    | 8%              | 6%               |
| Fracture                      | 2%              | 1%               |
| Leg pain                      | 4%              | 2%               |
| Arm pain                      | 2%              | 1%               |
| <u>Nervous system</u>         |                 |                  |
| Dizziness                     | 3%              | 2%               |
| <u>Skin and appendages</u>    |                 |                  |
| Pruritus                      | 2%              | 1%               |
| Dermatitis                    | 2%              | 1%               |
| <u>Special senses</u>         |                 |                  |
| Earache                       | 2%              | 1%               |

There were no differences in the incidence of adverse reactions based on age (among patients under 65), gender or race.

#### *Anaphylaxis Case Control Study*

A retrospective case-control study investigated risk factors for anaphylaxis to Xolair among patients treated with Xolair for asthma. Cases with an adjudicated history of anaphylaxis to Xolair were compared to controls with no such history. The study found that a self-reported history of anaphylaxis to foods, medications or other causes was more common among patients with Xolair anaphylaxis (57% of 30 cases) compared to controls (23% of 88 controls) [OR 8.1, 95% CI 2.7 to 24.3]. Because this is a case control study, the study cannot provide the incidence of anaphylaxis among Xolair users. From other sources, anaphylaxis to Xolair was observed in 0.1% of patients in clinical trials and at least 0.2% of patients based upon postmarketing reports [see *Warnings and Precautions* (5.1), *Adverse Reactions* (6.3)].

#### *Injection Site Reactions*

In adults and adolescents, injection site reactions of any severity occurred at a rate of 45% in Xolair-treated patients compared with 43% in placebo-treated patients. The types of injection site reactions included: bruising, redness, warmth, burning, stinging, itching, hive formation, pain, indurations, mass, and inflammation.

Severe injection site reactions occurred more frequently in Xolair-treated patients compared with patients in the placebo group (12% versus 9%).

The majority of injection site reactions occurred within 1 hour-post injection, lasted less than 8 days, and generally decreased in frequency at subsequent dosing visits.

#### Adverse Reactions from Clinical Studies in Pediatric Patients 6 to <12 Years of Age with Asthma

The data described below reflect Xolair exposure for 926 patients 6 to < 12 years of age, including 583 patients exposed for six months and 292 exposed for one year or more, in either placebo-controlled or other controlled asthma studies. The mean age of pediatric patients receiving Xolair was 8.8 years; 69% were male, and 64% were Caucasian. Pediatric patients received Xolair 75 mg to 375 mg every 2 or 4 weeks or, for patients assigned to control groups, standard therapy with or without a placebo. No cases of malignancy were reported in patients treated with Xolair in these trials.

The most common adverse reactions occurring at  $\geq 3\%$  in the pediatric patients receiving Xolair and more frequently than in patients treated with placebo were nasopharyngitis, headache, pyrexia, upper abdominal pain, pharyngitis streptococcal, otitis media, viral gastroenteritis, arthropod bite, and epistaxis.

The adverse events most frequently resulting in clinical intervention (e.g., discontinuation of Xolair, or the need for concomitant medication to treat an adverse event) were bronchitis (0.2%), headache (0.2%) and urticaria (0.2%). These events were observed at similar rates in Xolair-treated patients and control patients.

Adverse Reactions from Clinical Studies in Patients with Chronic Idiopathic Urticaria (CIU)

The safety of Xolair for the treatment of CIU was assessed in three placebo-controlled, multiple-dose clinical trials of 12 weeks' (CIU Trial 2) and 24 weeks' duration (CIU Trials 1 and 3). In CIU Trials 1 and 2, patients received Xolair 75, 150, or 300 mg or placebo every 4 weeks in addition to their baseline level of H1 antihistamine therapy throughout the treatment period. In CIU Trial 3 patients were randomized to Xolair 300 mg or placebo every 4 weeks in addition to their baseline level of H1 antihistamine therapy. The data described below reflect Xolair exposure for 733 patients enrolled and receiving at least one dose of Xolair in the three clinical trials, including 684 patients exposed for 12 weeks and 427 exposed for 24 weeks. The mean age of patients receiving Xolair 300 mg was 43 years, 75% were women, and 89% were white. The demographic profiles for patients receiving Xolair 150 mg and 75 mg were similar.

Table 6 shows adverse reactions that occurred in  $\geq 2\%$  of patients receiving Xolair (150 or 300 mg) and more frequently than those receiving placebo. Adverse reactions are pooled from Trial 2 and the first 12 weeks of Trials 1 and 3.

**Table 6. Adverse Reactions Occurring in  $\geq 2\%$  in Xolair-Treated Patients and More Frequently than in Patients Treated with Placebo (Day 1 to Week 12) in CIU Trials**

| Adverse Reactions*                                      | CIU Trials 1, 2 and 3 Pooled |                  |                    |
|---|------------------------------|------------------|--------------------|
|   | 150mg<br>(n=175)             | 300mg<br>(n=412) | Placebo<br>(n=242) |
| <u>Gastrointestinal disorders</u>                       |                              |                  |                    |
| Nausea  | 2 (1.1%)                     | 11 (2.7%)        | 6 (2.5%)           |
| <u>Infections and infestations</u>                      |                              |                  |                    |
| Nasopharyngitis   | 16 (9.1%)                    | 27 (6.6%)        | 17 (7.0%)          |
| Sinusitis   | 2 (1.1%)                     | 20 (4.9%)        | 5 (2.1%)           |
| Upper respiratory tract infection                       | 2 (1.1%)                     | 14 (3.4%)        | 5 (2.1%)           |
| Viral upper respiratory tract infection                 | 4 (2.3%)                     | 2 (0.5%)         | (0.0%)             |
| <u>Musculoskeletal and connective tissue disorders</u>  |                              |                  |                    |
| Arthralgia  | 5 (2.9%)                     | 12 (2.9%)        | 1 (0.4%)           |
| <u>Nervous system disorders</u>                         |                              |                  |                    |
| Headache  | 21 (12.0%)                   | 25 (6.1%)        | 7 (2.9%)           |
| <u>Respiratory, thoracic, and mediastinal disorders</u> |                              |                  |                    |
| Cough   | 2 (1.1%)                     | 9 (2.2%)         | 3 (1.2%)           |

\* by MedDRA (15.1) System Organ Class and Preferred Term

Additional reactions reported during the 24 week treatment period in Trials 1 and 3 [ $\geq 2\%$  of patients receiving Xolair (150 or 300 mg) and more frequently than those receiving placebo] included: toothache, fungal infection, urinary tract infection, myalgia, pain in extremity, musculoskeletal pain, peripheral edema, pyrexia, migraine, sinus headache, anxiety, oropharyngeal pain, asthma, urticaria, and alopecia.

### *Injection Site Reactions*

Injection site reactions of any severity occurred during the studies in more Xolair-treated patients [11 patients (2.7%) at 300 mg, 1 patient (0.6%) at 150 mg] compared with 2 placebo-treated patients (0.8%). The types of injection site reactions included: swelling, erythema, pain, bruising, itching, bleeding and urticaria. None of the events resulted in study discontinuation or treatment interruption.

### Cardiovascular and Cerebrovascular Events from Clinical Studies in Patients with Asthma

A 5-year observational cohort study was conducted in patients  $\geq 12$  years of age with moderate to severe persistent asthma and a positive skin test reaction to a perennial aeroallergen to evaluate the long term safety of Xolair, including the risk of malignancy [*see Warnings and Precautions (5.2)*]. A total of 5007 Xolair-treated and 2829 non-Xolair-treated patients enrolled in the study. Similar percentages of patients in both cohorts were current (5%) or former smokers (29%). Patients had a mean age of 45 years and were followed for a mean of 3.7 years. More Xolair-treated patients were diagnosed with severe asthma (50%) compared to the non-Xolair-treated patients (23%) and 44% of patients prematurely discontinued the study. Additionally, 88% of patients in the Xolair-treated cohort had been previously exposed to Xolair for a mean of 8 months.

A higher incidence rate (per 1000 patient-years) of overall cardiovascular and cerebrovascular serious adverse events (SAEs) was observed in Xolair-treated patients (13.4) compared to non-Xolair-treated patients (8.1). Increases in rates were observed for transient ischemic attack (0.7 versus 0.1), myocardial infarction (2.1 versus 0.8), pulmonary hypertension (0.5 versus 0), pulmonary embolism/venous thrombosis (3.2 versus 1.5), and unstable angina (2.2 versus 1.4), while the rates observed for ischemic stroke and cardiovascular death were similar among both study cohorts. The results suggest a potential increased risk of serious cardiovascular and cerebrovascular events in patients treated with Xolair. However, the observational study design, the inclusion of patients previously exposed to Xolair (88%), baseline imbalances in cardiovascular risk factors between the treatment groups, an inability to adjust for unmeasured risk factors, and the high study discontinuation rate limit the ability to quantify the magnitude of the risk.

A pooled analysis of 25 randomized double-blind, placebo-controlled clinical trials of 8 to 52 weeks in duration was conducted to further evaluate the imbalance in cardiovascular and cerebrovascular SAEs noted in the above observational cohort study. A total of 3342 Xolair-treated patients and 2895 placebo-treated patients were included in the pooled analysis. The patients had a mean age of 38 years, and were followed for a mean duration of 6.8 months. No notable imbalances were observed in the rates of cardiovascular and cerebrovascular SAEs listed above. However, the results of the pooled analysis were based on a low number of events, slightly younger patients, and shorter duration of follow-up than the observational cohort study; therefore, the results are insufficient to confirm or reject the findings noted in the observational cohort study.

## 6.2 Immunogenicity

Antibodies to Xolair were detected in approximately 1/1723 (< 0.1%) of patients treated with Xolair in the clinical studies evaluated for approval of asthma in patients 12 years of age and older. In three pediatric studies, antibodies to Xolair were detected in one patient out of 581 patients 6 to <12 years of age treated with Xolair and evaluated for antibodies. There were no detectable antibodies in the patients treated in the phase 3 CIU clinical trials, but due to levels of Xolair at the time of anti-therapeutic antibody sampling and missing samples for some patients, antibodies to Xolair could only have been determined in 88% of the 733 patients treated in these clinical studies. The data reflect the percentage of patients whose test results were considered positive for antibodies to Xolair in ELISA assays and are highly dependent on the sensitivity and specificity of the assays. Additionally, the observed incidence of antibody positivity in the assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to Xolair with the incidence of antibodies to other products may be misleading.

## 6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Xolair in adult and adolescent patients 12 years of age and older. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Anaphylaxis: Based on spontaneous reports and an estimated exposure of about 57,300 patients from June 2003 through December 2006, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2% of patients. Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to Xolair administration with no other identifiable cause. Signs and symptoms in these reported cases included bronchospasm, hypotension, syncope, urticaria, angioedema of the throat or tongue, dyspnea, cough, chest tightness, and/or cutaneous angioedema. Pulmonary involvement was reported in 89% of the cases. Hypotension or syncope was reported in 14% of cases. Fifteen percent of the reported cases resulted in hospitalization. A previous history of anaphylaxis unrelated to Xolair was reported in 24% of the cases.

Of the reported cases of anaphylaxis attributed to Xolair, 39% occurred with the first dose, 19% occurred with the second dose, 10% occurred with the third dose, and the rest after subsequent doses. One case occurred after 39 doses (after 19 months of continuous therapy, anaphylaxis occurred when treatment was restarted following a 3 month gap). The time to onset of anaphylaxis in these cases was up to 30 minutes in 35%, greater than 30 and up to 60 minutes in 16%, greater than 60 and up to 90 minutes in 2%, greater than 90 and up to 120 minutes in 6%, greater than 2 hours and up to 6 hours in 5%, greater than 6 hours and up to 12 hours in 14%, greater than 12 hours and up to 24 hours in 8%, and greater than 24 hours and up to 4 days in 5%. In 9% of cases the times to onset were unknown.



Twenty-three patients who experienced anaphylaxis were rechallenged with Xolair and 18 patients had a recurrence of similar symptoms of anaphylaxis. In addition, anaphylaxis occurred upon rechallenge with Xolair in 4 patients who previously experienced urticaria only.

Eosinophilic Conditions: Eosinophilic conditions have been reported [*see Warnings and Precautions (5.5)*].

Fever, Arthralgia, and Rash: A constellation of signs and symptoms including arthritis/arthralgia, rash (urticaria or other forms), fever and lymphadenopathy similar to serum sickness have been reported in post-approval use of Xolair [*see Warnings and Precautions (5.6)*].

Hematologic: Severe thrombocytopenia has been reported.

Skin: Hair loss has been reported.

## **7 DRUG INTERACTIONS**

No formal drug interaction studies have been performed with Xolair.

In patients with asthma the concomitant use of Xolair and allergen immunotherapy has not been evaluated.

In patients with CIU the use of Xolair in combination with immunosuppressive therapies has not been studied.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

The data with XOLAIR use in pregnant women are insufficient to inform on drug associated risk. Monoclonal antibodies, such as omalizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimesters of pregnancy.

In animal reproduction studies, no evidence of fetal harm was observed in Cynomolgus monkeys with subcutaneous doses of omalizumab up to approximately 10 times the maximum recommended human dose (MRHD) [*see Animal Data*].

In the US general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

#### Clinical Considerations

##### *Disease-associated maternal and/or embryo/fetal risk*

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small

for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

## Data

### *Animal Data*

Reproductive studies have been performed in Cynomolgus monkeys. There was no evidence of maternal toxicity, embryotoxicity, or teratogenicity when omalizumab was administered throughout the period of organogenesis at doses that produced exposures approximately 10 times the MHRD (on a mg/kg basis with maternal subcutaneous doses up to 75 mg/kg/week). Omalizumab did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation, delivery, and nursing.

## **8.2 Lactation**

### Risk Summary

There is no information regarding the presence of omalizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, omalizumab is a human monoclonal antibody (IgG1 kappa), and immunoglobulin (IgG) is present in human milk in small amounts. In Cynomolgus monkeys, neonatal serum levels of omalizumab after in utero exposure and 28 days of nursing were between 11% and 94% of the maternal serum level. Levels of omalizumab in milk were 0.15% of maternal serum concentration.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Xolair and any potential adverse effects on the breastfed child from omalizumab or from the underlying maternal condition.

## **8.4 Pediatric Use**

### Asthma

Safety and efficacy of Xolair for asthma were evaluated in 2 trials in 926 (Xolair 624; placebo 302) pediatric patients 6 to <12 years of age with moderate to severe persistent asthma who had a positive skin test or in vitro reactivity to a perennial aeroallergen. One trial was a pivotal trial of similar design and conduct to that of adult and adolescent Asthma Trials 1 and 2. The other trial was primarily a safety study and included evaluation of efficacy as a secondary outcome. In the pivotal trial, Xolair-treated patients had a statistically significant reduction in the rate of exacerbations (exacerbation was defined as worsening of asthma that required treatment with systemic corticosteroids or a doubling of the baseline ICS dose) [*see Clinical Studies (14.1)*].

Safety and efficacy in pediatric patients with asthma below 6 years of age have not been established.

### Chronic Idiopathic Urticaria

The safety and effectiveness of Xolair for adolescent patients with CIU were evaluated in 39 patients 12 to 17 years of age (Xolair 29, placebo 10) included in three randomized, placebo-controlled CIU trials. A numerical decrease in weekly itch score was observed, and adverse reactions were similar to those reported in patients 18 years and older.

Safety and efficacy in pediatric patients with CIU below 12 years of age have not been established.

### **8.5 Geriatric Use**

In clinical studies 134 asthma patients and 37 CIU phase 3 study patients 65 years of age or older were treated with Xolair. Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

## **10 OVERDOSAGE**

The maximum tolerated dose of Xolair has not been determined. Single intravenous doses of up to 4,000 mg have been administered to patients without evidence of dose limiting toxicities. The highest cumulative dose administered to patients was 44,000 mg over a 20 week period, which was not associated with toxicities.

## **11 DESCRIPTION**

Xolair is a recombinant DNA-derived humanized IgG1 $\kappa$  monoclonal antibody that selectively binds to human immunoglobulin E (IgE). The antibody has a molecular weight of approximately 149 kiloDaltons. Xolair is produced by a Chinese hamster ovary cell suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Xolair is a sterile, white, preservative free, lyophilized powder contained in a single use vial that is reconstituted with Sterile Water for Injection (SWFI), USP, and administered as a subcutaneous (SC) injection. Each 202.5 mg vial of omalizumab also contains L-histidine (1.8 mg), L-histidine hydrochloride monohydrate (2.8 mg), polysorbate 20 (0.5 mg) and sucrose (145.5 mg) and is designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI, USP.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

#### Asthma

Omalizumab inhibits the binding of IgE to the high-affinity IgE receptor (Fc $\epsilon$ RI) on the surface of mast cells and basophils. Reduction in surface-bound IgE on Fc $\epsilon$ RI-bearing cells limits the degree of release of mediators of the allergic response. Treatment with Xolair also reduces the number of Fc $\epsilon$ RI receptors on basophils in atopic patients.

#### Chronic Idiopathic Urticaria

Omalizumab binds to IgE and lowers free IgE levels. Subsequently, IgE receptors (Fc $\epsilon$ RI) on cells down-regulate. The mechanism by which these effects of omalizumab result in an improvement of CIU symptoms is unknown.

### **12.2 Pharmacodynamics**

## Asthma

In clinical studies, serum free IgE levels were reduced in a dose dependent manner within 1 hour following the first dose and maintained between doses. Mean serum free IgE decrease was greater than 96% using recommended doses. Serum total IgE levels (i.e., bound and unbound) increased after the first dose due to the formation of omalizumab:IgE complexes, which have a slower elimination rate compared with free IgE. At 16 weeks after the first dose, average serum total IgE levels were five-fold higher compared with pre-treatment when using standard assays. After discontinuation of Xolair dosing, the Xolair-induced increase in total IgE and decrease in free IgE were reversible, with no observed rebound in IgE levels after drug washout. Total IgE levels did not return to pre-treatment levels for up to one year after discontinuation of Xolair.

## Chronic Idiopathic Urticaria

In clinical studies in CIU patients, Xolair treatment led to a dose-dependent reduction of serum free IgE and an increase of serum total IgE levels, similar to the observations in asthma patients. Maximum suppression of free IgE was observed 3 days following the first subcutaneous dose. After repeat dosing once every 4 weeks, predose serum free IgE levels remained stable between 12 and 24 weeks of treatment. Total IgE levels in serum increased after the first dose due to the formation of omalizumab-IgE complexes which have a slower elimination rate compared with free IgE. After repeat dosing once every 4 weeks at 75 mg up to 300 mg, average predose serum total IgE levels at Week 12 were two-to three-fold higher compared with pre-treatment levels, and remained stable between 12 and 24 weeks of treatment. After discontinuation of Xolair dosing, free IgE levels increased and total IgE levels decreased towards pre-treatment levels over a 16-week follow-up period.

### **12.3 Pharmacokinetics**

After SC administration, omalizumab was absorbed with an average absolute bioavailability of 62%. Following a single SC dose in adult and adolescent patients with asthma, omalizumab was absorbed slowly, reaching peak serum concentrations after an average of 7-8 days. In patients with CIU, the peak serum concentration was reached at a similar time after a single SC dose. The pharmacokinetics of omalizumab was linear at doses greater than 0.5 mg/kg. In patients with asthma, following multiple doses of Xolair, areas under the serum concentration-time curve from Day 0 to Day 14 at steady state were up to 6-fold of those after the first dose. In patients with CIU, omalizumab exhibited linear pharmacokinetics across the dose range of 75 mg to 600 mg given as single subcutaneous dose. Following repeat dosing from 75 to 300 mg every 4 weeks, trough serum concentrations of omalizumab increased proportionally with the dose levels.

In vitro, omalizumab formed complexes of limited size with IgE. Precipitating complexes and complexes larger than 1 million daltons in molecular weight were not observed in vitro or in vivo. Tissue distribution studies in Cynomolgus monkeys showed no specific uptake of <sup>125</sup>I-omalizumab by any organ or tissue. The apparent volume of distribution of omalizumab in patients with asthma following SC administration was  $78 \pm 32$  mL/kg. In patients with CIU, based on population pharmacokinetics, distribution of omalizumab was similar to that in patients with asthma.

Clearance of omalizumab involved IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG included degradation in the liver reticuloendothelial system (RES) and endothelial cells. Intact IgG was also excreted in bile. In studies with mice and monkeys, omalizumab:IgE complexes were eliminated by interactions with Fc $\gamma$  receptors within the RES at rates that were generally faster than IgG clearance. In asthma patients omalizumab serum elimination half-life averaged 26 days, with apparent clearance averaging  $2.4 \pm 1.1$  mL/kg/day. Doubling body weight approximately doubled apparent clearance. In CIU patients, at steady state, based on population pharmacokinetics, omalizumab serum elimination half-life averaged 24 days and apparent clearance averaged 240 mL/day (corresponding to 3.0 mL/kg/day for an 80 kg patient).

### Special Populations

#### *Asthma*

The population pharmacokinetics of omalizumab was analyzed to evaluate the effects of demographic characteristics in patients with asthma. Analyses of these data suggested that no dose adjustments are necessary for age (6-76 years), race, ethnicity, or gender.

#### *Chronic Idiopathic Urticaria*

The population pharmacokinetics of omalizumab was analyzed to evaluate the effects of demographic characteristics and other factors on omalizumab exposure in patients with CIU. Covariate effects were evaluated by analyzing the relationship between omalizumab concentrations and clinical responses. These analyses demonstrate that no dose adjustments are necessary for age (12 to 75 years), race/ethnicity, gender, body weight, body mass index or baseline IgE level.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

No long-term studies have been performed in animals to evaluate the carcinogenic potential of Xolair.

There were no effects on fertility and reproductive performance in male and female Cynomolgus monkeys that received Xolair at subcutaneous doses up to 75 mg/kg/week (approximately 10 times the maximum recommended human dose on a mg/kg basis).

## **14 CLINICAL STUDIES**

### **14.1 Asthma**

#### Adult and Adolescent Patients 12 Years of Age and Older

The safety and efficacy of Xolair were evaluated in three randomized, double-blind, placebo-controlled, multicenter trials.

The trials enrolled patients 12 to 76 years old, with moderate to severe persistent (NHLBI criteria) asthma for at least one year, and a positive skin test reaction to a perennial

aeroallergen. In all trials, Xolair dosing was based on body weight and baseline serum total IgE concentration. All patients were required to have a baseline IgE between 30 and 700 IU/mL and body weight not more than 150 kg. Patients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of Xolair or a matching volume of placebo over each 4-week period. The maximum Xolair dose per 4 weeks was 750 mg.

In all three trials an exacerbation was defined as a worsening of asthma that required treatment with systemic corticosteroids or a doubling of the baseline ICS dose. Most exacerbations were managed in the out-patient setting and the majority were treated with systemic steroids. Hospitalization rates were not significantly different between Xolair and placebo-treated patients; however, the overall hospitalization rate was small. Among those patients who experienced an exacerbation, the distribution of exacerbation severity was similar between treatment groups.

#### *Asthma Trials 1 and 2*

At screening, patients in Asthma Trials 1 and 2 had a forced expiratory volume in one second (FEV<sub>1</sub>) between 40% and 80% predicted. All patients had a FEV<sub>1</sub> improvement of at least 12% following beta<sub>2</sub>-agonist administration. All patients were symptomatic and were being treated with inhaled corticosteroids (ICS) and short acting beta<sub>2</sub>-agonists. Patients receiving other concomitant controller medications were excluded, and initiation of additional controller medications while on study was prohibited. Patients currently smoking were excluded.

Each trial was comprised of a run-in period to achieve a stable conversion to a common ICS (beclomethasone dipropionate), followed by randomization to Xolair or placebo. Patients received Xolair for 16 weeks with an unchanged corticosteroid dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 weeks during which ICS dose reduction was attempted in a step-wise manner.

The distribution of the number of asthma exacerbations per patient in each group during a study was analyzed separately for the stable steroid and steroid-reduction periods.

In both Asthma Trials 1 and 2 the number of exacerbations per patient was reduced in patients treated with Xolair compared with placebo (Table 7).

Measures of airflow (FEV<sub>1</sub>) and asthma symptoms were also evaluated in these trials. The clinical relevance of the treatment-associated differences is unknown. Results from the stable steroid phase Asthma Trial 1 are shown in Table 8. Results from the stable steroid phase of Asthma Trial 2 and the steroid reduction phases of both Asthma Trials 1 and 2 were similar to those presented in Table 8.

**Table 7. Frequency of Asthma Exacerbations per Patient by Phase in Trials 1 and 2**

| Stable Steroid Phase (16 wks)     |                 |                  |                 |                  |
|-----------------------------------|-----------------|------------------|-----------------|------------------|
| Exacerbations per patient         | Asthma Trial 1  |                  | Asthma Trial 2  |                  |
|                                   | Xolair<br>N=268 | Placebo<br>N=257 | Xolair<br>N=274 | Placebo<br>N=272 |
| 0                                 | 85.8%           | 76.7%            | 87.6%           | 69.9%            |
| 1                                 | 11.9%           | 16.7%            | 11.3%           | 25.0%            |
| ≥ 2                               | 2.2%            | 6.6%             | 1.1%            | 5.1%             |
| p-Value                           | 0.005           |                  | <0.001          |                  |
| Mean number exacerbations/patient | 0.2             | 0.3              | 0.1             | 0.4              |
| Steroid Reduction Phase (12 wks)  |                 |                  |                 |                  |
| Exacerbations per patient         | Asthma Trial 1  |                  | Asthma Trial 2  |                  |
|                                   | Xolair<br>N=268 | Placebo<br>N=257 | Xolair<br>N=274 | Placebo<br>N=272 |
| 0                                 | 78.7%           | 67.7%            | 83.9%           | 70.2%            |
| 1                                 | 19.0%           | 28.4%            | 14.2%           | 26.1%            |
| ≥ 2                               | 2.2%            | 3.9%             | 1.8%            | 3.7%             |
| p-Value                           | 0.004           |                  | <0.001          |                  |
| Mean number exacerbations/patient | 0.2             | 0.4              | 0.2             | 0.3              |

**Table 8. Asthma Symptoms and Pulmonary Function During Stable Steroid Phase of Trial 1**

| Endpoint                     | Xolair<br>N=268* |                                   | Placebo<br>N=257* |                                   |
|------------------------------|------------------|-----------------------------------|-------------------|-----------------------------------|
|                              | Mean Baseline    | Median Change (Baseline to Wk 16) | Mean Baseline     | Median Change (Baseline to Wk 16) |
| Total asthma symptom score   | 4.3              | -1.5 <sup>†</sup>                 | 4.2               | -1.1 <sup>†</sup>                 |
| Nocturnal asthma score       | 1.2              | -0.4 <sup>†</sup>                 | 1.1               | -0.2 <sup>†</sup>                 |
| Daytime asthma score         | 2.3              | -0.9 <sup>†</sup>                 | 2.3               | -0.6 <sup>†</sup>                 |
| FEV <sub>1</sub> % predicted | 68               | 3 <sup>†</sup>                    | 68                | 0 <sup>†</sup>                    |

Asthma symptom scale: total score from 0 (least) to 9 (most); nocturnal and daytime scores from 0 (least) to 4 (most symptoms).

\* Number of patients available for analysis ranges 255-258 in the Xolair group and 238-239 in the placebo group.

<sup>†</sup> Comparison of Xolair versus placebo (p<0.05).

### Asthma Trial 3

In Asthma Trial 3, there was no restriction on screening FEV<sub>1</sub>, and unlike Asthma Trials 1 and 2, long-acting beta<sub>2</sub>-agonists were allowed. Patients were receiving at least 1000 µg/day fluticasone propionate and a subset was also receiving oral corticosteroids. Patients receiving other concomitant controller medications were excluded, and initiation of additional controller medications while on study was prohibited. Patients currently smoking were excluded.

The trial was comprised of a run-in period to achieve a stable conversion to a common ICS (fluticasone propionate), followed by randomization to Xolair or placebo. Patients were stratified by use of ICS-only or ICS with concomitant use of oral steroids. Patients received Xolair for 16 weeks with an unchanged corticosteroid dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 16 weeks during which ICS or oral steroid dose reduction was attempted in a step-wise manner.

The number of exacerbations in patients treated with Xolair was similar to that in placebo-treated patients (Table 9). The absence of an observed treatment effect may be related to differences in the patient population compared with Asthma Trials 1 and 2, study sample size, or other factors.

**Table 9. Percentage of Patients with Asthma Exacerbations by Subgroup and Phase in Trial 3**

|                                   | Stable Steroid Phase (16 wks)     |                    |                       |                   |
|-----------------------------------|-----------------------------------|--------------------|-----------------------|-------------------|
|                                   | Inhaled Only                      |                    | Oral + Inhaled        |                   |
|                                   | Xolair<br>N = 126                 | Placebo<br>N = 120 | Xolair<br>N = 50      | Placebo<br>N = 45 |
| % Patients with ≥ 1 exacerbations | 15.9%                             | 15.0%              | 32.0%                 | 22.2%             |
| Difference (95% CI)               | 0.9<br>(-9.7, 13.7)               |                    | 9.8<br>(-10.5, 31.4)  |                   |
|                                   | Steroid Reduction Phase (16 wks)  |                    |                       |                   |
|                                   | Xolair<br>N = 126                 | Placebo<br>N = 120 | Xolair<br>N = 50      | Placebo<br>N = 45 |
|                                   | % Patients with ≥ 1 exacerbations | 22.2%              | 26.7%                 | 42.0%             |
| Difference (95% CI)               | -4.4<br>(-17.6, 7.4)              |                    | -0.2<br>(-22.4, 20.1) |                   |

In all three of the trials, a reduction of asthma exacerbations was not observed in the Xolair-treated patients who had FEV<sub>1</sub> > 80% at the time of randomization. Reductions in exacerbations were not seen in patients who required oral steroids as maintenance therapy.



### Pediatric Patients 6 to < 12 Years of Age

The safety and efficacy of Xolair in pediatric patients 6 to <12 years of age with moderate to severe asthma is based on one randomized, double-blind, placebo controlled, multi-center trial (Trial 4) and an additional supportive study (Trial 5).

Trial 4 was a 52-week study that evaluated the safety and efficacy of Xolair as add-on therapy in 628 pediatric patients ages 6 to <12 years with moderate to severe asthma inadequately controlled despite the use of inhaled corticosteroids (fluticasone propionate DPI  $\geq 200$  mcg/day or equivalent) with or without other controller asthma medications. Eligible patients were those with a diagnosis of asthma >1 year, a positive skin prick test to at least one perennial aeroallergen, and a history of clinical features such as daytime and/or nighttime symptoms and exacerbations within the year prior to study entry. During the first 24 weeks of treatment, steroid doses remained constant from baseline. This was followed by a 28-week period during which inhaled corticosteroid adjustment was allowed.

The primary efficacy variable was the rate of asthma exacerbations during the 24-week, fixed steroid treatment phase. An asthma exacerbation was defined as a worsening of asthma symptoms as judged clinically by the investigator, requiring doubling of the baseline inhaled corticosteroid dose for at least 3 days and/or treatment with rescue systemic (oral or IV) corticosteroids for at least 3 days. At 24 weeks, the Xolair group had a statistically significantly lower rate of asthma exacerbations (0.45 vs. 0.64) with an estimated rate ratio of 0.69 (95% CI: 0.53, 0.90).

The Xolair group also had a lower rate of asthma exacerbations compared to placebo over the full 52-week double-blind treatment period (0.78 vs. 1.36; rate ratio: 0.57; 95% CI: 0.45, 0.72). Other efficacy variables such as nocturnal symptom scores, beta-agonist use, and measures of airflow (FEV1) were not significantly different in Xolair-treated patients compared to placebo.

Trial 5 was a 28-week randomized, double blind, placebo-controlled study that primarily evaluated safety in 334 pediatric patients, 298 of whom were 6 to <12 years of age, with moderate to severe asthma who were well-controlled with inhaled corticosteroids (beclomethasone dipropionate 168-420 mcg/day). A 16-week steroid treatment period was followed by a 12-week steroid dose reduction period. Patients treated with Xolair had fewer asthma exacerbations compared to placebo during both the 16-week fixed steroid treatment period (0.18 vs. 0.32; rate ratio: 0.58; 95% CI: 0.35, 0.96) and the 28-week treatment period (0.38 vs. 0.76; rate ratio: 0.50; 95% CI: 0.36, 0.71).

## **14.2 Chronic Idiopathic Urticaria**

### Adult and Adolescent Patients 12 Years of Age and Older

The safety and efficacy of Xolair for the treatment of CIU was assessed in two placebo-controlled, multiple-dose clinical trials of 24 weeks' duration (CIU Trial 1; n= 319) and 12 weeks' duration (CIU Trial 2; n=322). Patients received Xolair 75, 150, or 300 mg or placebo by SC injection every 4 weeks in addition to their baseline level of H1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week washout observation period. A total of

640 patients (165 males, 475 females) were included for the efficacy analyses. Most patients were white (84%) and the median age was 42 years (range 12–72).

Disease severity was measured by a weekly urticaria activity score (UAS7, range 0–42), which is a composite of the weekly itch severity score (range 0–21) and the weekly hive count score (range 0–21). All patients were required to have a UAS7 of  $\geq 16$ , and a weekly itch severity score of  $\geq 8$  for the 7 days prior to randomization, despite having used an H1 antihistamine for at least 2 weeks.

The mean weekly itch severity scores at baseline were fairly balanced across treatment groups and ranged between 13.7 and 14.5 despite use of an H1 antihistamine at an approved dose. The reported median durations of CIU at enrollment across treatment groups were between 2.5 and 3.9 years (with an overall subject-level range of 0.5 to 66.4 years).

In both CIU Trials 1 and 2, patients who received Xolair 150 mg or 300 mg had greater decreases from baseline in weekly itch severity scores and weekly hive count scores than placebo at Week 12. Representative results from CIU Trial 1 are shown (Table 10); similar results were observed in CIU Trial 2. The 75-mg dose did not demonstrate consistent evidence of efficacy and is not approved for use.

**Table 10. Change from Baseline to Week 12 in Weekly Itch Severity Score and Weekly Hive Count Score in CIU Trial 1\***

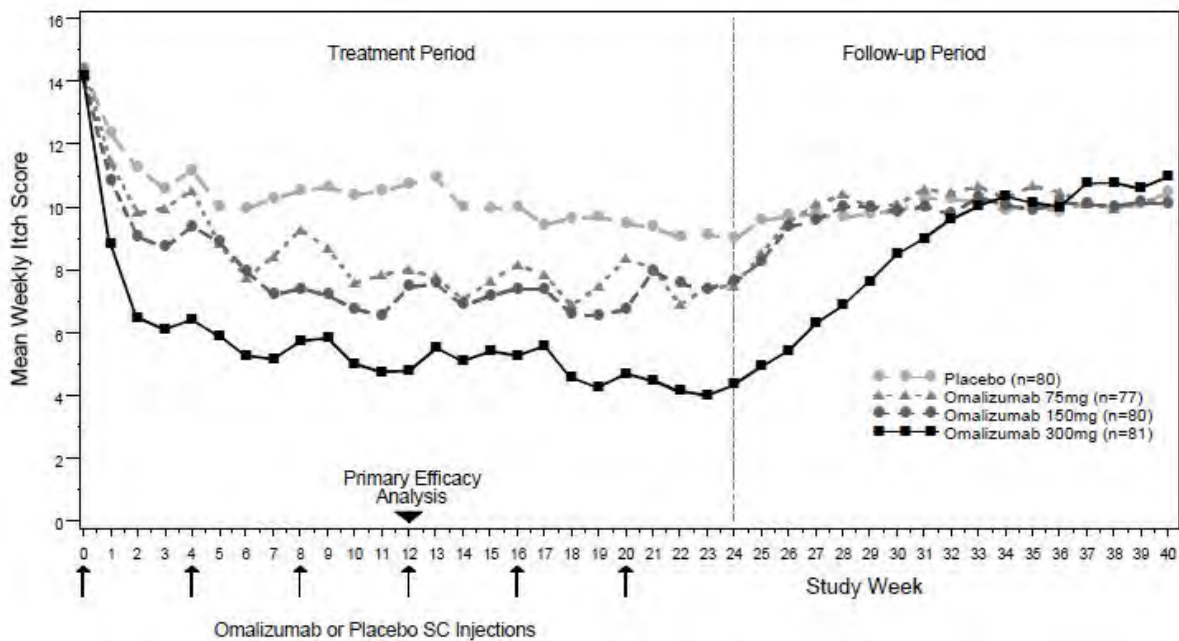
|                                      | Xolair<br>75mg | Xolair<br>150mg | Xolair<br>300mg | Placebo      |
|--------------------------------------|----------------|-----------------|-----------------|--------------|
| n                                    | 77             | 80              | 81              | 80           |
| Weekly Itch Severity Score           |                |                 |                 |              |
| Mean Baseline Score (SD)             | 14.5 (3.6)     | 14.1 (3.8)      | 14.2 (3.3)      | 14.4 (3.5)   |
| Mean Change Week 12(SD)              | -6.46 (6.14)   | -6.66 (6.28)    | -9.40 (5.73)    | -3.63 (5.22) |
| Difference in LS means vs. placebo   | -2.96          | -2.95           | -5.80           |              |
| 95% CI for difference                | -4.71, -1.21   | -4.72, -1.18    | -7.49, -4.10    | -            |
| Weekly Hive Count Score <sup>†</sup> |                |                 |                 |              |
| Mean Baseline Score (SD)             | 17.2 (4.2)     | 16.2 (4.6)      | 17.1 (3.8)      | 16.7 (4.4)   |
| Mean Change Week 12(SD)              | -7.36 (7.52)   | -7.78 (7.08)    | -11.35 (7.25)   | -4.37 (6.60) |
| Difference in LS means vs. placebo   | -2.75          | -3.44           | -6.93           |              |
| 95% CI for difference                | -4.95, -0.54   | -5.57, -1.32    | -9.10, -4.76    | -            |

\* Modified intent-to-treat (mITT) population: all patients who were randomized and received at least one dose of study medication.

<sup>†</sup> Score measured on a range of 0–21

The mean weekly itch severity score at each study week by treatment groups is shown in Figure 1. Representative results from CIU Trial 1 are shown; similar results were observed in CIU Trial 2. The appropriate duration of therapy for CIU with Xolair has not been determined.

**Figure 1. Mean Weekly Itch Severity Score by Treatment Group  
Modified Intent to Treat Patients in CIU Trial 1**



In CIU Trial 1, a larger proportion of patients treated with Xolair 300 mg (36%) reported no itch and no hives (UAS7=0) at Week 12 compared to patients treated with Xolair 150 mg (15%), Xolair 75 mg (12%), and placebo group (9%). Similar results were observed in CIU Trial 2.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Xolair is supplied as a lyophilized, sterile powder in a single-use, 5 mL vial without preservatives. Each vial delivers 150 mg of Xolair upon reconstitution with 1.4 mL SWFI, USP. Each carton contains one single-use vial of Xolair® (omalizumab) NDC 50242-040-62.

Xolair should be shipped at controlled ambient temperature ( $\leq 30^{\circ}\text{C}$  [ $\leq 86^{\circ}\text{F}$ ]). Store Xolair under refrigerated conditions 2 to 8°C (36 to 46°F). Do not use beyond the expiration date stamped on carton.

Use the solution for subcutaneous administration within 8 hours following reconstitution when stored in the vial at 2 to 8°C (36 to 46°F), or within 4 hours of reconstitution when stored at room temperature.

Reconstituted Xolair vials should be protected from direct sunlight.

## 17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

### Information for Patients

Provide and instruct patients to read the accompanying Medication Guide before starting treatment and before each subsequent treatment. The complete text of the Medication Guide is reprinted at the end of this document.

Inform patients of the risk of life-threatening anaphylaxis with Xolair including the following points [*see Boxed Warning and Warnings and Precautions (5.1)*]:

- There have been reports of anaphylaxis occurring up to 4 days after administration of Xolair
- Xolair should only be administered in a healthcare setting by healthcare providers
- Patients should be closely observed following administration
- Patients should be informed of the signs and symptoms of anaphylaxis
- Patients should be instructed to seek immediate medical care should such signs or symptoms occur

Instruct patients receiving Xolair not to decrease the dose of, or stop taking any other asthma or CIU medications unless otherwise instructed by their physician. Inform patients that they may not see immediate improvement in their asthma or CIU symptoms after beginning Xolair therapy.

## MEDICATION GUIDE

### XOLAIR® (ZOHL-air)

(omalizumab)

injection, for subcutaneous use

#### **What is the most important information I should know about XOLAIR?**

##### **XOLAIR may cause serious side effects, including:**

**Severe allergic reaction.** A severe allergic reaction called anaphylaxis can happen when you receive XOLAIR. The reaction can occur after the first dose, or after many doses. It may also occur right after a XOLAIR injection or days later. Anaphylaxis is a life-threatening condition and can lead to death. Go to the nearest emergency room right away if you have any of these symptoms of an allergic reaction:

- wheezing, shortness of breath, cough, chest tightness, or trouble breathing
- low blood pressure, dizziness, fainting, rapid or weak heartbeat, anxiety, or feeling of “impending doom”
- flushing, itching, hives, or feeling warm
- swelling of the throat or tongue, throat tightness, hoarse voice, or trouble swallowing

Your healthcare provider will monitor you closely for symptoms of an allergic reaction while you are receiving XOLAIR and for a period of time after your injection. Your healthcare provider should talk to you about getting medical treatment if you have symptoms of an allergic reaction after leaving the healthcare provider’s office or treatment center.

#### **What is XOLAIR?**

XOLAIR is an injectable prescription medicine used to treat:

- moderate to severe persistent asthma in patients 6 years of age and older whose asthma symptoms are not controlled by asthma medicines called inhaled corticosteroids. A skin or blood test is performed to see if you have allergies to year-round allergens.
- chronic idiopathic urticaria (CIU; chronic hives without a known cause) in patients 12 years of age and older who continue to have hives that are not controlled by H1 antihistamine treatment.

XOLAIR is not used to treat other allergic conditions, other forms of urticaria, acute bronchospasm or status asthmaticus.

#### **Who should not receive XOLAIR?**

##### **Do not receive XOLAIR if you:**

- are allergic to omalizumab or any of the ingredients. See the end of this Medication Guide for a complete list of ingredients in XOLAIR.

#### **What should I tell my healthcare provider before receiving XOLAIR?**

##### **Before receiving XOLAIR, tell your healthcare provider about all of your medical conditions, including if you:**

- have any other allergies (such as food allergy or seasonal allergies)
- have sudden breathing problems (bronchospasm)
- have ever had a severe allergic reaction called anaphylaxis
- have or have had a parasitic infection
- have or have had cancer
- are pregnant or plan to become pregnant. It is not known if XOLAIR may harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if XOLAIR passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby while you receive XOLAIR.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, or herbal supplements.

#### **How should I receive XOLAIR?**

- XOLAIR should be given by your healthcare provider in a healthcare setting.
- XOLAIR is given in 1 or more injections under the skin (subcutaneous), 1 time every 2 or 4 weeks.
- In asthma patients, a blood test for a substance called IgE must be performed prior to starting XOLAIR to determine the appropriate dose and dosing frequency.
- In patients with chronic hives, a blood test is not necessary to determine the dose or dosing

frequency.

- Do not decrease or stop taking any of your other asthma or hive medicine unless your healthcare providers tell you to.
- You may not see improvement in your symptoms right away after XOLAIR treatment.

**What are the possible side effects of XOLAIR?**

**XOLAIR may cause serious side effects, including:**

- See **“What is the most important information I should know about XOLAIR?”**
- **Cancer.** Cases of cancer were observed in some people who received XOLAIR.
- **Inflammation of your blood vessels.** Rarely, this can happen in people with asthma who receive XOLAIR. This usually, but not always, happens in people who also take a steroid medicine by mouth that is being stopped or the dose is being lowered. It is not known whether this is caused by XOLAIR. Tell your healthcare provider right away if you have:
  - rash
  - chest pain
  - shortness of breath
  - a feeling of pins and needles or numbness of your arms or legs
- **Fever, muscle aches, and rash.** Some people who take XOLAIR get these symptoms 1 to 5 days after receiving a XOLAIR injection. If you have any of these symptoms, tell your healthcare provider.
- **Parasitic infection.** Some people who are at a high risk for parasite (worm) infections, get a parasite infection after receiving XOLAIR. Your healthcare provider can test your stool to check if you have a parasite infection.
- **Heart and circulation problems.** Some people who receive XOLAIR have had chest pain, heart attack, blood clots in the lungs or legs, or temporary symptoms of weakness on one side of the body, slurred speech, or altered vision. It is not known whether these are caused by XOLAIR.

**The most common side effects of XOLAIR:**

- **In adults and children 12 years of age and older with asthma:** pain especially in your arms and legs, dizziness, feeling tired, skin rash, bone fractures, and pain or discomfort of your ears.
- **In children 6 to less than 12 years of age with asthma:** common cold symptoms, headache, fever, sore throat, pain or discomfort of your ear, abdominal pain, nausea, vomiting and nose bleeds.
- **In people with chronic idiopathic urticaria:** nausea, headaches, swelling of the inside of your nose, throat or sinuses, cough, joint pain, and upper respiratory tract infection.

These are not all the possible side effects of XOLAIR. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about the safe and effective use of XOLAIR.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information, talk to your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about XOLAIR that is written for health professionals. Do not use XOLAIR for a condition for which it was not prescribed.

For more information, go to [www.xolair.com](http://www.xolair.com) or call 1-866-4XOLAIR (1-866-496-5247).

**What are the ingredients in XOLAIR?**

**Active ingredient:** omalizumab

**Inactive ingredients:** L-histidine, L-histidine hydrochloride monohydrate, polysorbate 20 and sucrose

**Manufactured by:** Genentech, Inc. A Member of the Roche Group. 1 DNA Way, South San Francisco, CA 94080-4990.

**Jointly marketed by:**

Genentech USA, Inc. A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990

Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936-1080

Xolair® is a registered trademark of Novartis AG. ©2016 Genentech USA, Inc.

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised:7/2016

## 1.7 同種同効品一覧表

最新の添付文書を参照する

オマリズマブ（以下、本剤）は、ヒト化抗ヒト IgE モノクローナル抗体製剤であり、「特発性の慢性蕁麻疹（既存治療で効果不十分な患者に限る）」を追加効能又は効果として承認事項一部変更承認申請を行う。本承認事項一部変更承認申請時点で、本剤の薬理作用、追加効能・効果の観点から、本剤に類似していると考えられる同種同効品は存在しない。



## **1.8 添付文書（案）**

**最新の添付文書を参照する**

下線部：本申請に伴う追加部分

貯法：

凍結を避け、2～8℃に保存

使用期限：

包装に表示の使用期限内に  
使用すること

気管支喘息治療剤  
慢性蕁麻疹治療剤

(ヒト化抗ヒトIgEモノクローナル抗体製剤)

生物由来製品、劇薬、処方箋医薬品  
(注意－医師等の処方箋により使用すること)

ゾレア®皮下注用 75mg

ゾレア®皮下注用 150mg

Xolair® for s.c. injection

オマリズマブ (遺伝子組換え) 注射用凍結乾燥製剤

日本標準商品分類番号 87229、87449

|      |   |         |
|------|---|---------|
| 承認番号 | 75mg:22400AMX01381000<br>150mg:22300AMX01262000 |         |
|      | 75mg  | 150mg   |
| 薬価収載 | 2012年11月  | 2012年6月 |
| 販売開始 | 2012年11月  | 2009年3月 |
| 国際誕生 | 2002年6月   |         |
| 効能追加 | 20XX年XX月  |         |

 NOVARTIS

**【禁忌 (次の患者には投与しないこと)】**

本剤の成分に対し過敏症の既往歴のある患者

(赤枠)

**【組成・性状】**

本剤は、それぞれ1バイアル中に下記成分・分量を含有する凍結乾燥注射剤で、用時、日局注射用水で溶解して用いる。

| ゾレア<br>皮下注用<br>75mg  | 有効成分・含量                               | オマリズマブ (遺伝子組換え) 129.6mg<br>ただし、本剤の調製方法に基づき、日局注射用水0.9mLに溶解した溶液0.6mL中に含まれる量は75mgである。*  |
|----------------------|---------------------------------------|--|
|                      | 添加物                                   | 精製白糖 93.1mg<br>L-ヒスチジン塩酸塩水和物 1.8mg<br>L-ヒスチジン 1.2mg<br>ポリソルベート20 0.3mg               |
| 性状                   | 白色の塊で、溶解後は、無色～微黄色で、澄明又はわずかに混濁した粘性のある液 |  |
| pH                   | 5.8～6.5 (溶解後)                         |  |
| 浸透圧                  | 273～455mmol/kg (溶解後)                  |  |
| ゾレア<br>皮下注用<br>150mg | 有効成分・含量                               | オマリズマブ (遺伝子組換え) 202.5mg<br>ただし、本剤の調製方法に基づき、日局注射用水1.4mLに溶解した溶液1.2mL中に含まれる量は150mgである。* |
|                      | 添加物                                   | 精製白糖 145.5mg<br>L-ヒスチジン塩酸塩水和物 2.8mg<br>L-ヒスチジン 1.8mg<br>ポリソルベート20 0.5mg              |
| 性状                   | 白色の塊で、溶解後は、無色～微黄色で、澄明又はわずかに混濁した粘性のある液 |  |
| pH                   | 5.8～6.5 (溶解後)                         |  |
| 浸透圧                  | 273～455mmol/kg (溶解後)                  |  |

本剤の有効成分であるオマリズマブ (遺伝子組換え) は、チャイニーズハムスター卵巣細胞から産生されるヒト化マウスモノクローナル抗体である。オマリズマブ (遺伝子組換え) の製造工程において、ブタペプトン (胃) を使用している。

※本剤溶解後の溶液は粘性があるため、注射液吸引時の損失を考慮し、1バイアルから75mg又は150mgをそれぞれ注射するに足る量を確保するために過量充填されている。

**【効能又は効果】**

1. 気管支喘息 (既存治療によっても喘息症状をコントロールできない難治の患者に限る)
2. 特発性の慢性蕁麻疹 (既存治療で効果不十分な患者に限る)

**＜効能又は効果に関連する使用上の注意＞**

**1. 気管支喘息**

高用量の吸入ステロイド薬及び複数の喘息治療薬を併用しても症状が安定せず、通年性吸入抗原に対して陽性を示し、体重及び初回投与前血清中総IgE濃度が投与量換算表で定義される基準を満たす場合に本剤を追加して投与すること。

症状が安定しないとは、下記の症状のいずれかが改善しないことを示す。

**成人の場合**

- ・喘息に起因する明らかな呼吸機能の低下 (FEV<sub>1.0</sub>が予測正常値に対し80%未満)
- ・毎日喘息症状が観察される
- ・週1回以上夜間症状が観察される

**小児の場合**

- ・毎日喘息症状が観察される
- ・週1回以上夜間症状が観察される
- ・週1回以上日常生活が障害される

**2. 特発性の慢性蕁麻疹**

食物、物理的的刺激等の蕁麻疹の症状を誘発する原因が特定されず、ヒスタミンH<sub>1</sub>受容体拮抗薬の増量等の適切な治療を行っても、日常生活に支障をきたすほどの痒みを伴う膨疹が繰り返して継続的に認められる場合に本剤を追加して投与すること。

**【用法及び用量】**

**1. 気管支喘息**

通常、オマリズマブ (遺伝子組換え) として1回75～600mgを2又は4週間毎に皮下に注射する。1回あたりの投与量並びに投与間隔は、初回投与前の血清中総IgE濃度及び体重に基づき、下記の投与量換算表により設定する。

**投与量換算表 (1回投与量)**

**4週間毎投与**

| 投与前の血清中総IgE濃度 (IU/mL) | 体重 (kg)    |            |            |            |            |            |            |            |             |              |
|-----------------------|------------|------------|------------|------------|------------|------------|------------|------------|-------------|--------------|
|                       | ≥20<br>～25 | >25<br>～30 | >30<br>～40 | >40<br>～50 | >50<br>～60 | >60<br>～70 | >70<br>～80 | >80<br>～90 | >90<br>～125 | >125<br>～150 |
| ≥30～100               | 75 mg      | 75 mg      | 75 mg      | 150 mg     | 150 mg     | 150 mg     | 150 mg     | 150 mg     | 300 mg      | 300 mg       |
| >100～200              | 150 mg     | 150 mg     | 150 mg     | 300 mg     | 300 mg     | 300 mg     | 300 mg     | 300 mg     | 450 mg      | 600 mg       |
| >200～300              | 150 mg     | 150 mg     | 225 mg     | 300 mg     | 300 mg     | 450 mg     | 450 mg     | 450 mg     | 600 mg      |              |
| >300～400              | 225 mg     | 225 mg     | 300 mg     | 450 mg     | 450 mg     | 450 mg     | 600 mg     | 600 mg     |             |              |
| >400～500              | 225 mg     | 300 mg     | 300 mg     | 450 mg     | 450 mg     | 600 mg     | 600 mg     |            |             |              |
| >500～600              | 300 mg     | 300 mg     | 450 mg     | 600 mg     | 600 mg     |            |            |            |             |              |
| >600～700              | 300 mg     |            | 450 mg     | 600 mg     |            |            |            |            |             |              |

|              |                                     |
|--------------|-------------------------------------|
| >700～800     | 4週間毎投与の表に該当しない場合には2週間毎投与の表に従い投与すること |
| >800～900     |                                     |
| >900～1,000   |                                     |
| >1,000～1,100 |                                     |
| >1,100～1,200 |                                     |
| >1,200～1,300 |                                     |
| >1,300～1,500 |                                     |

## 2週間毎投与

| 投与前の血清中総IgE濃度 (IU/mL) | 体重 (kg)                             |        |        |        |        |        |        |        |         |          |
|-----------------------|-------------------------------------|--------|--------|--------|--------|--------|--------|--------|---------|----------|
|                       | ≥20～25                              | >25～30 | >30～40 | >40～50 | >50～60 | >60～70 | >70～80 | >80～90 | >90～125 | >125～150 |
| ≥30～100               | 2週間毎投与の表に該当しない場合には4週間毎投与の表に従い投与すること |        |        |        |        |        |        |        |         |          |
| >100～200              |                                     |        |        |        |        |        |        |        |         |          |
| >200～300              |                                     |        |        |        |        |        |        |        |         |          |
| >300～400              |                                     |        |        |        |        |        |        |        |         |          |
| >400～500              |                                     |        |        |        |        |        |        |        |         |          |
| >500～600              |                                     |        |        |        |        |        |        |        |         |          |
| >600～700              |                                     |        |        |        |        |        |        |        |         |          |
| >700～800              |                                     |        |        |        |        |        |        |        |         |          |
| >800～900              |                                     |        |        |        |        |        |        |        |         |          |
| >900～1,000            |                                     |        |        |        |        |        |        |        |         |          |
| >1,000～1,100          |                                     |        |        |        |        |        |        |        |         |          |
| >1,100～1,200          |                                     |        |        |        |        |        |        |        |         |          |
| >1,200～1,300          |                                     |        |        |        |        |        |        |        |         |          |
| >1,300～1,500          |                                     |        |        |        |        |        |        |        |         |          |

投与量換算表では、本剤の臨床推奨用量である0.008mg/kg/[IU/mL]以上（2週間間隔皮下投与時）又は0.016mg/kg/[IU/mL]以上（4週間間隔皮下投与時）となるよう投与量が設定されている。

## 2. 特発性の慢性蕁麻疹

**通常、成人及び12歳以上の小児にはオマリズマブ（遺伝子組換え）として1回300mgを4週間毎に皮下に注射する。**

### <用法及び用量に関連する使用上の注意>

#### 1. 気管支喘息

- 75mgバイアル：1バイアルあたり0.9mLの日局注射用水で溶解する。溶液0.6mLがオマリズマブ（遺伝子組換え）の投与量75mgに相当する。  
150mgバイアル：1バイアルあたり1.4mLの日局注射用水で溶解する。溶液1.2mLがオマリズマブ（遺伝子組換え）の投与量150mgに相当する。  
（「7. 適用上の注意」の項参照）
- 投与量並びに投与間隔は、初回投与前の血清中総IgE濃度及び体重を基に、投与量換算表により設定し、**投与量換算表に該当しない患者への投与は行わないこと。**
- 本剤投与中に大幅に体重が増加した場合には、本剤の臨床推奨用量が投与されない可能性があるため、投与量換算表に基づいて投与量並びに投与間隔を再設定すること。特に小児では、成長に伴う体重の増加に注意すること。

- 本剤投与によりIgEの消失半減期が延長し、血清中総IgE濃度が上昇するので**本剤投与中に測定した血清中総IgE濃度による用法・用量の再設定は行わないこと。**また、本剤投与中止後1年間は血清中総IgE濃度の上昇が持続する場合がありますので、1年未満に投与を再開する場合は、最初の用量設定時に得られた血清中総IgE濃度に基づいて用量を設定すること。ただし、本剤の投与中断期間が1年以上の場合は、血清中総IgE濃度を再測定してもよい。（「6. 臨床検査結果に及ぼす影響」の項参照）
- 本剤投与中に喘息症状の改善が認められた場合においても、投与量換算表により設定された投与量を変更しないこと。

## 2. 特発性の慢性蕁麻疹

日本人を対象とした臨床試験において、本剤の12週以降の使用経験は無いため、12週以降も継続して投与する場合は、患者の状態を考慮し、その必要性を慎重に判断すること。（「8. その他の注意」(5)、【臨床成績】の項参照）

### 【使用上の注意】

#### 1. 重要な基本的注意

- 本剤の投与は、各適応疾患の治療に精通している医師のもとで行うこと。
- 本剤の投与により**ショック、アナフィラキシー**が発現する可能性があるため、観察を十分に行うこと。また、異常が認められた場合には投与を中止し、直ちに適切な処置を行うこと。なお、ショック、アナフィラキシーは本剤投与後2時間以内に発現することが多いが、2時間以上経過してから発現することもある。また、長期間の定期的投与後においても発現することがある。本剤投与後にショック、アナフィラキシーが発現する可能性があること、及びその徴候や症状について患者に十分説明し、異常が認められた場合には、速やかに担当医師に連絡するよう、患者を指導すること。（「2. 副作用（1）重大な副作用」及び「8. その他の注意」（1）の項参照）
- 気管支喘息患者に投与する場合、本剤は気管支拡張薬、ステロイド薬、抗ヒスタミン薬等と異なり、すでに起こっている発作や症状を速やかに軽減する薬剤ではないので、患者に十分説明しておく必要がある。
- 気管支喘息患者に本剤を投与中、大発作をみた場合は気管支拡張薬あるいはステロイド薬を投与する必要がある。
- 長期ステロイド療法を受けている気管支喘息患者で、本剤投与によりステロイド薬の減量をはかる場合には十分な管理下で徐々に行うこと。
- 本剤投与中に、アレルギー性肉芽腫性血管炎（Churg-Strauss症候群）があらわれることがあり、これらの多くは経ロステロイド剤の減量・中止時に発現している。本剤使用時は、好酸球数の推移及び発疹、肺症状の悪化（肺の浸潤等）、心臓合併症（心筋炎等）、ニューロパシー等の血管炎症状に注意すること。
- 本剤の投与中止により、通常、遊離IgE濃度及び症状が治療前の状態に戻る。

- (8) 用法及び用量どおり、気管支喘息患者に投与する場合は16週間、特発性の慢性蕁麻疹患者に投与する場合は12週間使用しても効果が認められない場合には、漫然と投与を続けないよう注意すること。
- (9) 本剤投与中にめまい、疲労、失神、傾眠があらわれることがあるため、自動車の運転等危険を伴う機械の操作に従事する場合には十分に注意させること。
- (10) 本剤はIgEと複合体を形成し、遊離IgEを減少させる。IgEは寄生虫感染に対する宿主防御機能に関与する因子の1つと考えられていることから、寄生虫感染のリスクが高い地域に旅行する場合には注意すること。

## 2. 副作用

### 気管支喘息

国内で成人気管支喘息患者を対象として実施された臨床試験284例中134例(47.2%)に副作用(臨床検査値異常を含む)が認められた。主な臨床症状は、注射部位紅斑53例(18.7%)、注射部位そう痒感26例(9.2%)、注射部位腫脹24例(8.5%)、注射部位疼痛20例(7.0%)、注射部位熱感14例(4.9%)、注射部位硬結13例(4.6%)、注射部位出血12例(4.2%)、蕁麻疹、けん怠感各5例(1.8%)等であった。(成人承認時までの集計)

国内で小児気管支喘息患者を対象として実施された臨床試験38例中10例(26.3%)に副作用(臨床検査値異常を含む)が認められた。主な臨床症状は、頭痛4例(10.5%)、注射部位疼痛3例(7.9%)、注射部位紅斑、注射部位腫脹、蕁麻疹各2例(5.3%)等であった。

(小児承認時までの集計)

### 特発性の慢性蕁麻疹

特発性の慢性蕁麻疹患者を対象として実施された国際共同臨床試験において、本剤を投与した144例(日本人69例含む)中13例(9.0%)に副作用(臨床検査値異常を含む)が認められた。主な臨床症状は、頭痛3例(2.1%)、鼻咽頭炎2例(1.4%)等であった。日本人患者では69例中9例(13.0%)に副作用が認められた。

(効能又は効果の一変承認時までの集計)

### (1) 重大な副作用

**ショック、アナフィラキシー**(頻度不明)：気管支痙攣、呼吸困難、血圧低下、失神、蕁麻疹、舌浮腫、口唇浮腫、咽・喉頭浮腫等のショック、アナフィラキシーがあらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止し、直ちに適切な処置を行うこと。

### (2) その他の副作用

|                  | 頻度不明                      | 5%以上 <sup>注1)</sup> | 1%~5%未満 <sup>注1)</sup> | 1%未満 <sup>注1)</sup> |
|------------------|---------------------------|---------------------|------------------------|---------------------|
| <b>感染症及び寄生虫症</b> | 上気道感染、咽頭炎、副鼻腔炎、寄生虫感染、尿路感染 | —                   | —                      | 鼻咽頭炎                |
| <b>血液</b>        | 出血                        | —                   | —                      | 血小板数減少              |
| <b>神経系障害</b>     | 錯感覚、失神                    | —                   | 頭痛                     | 傾眠、めまい              |
| <b>血管障害</b>      | 起立性低血圧                    | —                   | —                      | 潮紅                  |

|                     | 頻度不明                    | 5%以上 <sup>注1)</sup> | 1%~5%未満 <sup>注1)</sup> | 1%未満 <sup>注1)</sup>   |
|---------------------|-------------------------|---------------------|------------------------|-----------------------|
| <b>呼吸器、胸郭及び縦隔障害</b> | 咳嗽、アレルギー性気管支痙攣、喉頭浮腫     | —                   | —                      | —                     |
| <b>胃腸障害</b>         | 下痢、上腹部痛                 | —                   | —                      | 消化不良、悪心               |
| <b>過敏症</b>          | 血管浮腫、血清病 <sup>注2)</sup> | —                   | 蕁麻疹                    | そう痒症、発疹               |
| <b>皮膚</b>           | 光線過敏、脱毛                 | —                   | —                      | —                     |
| <b>筋骨格系</b>         | 関節痛、筋痛、関節腫脹             | —                   | —                      | 四肢痛、筋骨格痛              |
| <b>全身障害</b>         | 体重増加、インフルエンザ様疾患         | —                   | けん怠感                   | 熱感、疲労、腕の腫脹、発熱         |
| <b>注射部位</b>         | —                       | 紅斑、腫脹、そう痒感、疼痛       | 出血、熱感、硬結               | 発疹、腫瘍、浮腫、蕁麻疹、しびれ感、不快感 |

注1) 国内で患者を対象に実施された全ての臨床試験から算出した。

注2) III型過敏反応であり、関節炎及び関節痛、発疹(蕁麻疹又はその他の発疹)、発熱及びリンパ節腫脹を特徴とする。

### 3. 高齢者への投与

高齢者では一般に生理機能(腎機能、肝機能、免疫機能等)が低下しているため、慎重に投与すること。

### 4. 妊婦、産婦、授乳婦等への投与

- (1) 妊婦又は妊娠している可能性のある婦人には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。〔動物実験(サル)で本剤が胎盤を通過することが報告されている。〕
- (2) 授乳中の婦人には投与を避けることが望ましい。やむを得ず投与する場合には授乳を避けさせること。〔動物実験(サル)で乳汁中への移行が報告されている。〕

### 5. 小児等への投与

- (1) 気管支喘息においては、低出生体重児、新生児、乳児又は6歳未満の幼児に対する安全性は確立していない(使用経験がない)。
- (2) 6歳以上の小児気管支喘息患者を対象とした臨床試験において、頭痛、発熱、上腹部痛が多く認められている。
- (3) 特発性の慢性蕁麻疹においては、低出生体重児、新生児、乳児、幼児又は12歳未満の小児に対する安全性は確立していない(使用経験がない)。

### 6. 臨床検査結果に及ぼす影響

本剤は血中IgEと複合体を形成するため、IgEの消失半減期が延長し、血清中総IgE濃度が上昇する。従って、本剤投与中のIgE測定値を、気管支喘息の用法・用量の再設定には用いないこと。また、高IgE血症を示す疾患(アレルギー性気管支肺アスペルギルス症等)の診断やアレルギー性の喘息の治療効果の診断の根拠として用いないこと。

### 7. 適用上の注意

#### (1) 投与経路：

本剤の投与は、皮下投与のみとし、静脈内及び筋肉内への投与は行わないこと。

**(2) 調製前の準備：**

投与量が150mgを超える場合は複数のバイアルを使用する（「(4) 投与時 投与液量一覧表」参照）。この場合、必要数の注射筒及び注射針（18ゲージ、25ゲージ）を用意すること。

**(3) 調製方法：**

- 1) 本剤の溶解には日局注射用水以外は使用しないこと。
- 2) 溶解方法
  - ① 18ゲージの注射針を装着した注射筒を用いて、1バイアルあたり日局注射用水を75mgバイアルの場合0.9mL、150mgバイアルの場合1.4mLを採取し、バイアル内の粉末にかかるように注入し、バイアルを立てた状態で約1分間渦を描くように回転させる。この間バイアルは振ったりせず静かに回し、泡が立たないようにすること。
  - ② 次いで約5分毎に5～10秒間バイアルを回し、完全に粉末を溶解させる。
  - ③ 溶解には約15～20分程度を要するが、20分以上かかる場合もある。その場合、溶液中にゲル状の粒子が見えなくなるまで②の操作を繰り返す。40分以内に溶解しない場合には使用しないこと。また、溶解時に泡立ちが見られることがある。
- 3) 溶解後は出来るだけ速やかに使用すること。直ちに使用しない場合は、2～8℃で保存し、8時間以内に使用すること。使用後の残液は使用しないこと。

**(4) 投与時：**

- 1) 外観に異常を認めた場合には使用しないこと。
- 2) 下記投与液量一覧表を参考に、必要バイアル数を溶解し、投与に必要な総投与液量を18ゲージの注射針を装着した注射筒を用いて採取する。  
**75mgバイアル：本剤1バイアルを日局注射用水0.9mLに溶解した溶液0.6mLがオマリズマブ（遺伝子組換え）の投与量75mgに相当する。**  
**150mgバイアル：本剤1バイアルを日局注射用水1.4mLに溶解した溶液1.2mLがオマリズマブ（遺伝子組換え）の投与量150mgに相当する。**
- 3) 採取後25ゲージの注射針に交換し、皮下注射する。溶液は粘性があるため、注射するのに5～10秒を要する場合がある。
- 4) 1回につき1.2mL（150mg）を超えて投与する場合には、1箇所あたり1.2mLを超えないように部位を分けて投与すること。

**投与液量一覧表**

| オマリズマブ<br>（遺伝子組換え）投与量 | 必要バイアル数の例<br>（組み合わせはこの限りではない） |           | 総投与液量 |
|-----------------------|-------------------------------|-----------|-------|
|                       | 75mgバイアル                      | 150mgバイアル |       |
| 75mg                  | 1本                            | —         | 0.6mL |
| 150mg                 | —                             | 1本        | 1.2mL |
| 225mg                 | 1本                            | 1本        | 1.8mL |
| 300mg                 | —                             | 2本        | 2.4mL |
| 375mg                 | 1本                            | 2本        | 3.0mL |
| 450mg                 | —                             | 3本        | 3.6mL |
| 525mg                 | 1本                            | 3本        | 4.2mL |
| 600mg                 | —                             | 4本        | 4.8mL |

**8. その他の注意**

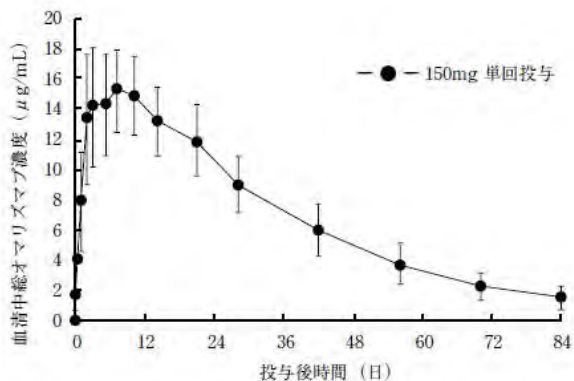
- (1) 国内臨床試験において、アナフィラキシーは報告されていないが、気管支喘息患者を対象とした海外臨床試験において報告されており、発現頻度は成人で0.1%（7例/5,367例）、小児で0.2%（1例/624例）であった。また、海外市販後の自発報告において、アナフィラキシー及びアナフィラキシーの可能性のある過敏症反応の発現頻度は、少なくとも0.2%と推定され、そのうち約30%は本剤投与2時間以降に発現していた。
- (2) 悪性腫瘍の発現頻度は、国内及び海外の無作為化プラセボ対照二重盲検臨床試験において、本剤群4,254例で4.14例/1,000人・年（14例/3,382人・年）、対照群3,178例で4.45例/1,000人・年（11例/2,474人・年）であった（発現頻度比：0.93[95%信頼区間：0.39, 2.27]）。また、5年間の追跡調査を行った気管支喘息患者を対象とした海外の市販後観察研究においては、本剤群5,007例で16.01件/1,000人・年（295件/18,426人・年）、対照群2,829例で19.07件/1,000人・年（190件/9,963人・年）であった（発現頻度比：0.84[95%信頼区間：0.62, 1.13]）。なお、本剤を悪性腫瘍のリスクが高い患者（例：高齢者、喫煙者）に使用した場合の影響は不明である。本剤のがん原性試験は、一般的にがん原性試験に使用されるマウス及びラットのIgEと結合しないことから、実施されていない。
- (3) 動脈血栓塞栓イベントの発現頻度は、国内及び海外の投与期間8週間以上無作為化プラセボ対照二重盲検臨床試験において、本剤群3,342例で2.69例/1,000人・年（5例/1,856人・年）、対照群2,895例で2.38例/1,000人・年（4例/1,680人・年）であった（発現頻度比：1.13[95%信頼区間：0.24, 5.71]）。内訳は、本剤群で心筋梗塞が2例、脳卒中、不安定狭心症、一過性脳虚血発作がそれぞれ1例、対照群で心血管死が3例、不安定狭心症が1例であった。また、5年間の追跡調査を行った気管支喘息患者を対象とした海外の市販後観察研究においては、本剤群5,007例で7.52件/1,000人・年（115件/15,286人・年）、対照群2,829例で5.12件/1,000人・年（51件/9,963人・年）であり、ベースラインの心血管危険因子で調整した多変量解析では、ハザード比1.32[95%信頼区間：0.91, 1.91]であった。
- (4) 気管支喘息患者を対象とした本剤の臨床試験は、国内成人臨床試験で48週間、国内小児臨床試験で24週間、海外成人臨床試験で5年間、海外小児臨床試験で3年間までの期間で実施されており、これらの期間を超えた本剤の長期投与時の安全性は確立していない。
- (5) 特発性の慢性蕁麻疹患者を対象とした本剤の臨床試験は、日本人の成人及び12歳以上の小児を含む臨床試験で12週間、海外の成人及び12歳以上の小児の臨床試験で最長24週間で実施されており、これらの期間を超えた本剤の長期投与時の安全性は確立していない。
- (6) 動物を用いた反復皮下投与毒性試験において、カニクイザルでは15mg/kg/週以上（幼若動物）及び30mg/kg/週以上（成熟動物）の群で、チンパンジーでは250mg/kg/週以上の群で血小板数の減少が報告されている。

(7) 本剤投与により、抗オマリズマブ抗体が発現することがある。

### 【薬物動態】

#### 国内成人単回投与試験の成績<sup>1)</sup>

日本人健康成人男子19名（血清中総IgE濃度：32～96IU/mL、体重：50.5～69.8kg）に、本剤150mgを単回皮下投与した。その時の血清中オマリズマブ（遺伝子組換え）濃度推移及び薬物動態パラメータは次のとおりであった。



血清中オマリズマブ（遺伝子組換え）濃度推移（平均値±標準偏差）

血清中オマリズマブ（遺伝子組換え）の薬物動態パラメータ (n=19)

| 投与量 (mg) | T <sub>max</sub> (日) | C <sub>max</sub> (µg/mL) | T <sub>1/2</sub> (日) | AUC <sub>0-inf</sub> (日・µg/mL) | V <sub>d</sub> /F (L) | CL/F (mL/日)   |
|----------|----------------------|--------------------------|----------------------|--------------------------------|-----------------------|---------------|
| 150      | 7<br>[2~14]          | 16.7<br>± 2.7            | 21.0<br>± 3.5        | 642<br>± 134                   | 7.25<br>± 1.33        | 242<br>± 45.4 |

T<sub>max</sub>は中央値[範囲]、その他は平均値±標準偏差

#### 母集団解析（日本人及び外国人）の成績<sup>2)</sup>

母集団解析の結果から、日本人及び外国人に投与量換算表に従って本剤（日本人：75～375mg、外国人：75～600mg）を皮下投与した際の薬物動態及び遊離IgE濃度の抑制効果は同様であることが示された。

### 【臨床成績】

#### 1. 気管支喘息

##### (1) 国内成人臨床試験<sup>3)</sup>

中等症から重症のアレルギー性喘息患者（高用量吸入ステロイド薬に加え、喘息治療薬1剤以上を併用してもコントロール不十分な患者）を対象としたプラセボ対照二重盲検比較試験において、本剤を既存治療に上乘せ投与した。朝のピークフローのベースライン値は本剤群（151例）323L/min、プラセボ群（164例）328L/minであり、最終評価時の平均改善量は本剤群で15.45L/min、プラセボ群で2.25L/min、群間差 [95%信頼区間] は13.19L/min [5.93, 20.46] と、プラセボ群に比して本剤群で有意に多かった (p<0.001、投与群、投与間隔及びベースライン値を共変量としたANCOVA)。

高用量の吸入ステロイド薬及び喘息治療薬を2剤以上併用もしくは経口ステロイド薬を併用しているにもかかわらず、喘息症状がある（毎日の喘息症状がある、週1回以上の夜間症状がある、%FEV<sub>1.0</sub>が予測値の80%未満のいずれかを満たす）という条件に合致する部分

集団（効能・効果に合致する部分集団）においては、朝のピークフローのベースライン値は本剤群（70例）308L/min、プラセボ群（91例）301L/minであり、最終評価時の平均改善量は本剤群で13.92L/min、プラセボ群で3.15L/min、群間差 [95%信頼区間] は10.77L/min [1.49, 20.04] と、プラセボ群に比して本剤群で有意に多く (p=0.023、投与群、投与間隔及びベースライン値を共変量としたANCOVA)、試験全体での結果とはほぼ同様であった。

##### (2) 海外成人臨床試験<sup>4)</sup>

重症持続型アレルギー性喘息患者（高用量吸入ステロイド薬に加え、長時間作用型β<sub>2</sub>刺激薬を併用してもコントロール不十分な患者）を対象としたプラセボ対照二重盲検比較試験において、本剤を上乘せ投与した結果、治験薬投与期間（28週間）あたりの喘息増悪（全身性ステロイド薬による治療を必要とする喘息症状の悪化）の頻度は、本剤群（209例）0.68回、プラセボ群（210例）0.91回、群間比 [95%信頼区間] は0.738 [0.552, 0.998] と、プラセボ群に比して本剤群で有意に低かった (p=0.042、投与群、投与間隔、実施国、喘息治療薬及びベースライン値を共変量としたポアソン回帰分析)。

##### (3) 国内小児臨床試験<sup>5)</sup>

最重症持続型の小児（6～15歳）アレルギー性喘息患者（吸入ステロイド薬 (>200µg/day フルチカゾンプロピオン酸エステル又は相当量)に加え、喘息治療薬2剤以上を併用してもコントロール不十分な患者）を対象とした非対照非盲検試験において、本剤を38例に24週間上乘せ投与した。治験薬投与期間（24週間）終了時の血清中遊離IgE濃度 (ng/mL) の幾何平均 [95%信頼区間] は15.551 [13.844, 17.469] と、目標濃度の25ng/mL以下に抑制された。また、喘息増悪（吸入ステロイド薬の維持用量からの倍増を3日間以上必要とする、又は全身性ステロイド薬による治療を必要とする喘息症状の悪化）の頻度は、ベースライン（試験開始前1年間と試験中の観察期間を合わせた期間）の2.99回/患者・年に対して治験薬投与期間（24週間）では0.92回/患者・年であった。

##### (4) 海外小児臨床試験<sup>6,7)</sup>

中等症～重症持続型の小児（6～11歳）アレルギー性喘息患者（吸入ステロイド薬 (≥200µg/day フルチカゾンプロピオン酸エステル又は相当量)単剤又は他の喘息治療薬を併用してもコントロール不十分な患者）を対象としたプラセボ対照二重盲検比較試験において、本剤を52週間上乘せ投与した。吸入ステロイド薬固定期間（24週間）あたりの喘息増悪（吸入ステロイド薬の維持用量からの倍増を3日間以上、又は全身性ステロイド薬による治療を3日間以上必要とする喘息症状の悪化）の頻度は、本剤群（384例）0.45回、プラセボ群（192例）0.64回、群間比 [95%信頼区間] は0.693 [0.553, 0.903] (p=0.007)、治験薬投与期間（52週間）あたりの喘息増悪の頻度は、本剤群（384例）0.78回、プラセボ群（192例）1.36回、群間比 [95%信頼区間] は0.573 [0.453, 0.725] (p<0.001) と、いずれもプラセボ群に比して本剤群で有意に低かった（投与群、投与間隔、実施国、喘息増悪歴を共変量としたポアソン回帰分析）。

吸入ステロイド薬 (>200µg/day フルチカゾンプロピオン酸エステル又は相当量) 及び喘息治療薬を2剤以上併用しているにもかかわらず、喘息症状がある(毎日の喘息症状がある、週1回以上の夜間症状がある、週1回以上の日常生活障害がある、のいずれかを満たす) という条件に合致する部分集団(効能・効果に合致する部分集団)においては、吸入ステロイド薬固定期間(24週間)あたりの喘息増悪の頻度は、本剤群(111例) 0.73回、プラセボ群(48例) 1.15回、群間比 [95%信頼区間] は0.638 [0.421, 0.966] (p=0.034)、治験薬投与期間(52週間)あたりの喘息増悪の頻度は、本剤群(111例) 1.29回、プラセボ群(48例) 2.38回、群間比 [95%信頼区間] は0.541 [0.366, 0.799] (p=0.002) と、いずれもプラセボ群に比して本剤群で有意に低く(投与群、投与間隔、喘息増悪歴を共変量としたポアソン回帰分析)、試験全体での結果とほぼ同様であった。

## 2. 特発性の慢性蕁麻疹

### 国際共同臨床試験<sup>8)</sup>

既存治療で効果不十分な12歳以上の特発性の慢性蕁麻疹患者(ヒスタミン<sub>H1</sub>受容体拮抗薬で効果不十分な患者)を対象としたプラセボ対照二重盲検比較試験において、218例(日本人105例)に本剤をヒスタミン<sub>H1</sub>受容体拮抗薬に上乗せ投与した。

プラセボ又は本剤150mg又は300mgを4週間隔で3回皮下投与した。12週後の週間そう痒スコア<sup>※</sup>のベースラインからの変化量、週間膨疹スコア<sup>※※</sup>のベースラインからの変化量及びUAS7<sup>※※※</sup>が0(以下、UAS7=0)となった患者の割合を次表に示す。

(本剤の承認された用法及び用量は【用法及び用量】の項参照)

<sup>※</sup>1週間のそう痒スコア(1日0~3)を累計したスコア。

<sup>※※</sup>1週間の膨疹スコア(1日0~3)を累計したスコア。

<sup>※※※</sup>7-day Urticaria Activity Score : 1週間のそう痒スコア及び膨疹スコアを累計したスコア。

|                | 300mg群            | 150mg群            | プラセボ群           | 群間差<br>[95%信頼区間]、p値                             |   |
|----------------|-------------------|-------------------|-----------------|---|---|
|                |                   |                   |                 | 300mg群  | 150mg群  |
| 全体集団           |                   |                   |                 |   |   |
| 週間そう痒スコア       | -10.22<br>(73例)   | -8.80<br>(70例)    | -6.51<br>(74例)  | -3.70<br>[-5.31, -2.10]<br>p<0.001 <sup>Δ</sup> | -2.29<br>[-3.92, -0.65]<br>p=0.006 <sup>Δ</sup> |
| 週間膨疹スコア        | -12.17<br>(73例)   | -10.04<br>(70例)   | -7.41<br>(74例)  | -4.76<br>[-6.84, -2.67] <sup>b</sup>            | -2.63<br>[-4.75, -0.50] <sup>b</sup>            |
| UAS7=0<br>達成割合 | 35.6%<br>(26/73例) | 18.6%<br>(13/70例) | 4.1%<br>(3/74例) |   |   |
| 日本人部分集団        |                   |                   |                 |   |   |
| 週間そう痒スコア       | -9.54<br>(35例)    | -7.29<br>(34例)    | -5.17<br>(36例)  | -4.37<br>[-6.77, -1.97] <sup>Δ</sup>            | -2.12<br>[-4.54, 0.30] <sup>Δ</sup>             |
| 週間膨疹スコア        | -12.06<br>(35例)   | -8.36<br>(34例)    | -5.77<br>(36例)  | -6.29<br>[-9.41, -3.17] <sup>Δ</sup>            | -2.59<br>[-5.74, 0.55] <sup>Δ</sup>             |
| UAS7=0<br>達成割合 | 31.4%<br>(11/35例) | 11.8%<br>(4/34例)  | 2.8%<br>(1/36例) |   |   |

a) 国、投与群、週、投与群と週の交互作用を固定効果、被験者を変量効果、ベースライン値を共変量とする反復測定混合モデルを用いて検定。

b) 国、投与群、週、投与群と週の交互作用を固定効果、被験者を変量効果、ベースライン値を共変量とする反復測定混合モデル。

c) 投与群、週、投与群と週の交互作用を固定効果、被験者を変量効果、ベースライン値を共変量とする反復測定混合モデル。

### 【薬効薬理】

本剤は、ヒト化抗ヒトIgEモノクローナル抗体であり、IgEと高親和性受容体(FcεRI)の結合を阻害することで、好塩基球、肥満細胞等の炎症細胞の活性化を抑制する。

#### 1. IgEに対する阻害作用<sup>3, 9, 10)</sup>

本剤はヒトIgEとFcεRIの結合を競合的に阻害し、血清中遊離IgE濃度を減少させた。なお、本剤はすでにFcεRIと結合したIgEには結合しない。

#### 2. ヒスタミン遊離に対する効果<sup>10)</sup>

ブタクサ特異的IgEでの感作時に本剤を添加することにより、ブタクサ抗原刺激によるヒト好塩基球からのヒスタミン遊離が抑制された。

#### 3. 気道収縮に対する効果<sup>11, 12)</sup>

気管支喘息患者において、抗原吸入による即時型喘息反応及び遅発型喘息反応が抑制された。

#### 4. 気道過敏性に対する効果<sup>13)</sup>

気管支喘息患者において、メサコリンに対する気道過敏性が改善した。

### 【有効成分に関する理化学的知見】

一般名：オマリズマブ(遺伝子組換え)

Omalizumab (Genetical Recombination)

分子量：約149,000

本質：ヒト化マウス抗ヒトIgEモノクローナル抗体由来する軽鎖(C<sub>1048</sub>H<sub>1609</sub>N<sub>278</sub>O<sub>350</sub>S<sub>6</sub>;分子量: 23,895.03)と重鎖(C<sub>2204</sub>H<sub>3389</sub>N<sub>588</sub>O<sub>673</sub>S<sub>15</sub>;分子量: 49,372.00)をコードするDNAの導入によりチャイニーズハムスター卵巣細胞で産生される糖蛋白質

### 【承認条件】

医薬品リスク管理計画を策定の上、適切に実施すること。

### 【包装】

ゾレア皮下注用75mg 1バイアル

ゾレア皮下注用150mg 1バイアル

### 【主要文献】

- 社内資料：薬物動態試験 [XOLU00001]
- 社内資料：母集団薬物動態/薬力学解析 [XOLU00017]
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- 社内資料：喘息患者を対象とした国内小児臨床試験 [XOLU00014]
- Lanier, B. et al.: J Allergy Clin Immunol. 124(6), 1210, 2009 [XOLM00980]
- 社内資料：喘息患者を対象とした海外小児臨床試験 [XOLU00015]



- 8) 社内資料：特発性の慢性蕁麻疹患者を対象とした国際  
共同試験 [20170085]
- 9) 社内資料：薬理試験（阻害様式） [XOLU00003]
- 10) 社内資料：薬理試験（ヒスタミン遊離に対する効果及  
びFcεRI結合IgEへの影響） [XOLU00008]
- 11) Fahy, J. V. et al.: Am. J. Respir. Crit. Care Med. 155(6),  
1828, 1997 [XOLM00016]
- 12) Zielen, S. et al.: Int Arch Allergy Immunol 160(1), 102,  
2013 [XOLM01866]
- 13) Boulet, L. P. et al.: Am. J. Respir. Crit. Care Med.  
155(6),1835, 1997 [XOLM00017]

**【文献請求先】**

主要文献に記載の社内資料につきましても下記にご請求  
下さい。

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**1.8.2 効能・効果（案），用法・用量（案）及び  
その設定根拠**

## 目 次

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## 略号一覧

| 略号    | 省略していない表現（英）                    | 省略していない表現（日）                |
|-------|---------------------------------|-----------------------------|
| CU    | chronic urticaria               | 慢性蕁麻疹                       |
| FcεRI | high affinity IgE receptor      | 高親和性 IgE 受容体                |
| H1AH  | H <sub>1</sub> antihistamine    | ヒスタミン H <sub>1</sub> 受容体拮抗薬 |
| H2AH  | H <sub>2</sub> antihistamine    | ヒスタミン H <sub>2</sub> 受容体拮抗薬 |
| IgE   | immunoglobulin E                | 免疫グロブリン E                   |
| LTRA  | leukotriene receptor antagonist | ロイコトリエン受容体拮抗薬               |
| MID   | minimally important difference  | 意義のある最小の差                   |
| PD    | pharmacodynamics                | 薬力学                         |
| PK    | pharmacokinetics                | 薬物動態                        |
| QOL   | quality of life                 | 生活の質                        |

## 用語の定義一覧

| 用語      | 定義  |
|---------|---|
| 試験の表記方法 | 治験実施計画書番号は，試験番号で示した。<br>例)<br>CIGE025E2306→E2306 試験 |

## 1 効能又は効果及びその設定根拠

### 1.1 効能又は効果

特発性の慢性蕁麻疹（既存治療で効果不十分な患者に限る）

### 1.2 効能又は効果の設定根拠

オマリズマブは、ヒト化抗ヒト免疫グロブリン E (immunoglobulin E, IgE) モノクローナル抗体で、血中や皮膚内の遊離 IgE に結合し、肥満細胞や好塩基球表面に発現している高親和性 IgE 受容体 (high affinity IgE receptor, FcεRI) と IgE との結合を競合的に阻害する。

慢性蕁麻疹 (chronic urticaria, CU) に対するオマリズマブの作用機序は、一つの仮説として次のように考えられる。オマリズマブが遊離 IgE に結合して血中及び皮膚組織の遊離 IgE 濃度を低下させることにより、肥満細胞及び好塩基球表面の FcεRI の発現が抑制される。その結果、FcεRI の下流シグナル経路が制御されて、肥満細胞及び好塩基球の活性化、並びにこれらの細胞からの脱顆粒が抑制され、膨疹・紅斑・痒みといった症状の発現抑制効果が期待できる (Kaplan and Greaves 2009, Saavedra and Sur 2011)。

日本皮膚科学会による蕁麻疹診療ガイドライン 2011（以下「日皮会ガイドライン 2011」）が推奨する CU の薬物治療方針によれば、CU に対する第一選択薬は第二世代ヒスタミン H<sub>1</sub> 受容体拮抗薬 (H<sub>1</sub> antihistamine, H1AH) である。しかし、承認範囲用量の第二世代 H1AH では十分な効果が得られない患者も存在する。そのような患者には、同じ薬剤の倍量投与や他の第二世代 H1AH への変更が推奨されるが、全体として第二世代 H1AH に有効な患者はいまだ 50%未満と少ない (Maurer et al. 2011, Kaplan 2012, Sánchez-Borges et al. 2014)。第二世代 H1AH で効果不十分な患者に対しては、ヒスタミン H<sub>2</sub> 受容体拮抗薬 (H<sub>2</sub> antihistamine, H2AH) やロイコトリエン受容体拮抗薬 (leukotriene receptor antagonist, LTRA) 等の補助的治療薬との併用が推奨されるが、有効性が検証された薬剤は少なく、また効果は一部の症例に限定的である (Khan 2013, Fedorowicz et al. 2012)。補助的治療薬を使用しても強い症状が続く場合は、副腎皮質ステロイド (プレドニゾン換算量で 15 mg/日まで) の使用が推奨されるが、長期的予後に対する治療効果のエビデンスはほとんどなく、逆に疾患を遷延化させやすいという専門家の意見もある (西岡 2006)。これらの治療で効果不十分、あるいはこれらの治療に不耐容の場合は、試行的治療としてシクロスポリン、メトトレキサート等の免疫抑制薬が使用されているが、リスク・ベネフィットの観点からその使用は重症例に限定される (日皮会ガイドライン 2011)。

また、上記に挙げられた薬剤の中で、蕁麻疹、又は蕁麻疹に伴うそう痒を効能・効果として承認されている薬剤は、H1AH 及び副腎皮質ステロイド (重症例に限る) のみである。H2AH,

LTRA，及びシクロスポリン等の免疫抑制薬は蕁麻疹，又は蕁麻疹に伴うそう痒を効能・効果として承認されておらず，蕁麻疹に対する適応を持つ薬剤は限られている。

これらの状況を踏まえ，標準治療である第二世代 H1AH で効果不十分な CU 患者に対する有効な治療薬が必要であり，オマリズマブは，他の治療薬とは異なる作用機序を有することから，既存治療で効果不十分な CU 患者に対する新規の有効な治療法になり得ると期待された。

H1AH で効果不十分な日本人の CU 患者に対するオマリズマブの有効性及び安全性は，日本及び韓国で実施した国際共同第 III 相臨床試験（E2306 試験）の結果を中心に評価した。主要評価項目である最終評価時（Week 12）の週間そう痒スコアのベースラインからの変化量に対する群間比較の結果，オマリズマブ 300 mg 及び 150 mg のプラセボに対する優越性が検証された。E2306 試験で，オマリズマブの忍容性は良好であることが確認された。試験期間中（投与期及び追跡調査期）のオマリズマブ投与群の有害事象発現率はプラセボ群と同程度で，発現した有害事象のほとんどが軽度または中等度であった。本試験で認められた有害事象は，外国の CU 患者での臨床試験や既承認の気管支喘息患者を対象とした国内外の臨床・市販後安全性データから予測されるもので，新たな安全性上の懸念は認められなかった。

以上より，E2306 試験で既存治療に効果不十分な CU 患者に対する有効性及び安全性が確認されたことから，オマリズマブの効能又は効果を「慢性蕁麻疹（既存治療で効果不十分な患者に限る）」と設定した。

さらに，審査中の独立行政法人医薬品医療機器総合機構との協議内容を踏まえ，本剤の投与対象をより明確にするため，効能又は効果（案）を「特発性の慢性蕁麻疹（既存治療で効果不十分な患者に限る）」に変更した。

### 1.3 効能又は効果に関連する使用上の注意

食物，物理的刺激等の蕁麻疹の症状を誘発する原因が特定されず，ヒスタミン H<sub>1</sub> 受容体拮抗薬の増量等の適切な治療を行っても，日常生活に支障をきたすほどの痒みを伴う膨疹が繰り返して継続的に認められる場合に本剤を追加して投与すること。

### 1.4 効能又は効果に関連する使用上の注意の設定根拠

審査中の独立行政法人医薬品医療機器総合機構との協議内容を踏まえ，本剤の投与対象をより具体的に説明し明確にするため，効能又は効果に関連する使用上の注意（案）として設定した。

## 2 用法及び用量及びその設定根拠

### 2.1 用法及び用量

通常、成人及び12歳以上の小児にはオマリズマブ（遺伝子組換え）として1回300 mgを4週間毎に皮下に注射する。

### 2.2 用法及び用量の設定根拠

オマリズマブのCUにおける申請推奨用法・用量は「通常、成人及び12歳以上の小児にはオマリズマブ（遺伝子組換え）として1回300 mgを4週間毎に皮下に注射する。」とした。これは、オマリズマブの臨床試験で有効性が検証され、安全性が確認された用法・用量である。

#### 2.2.1 用法の設定根拠

推奨用法は、外国の第II相試験（Q4577g試験）の結果、外国第III相試験（Q4881g, Q4882g, Q4883g試験）のデータに基づいたモデル&シミュレーション、及びE2306試験の結果を踏まえ設定した。

外国では、第III相検証試験で用いる至適用法・用量を決定するにあたり、オマリズマブ75 mg, 300 mg, 600 mgを用い、単回投与したときの用量反応性を検討する第II相用量反応試験（Q4577g試験）を実施した。Q4577g試験の結果、臨床効果は投与4週後に最大となることが明らかとなったことから、以降の試験では投与間隔を4週間として計画した。なお、4週間隔投与の妥当性は、外国第III相試験（Q4881g, Q4882g, Q4883g試験）のデータを用いて構築した母集団薬物動態（pharmacokinetics, PK）/薬力学（pharmacodynamics, PD）モデルによっても評価した。シミュレーションの結果、オマリズマブは投与間隔を4週間とした場合に、CUの症状を良好にコントロールできることが示された（2.7.2-3.4.4項）。

\_\_\_\_\_するため、オマリズマブの有効性・安全性に関する\_\_\_\_\_したところ、以下の観点からオマリズマブは\_\_\_\_\_が考えられた（\_\_\_\_\_項）。

- \_\_\_\_\_
  - \_\_\_\_\_に関して、\_\_\_\_\_
- \_\_\_\_\_と考えられたこと

そのため、\_\_\_\_\_と考え、E2306試験では4週間ごとに皮下に投与する方法を選択した。その結果、投与開始

後速やかに十分な CU の臨床症状の改善が認められるとともに、その効果は次回の投与まで持続することが確認できた。

以上より、「4 週間毎に皮下に注射する」を推奨用法と設定した。

## 2.2.2 用量の設定根拠

固定用量の妥当性について、外国第 III 相試験（Q4881g, Q4882g, Q4883g 試験）から得られた母集団 PK/PD モデルを用い、「固定用量（150 mg, 300 mg）」、「体重による用量調節」、及び「体重とベースライン IgE 濃度による用量調節」のそれぞれの血清中オマリズマブ濃度へ及びばす影響を比較評価した上で検討した。オマリズマブの投与は 4 週間隔とし、Week 12 の血清中オマリズマブ濃度を推定した。その結果、体重による用量調節は固定用量よりも Week 12 の血清中オマリズマブ濃度のばらつきを約 40%低下させたが、体重とベースライン IgE 濃度によって用量調節した場合は固定用量よりもばらつきを 200%超増加させた。したがって、CU 患者では、ベースライン IgE 濃度に基づく用量調節はオマリズマブの血清中濃度のばらつきを増加させる可能性が示唆された（2.7.2-3.2.4 項）。

また、母集団 PK/PD モデル及び PK-有効性モデルを用い、上記 3 つの用法・用量が有効性（Week 12 の週間そう痒スコアの変化量及び完全寛解の割合）のばらつき（個体間変動）に及びばす影響をシミュレーションにより比較評価した。その結果、「体重による用量調節」及び「体重とベースライン IgE 濃度による用量調節」のいずれも、固定用量に比べて有効性のばらつきを臨床的に意味のある程度には改善（減少）しなかった（2.7.2-3.3.4 項）。したがって、CU 患者に対しては体重とベースライン IgE 濃度による用量調節は不要で、固定用量による投与が適切であると判断した。

また、推奨用量を 300 mg と設定することについては、E2306 試験の結果を中心に、外国第 III 相試験（Q4881g, Q4882g, Q4883g 試験）の結果も踏まえ、判断した。

E2306 試験の結果、オマリズマブ 300 mg, 150 mg の有効性はプラセボに比べて優れることが検証できた。用量別では、300 mg は主要評価及びすべての副次評価項目で、150 mg は主要評価項目及びほとんどの副次評価項目でプラセボ群との比較で有意な差が認められ、また、生活の質（quality of life, QOL）の改善を含むすべての評価項目で 300 mg の有効性は 150 mg よりも高いことが示された。特に、CU の治療で重要な臨床上の課題である「安定した症状のコントロール（レスポンドー）」が得られる被験者の割合は、300 mg 投与では約 6 割（57.5%）と多く（150 mg 群 42.9%）、また「症状（そう痒及び膨疹）の完全な消失（完全寛解）」が得られる被験者は、300 mg 投与が 150 mg 投与に比べて約 2 倍多く認められた（それぞれ 35.6%, 18.6%）。また、300 mg 群では投与 12 週後に約 9 割（87.7%）の被験者のそう痒症状が臨床的に意義のあるレベル（minimally important difference, MID）まで改善した（2.5-6.1 項）。

外国の第 III 相試験の結果も E2306 試験と同様で、オマリズマブの有効性に関する結論は頑健であると考えられる。

以上より、オマリズマブ 300 mg, 150 mg はいずれも H1AH で効果不十分な CU 患者に有効であることが確認できたが、300 mg 投与の有効性は 150 mg よりも高く、かつ確実であると考えられた。

安全性では、オマリズマブ 300 mg, 150 mg の忍容性は良好で、用量の増加にともなって有害事象の発現率が高くなることはなく、有害事象の重症度が悪化することもなかった。E2306 試験で認められた有害事象は、外国の CU 患者での臨床試験や既承認の適応症での臨床・市販後安全性データから予測されるもので、新たな事象は認められなかった。

以上より、300 mg を申請用量と設定した。

### 2.2.3 対象患者の設定根拠

E2306 試験及び外国第 III 相試験（Q4881g, Q4882g, Q4883g 試験）結果に基づき、オマリズマブの対象患者を 12 歳以上と設定した。

12 歳以上 18 歳未満の CU 患者の推奨用法・用量に関しては、E2306 試験、外国第 III 相試験に参加したこの年齢層の患者が少ないため、断定的な結論を得ることは難しい。しかしながら、青少年（12 歳以上 18 歳未満）の CU 患者の疾患の自然経過、臨床的・病理学的特性及び治療指針は成人と同様であり（Zuberbier et al. 2014），国内外の第 III 相試験の結果からも、12 歳以上 18 歳未満の CU 患者でのオマリズマブ 4 週間隔投与の臨床効果は成人の CU 患者と同様に有効で、これらの年齢層の患者に特別な安全性の懸念はないことが明らかとなった。したがって、12 歳以上 18 歳未満の CU 患者の推奨用法・用量は、E2306 試験の全体集団の結果を中心に決定した推奨用法・用量と同じとすることは妥当と考えた。

なお、12 歳未満の小児に対する使用経験はなく、有効性・安全性は確立されていない。

## 2.3 用法及び用量に関連する使用上の注意

日本人を対象とした臨床試験において、本剤の 12 週以降の使用経験は無いため、12 週以降も継続して投与する場合は、患者の状態を考慮し、その必要性を慎重に判断すること。（「8. その他の注意」 (5)，【臨床成績】の項参照）

## 2.4 用法及び用量に関連する使用上の注意の設定根拠

審査中の独立行政法人医薬品医療機器総合機構との協議内容を踏まえ、日本人の CU 患者において、本剤を 12 週以降も継続して投与したときの臨床試験成績が得られていないことから、12 週以上の継続投与の必要性を慎重に判断する必要があると考えたため、用法及び用量に関連する使用上の注意（案）として設定した。



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### **1.8.3 使用上の注意（案）及びその設定根拠**

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## 1 禁忌欄

### 1.1 禁忌

**【禁忌（次の患者には投与しないこと）】**

本剤の成分に対し過敏症の既往歴のある患者

### 1.2 禁忌の設定根拠

現行添付文書の変更を要する追加情報はないため、現行添付文書に基づき設定した。

## 2 重要な基本的注意欄

### 2.1 重要な基本的注意

- (1) 本剤の投与は、各適応疾患の治療に精通している医師のもとで行うこと。
- (2) 本剤の投与によりショック、アナフィラキシーが発現する可能性があるため、観察を十分に行うこと。また、異常が認められた場合には投与を中止し、直ちに適切な処置を行うこと。なお、ショック、アナフィラキシーは本剤投与後 2 時間以内に発現することが多いが、2 時間以上経過してから発現することもある。また、長期間の定期的投与後においても発現することがある。本剤投与後にショック、アナフィラキシーが発現する可能性があること、及びその徴候や症状について患者に十分説明し、異常が認められた場合には、速やかに担当医師に連絡するよう、患者を指導すること。（「2. 副作用（1）重大な副作用」及び「8. その他の注意」（1）の項参照）
- (3) 気管支喘息患者に投与する場合、本剤は気管支拡張薬、ステロイド薬、抗ヒスタミン薬等と異なり、すでに起こっている発作や症状を速やかに軽減する薬剤ではないので、患者に十分説明しておく必要がある。
- (4) 気管支喘息患者に本剤を投与中、大発作をみた場合は気管支拡張薬あるいはステロイド薬を投与する必要がある。
- (5) 長期ステロイド療法を受けている気管支喘息患者で、本剤投与によりステロイド薬の減量をはかる場合には十分な管理下で徐々に行うこと。
- (6) 本剤投与中に、アレルギー性肉芽腫性血管炎（Churg-Strauss 症候群）があらわれることがあり、これらの多くは経口ステロイド剤の減量・中止時に発現している。本剤使用時は、好酸球数の推移及び発疹、肺症状の悪化（肺の浸潤等）、心臓合併症（心筋炎等）、ニューロパシー等の血管炎症状に注意すること。
- (7) 本剤の投与中止により、通常、遊離 IgE 濃度及び症状が治療前の状態に戻る。

- (8) 用法及び用量どおり、気管支喘息患者に投与する場合は 16 週間、特発性の慢性蕁麻疹患者に投与する場合は 12 週間使用しても効果が認められない場合には、漫然と投与を続けないよう注意すること。
- (9) 本剤投与中にめまい、疲労、失神、傾眠があらわれることがあるため、自動車の運転等危険を伴う機械の操作に従事する場合には十分に注意させること。
- (10) 本剤は IgE と複合体を形成し、遊離 IgE を減少させる。IgE は寄生虫感染に対する宿主防御機能に関与する因子の 1 つと考えられていることから、寄生虫感染のリスクが高い地域に旅行する場合には注意すること。

(下線部：一変申請に伴う改訂)

## 2.2 重要な基本的注意の設定根拠

- (1)気管支喘息及び慢性蕁麻疹両疾患の治療に精通している医師が使用するよう記載を変更した。
- (3)(5)気管支喘息患者に対する注意であることから、対象を明記した。
- (6)気管支喘息、慢性蕁麻疹の区別なく当てはまる記載であることから、喘息に関する記載を削除した。
- (8) 慢性蕁麻疹患者においても漫然と使用することのないよう追記した。慢性蕁麻疹患者における期間は、日本人患者を含む臨床試験の投与期間とした。
- その他は、現行添付文書の変更を要する追加情報はないため、現行添付文書に基づき設定した。

## 3 副作用欄

### 3.1 副作用

#### 気管支喘息

国内で成人気管支喘息患者を対象として実施された臨床試験 284 例中 134 例 (47.2%) に副作用 (臨床検査値異常を含む) が認められた。主な臨床症状は、注射部位紅斑 53 例 (18.7%)、注射部位そう痒感 26 例 (9.2%)、注射部位腫脹 24 例 (8.5%)、注射部位疼痛 20 例 (7.0%)、注射部位熱感 14 例 (4.9%)、注射部位硬結 13 例 (4.6%)、注射部位出血 12 例 (4.2%)、蕁麻疹、けん怠感各 5 例 (1.8%) 等であった。

(成人承認時までの集計)

国内で小児気管支喘息患者を対象として実施された臨床試験 38 例中 10 例 (26.3%) に副作用 (臨床検査値異常を含む) が認められた。主な臨床症状は、頭痛 4 例 (10.5%)、注射部位疼痛 3 例 (7.9%)、注射部位紅斑、注射部位腫脹、蕁麻疹各 2 例 (5.3%) 等であった。

(小児承認時までの集計)

#### 特発性の慢性蕁麻疹

特発性の慢性蕁麻疹患者を対象として実施された国際共同臨床試験において、本剤を投与した 144 例 (日本人 69 例含む) 中 13 例 (9.0%) に副作用 (臨床検査値異常を含む) が認められた。

主な臨床症状は、頭痛 3 例（2.1%）、鼻咽頭炎 2 例（1.4%）等であった。日本人患者では 69 例中 9 例（13.0%）に副作用が認められた。

（効能又は効果の一変承認時までの集計）

(1) 重大な副作用

ショック、アナフィラキシー（頻度不明）：気管支痙攣，呼吸困難，血圧低下，失神，蕁麻疹，舌浮腫，口唇浮腫，咽・喉頭浮腫等のショック，アナフィラキシーがあらわれることがあるので，観察を十分に行い，異常が認められた場合には投与を中止し，直ちに適切な処置を行うこと。

(2) その他の副作用

|                     | 頻度不明                      | 5%以上 <sup>注1)</sup> | 1%～5%未満 <sup>注1)</sup> | 1%未満 <sup>注1)</sup>   |
|---------------------|---------------------------|---------------------|------------------------|-----------------------|
| <b>感染症及び寄生虫症</b>    | 上気道感染，咽頭炎，副鼻腔炎，寄生虫感染，尿路感染 | —                   | —                      | 鼻咽頭炎                  |
| <b>血液</b>           | 出血                        | —                   | —                      | 血小板数減少                |
| <b>神経系障害</b>        | 錯感覚，失神                    | —                   | 頭痛                     | 傾眠，めまい                |
| <b>血管障害</b>         | 起立性低血圧                    | —                   | —                      | 潮紅                    |
| <b>呼吸器，胸郭及び縦隔障害</b> | 咳嗽，アレルギー性気管支痙攣，喉頭浮腫       | —                   | —                      | —                     |
| <b>胃腸障害</b>         | 下痢，上腹部痛                   | —                   | —                      | 消化不良，悪心               |
| <b>過敏症</b>          | 血管浮腫，血清病 <sup>注2)</sup>   | —                   | 蕁麻疹                    | そう痒症，発疹               |
| <b>皮膚</b>           | 光線過敏，脱毛                   | —                   | —                      | —                     |
| <b>筋骨格系</b>         | 関節痛，筋痛，関節腫脹               | —                   | —                      | 四肢痛，筋骨格痛              |
| <b>全身障害</b>         | 体重増加，インフルエンザ様疾患           | —                   | けん怠感                   | 熱感，疲労，腕の腫脹，発熱         |
| <b>注射部位</b>         | —                         | 紅斑，腫脹，そう痒感，疼痛       | 出血，熱感，硬結               | 発疹，腫瘍，浮腫，蕁麻疹，しびれ感，不快感 |

注 1) 国内で患者を対象に実施された全ての臨床試験から算出した。

注 2) III 型過敏反応であり，関節炎及び関節痛，発疹（蕁麻疹又はその他の発疹），発熱及びリンパ節腫脹を特徴とする。

（下線部：一変申請に伴う改訂）

3.2 副作用の設定根拠

慢性蕁麻疹として E2306 試験の副作用発生状況の概要を追記した。

CDS の「7. Adverse drug reactions」の項に記載されている慢性蕁麻疹を対象とした臨床試験の副作用のうち現行添付文書に記載されていなかった副作用：上気道感染，鼻咽頭炎，副鼻腔炎，尿路感染，四肢痛，筋骨格痛を「その他の副作用」に追記した。また，追加副作用の SOC「感染症及び寄生虫症」が分類名になかったため新たに分類名に追加し，現行添付文書の分類名「その他」に記載の「寄生虫感染」及び分類名「呼吸器，胸郭及び縦隔障害」に記載の「咽頭炎」をこの分類に移動した。分類名「その他」には副作用がなくなったことから削除した。

「重大な副作用」及び「その他の副作用」の頻度は，小児承認時までの集計である B1301，B1301E1，A1303，A1304，A1305，A1306（A1303 extension），及び A1307 試験（すべて国内試験）の本剤投与患者の集計に，E2306 試験で本剤を投与された日本人患者を追加した計 593 例で認められた副作用の集計に基づき記載した。これらの臨床試験で認められていない副作用については頻度不明とした。

## 4 高齢者への投与欄

### 4.1 高齢者への投与

高齢者では一般に生理機能（腎機能，肝機能，免疫機能等）が低下しているため，慎重に投与すること。

### 4.2 高齢者への投与の設定根拠

現行添付文書の変更を要する追加情報はないため，現行添付文書に基づき設定した。

## 5 妊婦，産婦，授乳婦等への投与欄

### 5.1 妊婦，産婦，授乳婦等への投与

- (1) 妊婦又は妊娠している可能性のある婦人には，治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。〔動物実験（サル）で本剤が胎盤を通過することが報告されている。〕
- (2) 授乳中の婦人には投与を避けることが望ましい。やむを得ず投与する場合には授乳を避けさせること。〔動物実験（サル）で乳汁中への移行が報告されている。〕

### 5.2 妊婦，産婦，授乳婦等への投与の設定根拠

現行添付文書の変更を要する追加情報はないため，現行添付文書に基づき設定した。

## 6 小児等への投与欄

### 6.1 小児等への投与

- (1) 気管支喘息においては、低出生体重児、新生児、乳児又は 6 歳未満の幼児に対する安全性は確立していない（使用経験がない）。
- (2) 6 歳以上の小児気管支喘息患者を対象とした臨床試験において、頭痛、発熱、上腹部痛が多く認められている。
- (3) 特発性の慢性蕁麻疹においては、低出生体重児、新生児、乳児、幼児又は 12 歳未満の小児に対する安全性は確立していない（使用経験がない）。

（下線部：一変申請に伴う改訂）

### 6.2 小児等への投与の設定根拠

- (1)(2)気管支喘息における記載であることから、対象を明記した。
- (3)国内外の慢性蕁麻疹における臨床試験において、12 歳未満の患者へは投与経験がないことから設定した。

## 7 臨床検査結果に及ぼす影響欄

### 7.1 臨床検査結果に及ぼす影響

本剤は血中 IgE と複合体を形成するため、IgE の消失半減期が延長し、血清中総 IgE 濃度が上昇する。従って、本剤投与中の IgE 測定値を、気管支喘息の用法・用量の再設定には用いないこと。また、高 IgE 血症を示す疾患（アレルギー性気管支肺アスペルギルス症等）の診断やアレルギー性の喘息の治療効果の診断の根拠として用いないこと。

（下線部：一変申請に伴う改訂）

### 7.2 臨床検査結果に及ぼす影響の設定根拠

IgE 値に基づいて投与量を設定するのは気管支喘息へ使用する場合であるため、対象を明記した。

## 8 適用上の注意欄

### 8.1 適用上の注意

#### (1) 投与経路：

本剤の投与は、皮下投与のみとし、静脈内及び筋肉内への投与は行わないこと。

#### (2) 調製前の準備：

投与量が 150mg を超える場合は複数のバイアルを使用する（「(4) 投与時 投与液量一覧表」参照）。この場合、必要数の注射筒及び注射針（18 ゲージ、25 ゲージ）を用意すること。

#### (3) 調製方法：



- 1) 本剤の溶解には日局注射用水以外は使用しないこと。
- 2) 溶解方法
  - ① 18 ゲージの注射針を装着した注射筒を用いて、1 バイアルあたり日局注射用水を 75mg バイアルの場合 0.9mL、150mg バイアルの場合 1.4mL を採取し、バイアル内の粉末にかかるように注入し、バイアルを立てた状態で約 1 分間渦を描くように回転させる。この間バイアルは振ったりせず静かに回し、泡が立たないようにすること。
  - ② 次いで約 5 分毎に 5～10 秒間バイアルを回し、完全に粉末を溶解させる。
  - ③ 溶解には約 15～20 分程度を要するが、20 分以上かかる場合もある。その場合、溶液中にゲル状の粒子が見えなくなるまで②の操作を繰り返す。40 分以内に溶解しない場合には使用しないこと。また、溶解時に泡立ちが見られることがある。
- 3) 溶解後は出来るだけ速やかに使用すること。直ちに使用しない場合は、2～8 °C で保存し、8 時間以内に使用すること。使用後の残液は使用しないこと。

**(4) 投与時：**

- 1) 外観に異常を認めた場合には使用しないこと。
- 2) 下記投与液量一覧表を参考に、必要バイアル数を溶解し、投与に必要な総投与液量を 18 ゲージの注射針を装着した注射筒を用いて採取する。  
**75mg バイアル：本剤 1 バイアルを日局注射用水 0.9mL に溶解した溶液 0.6mL がオマリズマブ（遺伝子組換え）の投与量 75mg に相当する。**  
**150mg バイアル：本剤 1 バイアルを日局注射用水 1.4mL に溶解した溶液 1.2mL がオマリズマブ（遺伝子組換え）の投与量 150mg に相当する。**
- 3) 採取後 25 ゲージの注射針に交換し、皮下注射する。溶液は粘性があるため、注射するのに 5～10 秒を要する場合がある。
- 4) 1 回につき 1.2mL（150mg）を超えて投与する場合には、1 箇所あたり 1.2mL を超えないように部位を分けて投与すること。

**投与液量一覧表**

| オマリズマブ（遺伝子組換え）投与量 | 必要バイアル数の例<br>(組み合わせはこの限りではない) |            | 総投与液量 |
|-------------------|-------------------------------|------------|-------|
|                   | 75mg バイアル                     | 150mg バイアル |       |
| 75mg              | 1 本                           | —          | 0.6mL |
| 150mg             | —                             | 1 本        | 1.2mL |
| 225mg             | 1 本                           | 1 本        | 1.8mL |
| 300mg             | —                             | 2 本        | 2.4mL |
| 375mg             | 1 本                           | 2 本        | 3.0mL |
| 450mg             | —                             | 3 本        | 3.6mL |
| 525mg             | 1 本                           | 3 本        | 4.2mL |
| 600mg             | —                             | 4 本        | 4.8mL |

（下線部：一変申請に伴う改訂）

## 8.2 適用上の注意の設定根拠

現行添付文書の変更を要する追加情報はないため、現行添付文書に基づき設定したが、投与液量一覧表の記載整備を行った。

## 9 その他の注意欄

### 9.1 その他の注意

- (1) 国内臨床試験において、アナフィラキシーは報告されていないが、気管支喘息患者を対象とした海外臨床試験において報告されており、発現頻度は成人で 0.1% (7 例/5,367 例)、小児で 0.2% (1 例/624 例) であった。また、海外市販後の自発報告において、アナフィラキシー及びアナフィラキシーの可能性のある過敏症反応の発現頻度は、少なくとも 0.2%と推定され、そのうち約 30%は本剤投与 2 時間以降に発現していた。
- (2) 悪性腫瘍の発現頻度は、国内及び海外の無作為化プラセボ対照二重盲検臨床試験において、本剤群 4,254 例で 4.14 例/1,000 人・年 (14 例/3,382 人・年)、対照群 3,178 例で 4.45 例/1,000 人・年 (11 例/2,474 人・年) であった (発現頻度比 : 0.93 [95%信頼区間 : 0.39, 2.27])。また、5 年間の追跡調査を行った気管支喘息患者を対象とした海外の市販後観察研究においては、本剤群 5,007 例で 16.01 件/1,000 人・年 (295 件/18,426 人・年)、対照群 2,829 例で 19.07 件/1,000 人・年 (190 件/9,963 人・年) であった (発現頻度比 : 0.84 [95%信頼区間 : 0.62, 1.13])。なお、本剤を悪性腫瘍のリスクが高い患者 (例 : 高齢者、喫煙者) に使用した場合の影響は不明である。本剤のがん原性試験は、一般的にがん原性試験に使用されるマウス及びラットの IgE と結合しないことから、実施されていない。
- (3) 動脈血栓塞栓イベントの発現頻度は、国内及び海外の投与期間 8 週間以上無作為化プラセボ対照二重盲検臨床試験において、本剤群 3,342 例で 2.69 例/1,000 人・年 (5 例/1,856 人・年)、対照群 2,895 例で 2.38 例/1,000 人・年 (4 例/1,680 人・年) であった (発現頻度比 : 1.13 [95%信頼区間 : 0.24, 5.71])。内訳は、本剤群で心筋梗塞が 2 例、脳卒中、不安定狭心症、一過性脳虚血発作がそれぞれ 1 例、対照群で心血管死が 3 例、不安定狭心症が 1 例であった。また、5 年間の追跡調査を行った気管支喘息患者を対象とした海外の市販後観察研究においては、本剤群 5,007 例で 7.52 件/1,000 人・年 (115 件/15,286 人・年)、対照群 2,829 例で 5.12 件/1,000 人・年 (51 件/9,963 人・年) であり、ベースラインの心血管危険因子で調整した多変量解析では、ハザード比 1.32 [95%信頼区間 : 0.91, 1.91] であった。
- (4) 気管支喘息患者を対象とした本剤の臨床試験は、国内成人臨床試験で 48 週間、国内小児臨床試験で 24 週間、海外成人臨床試験で 5 年間、海外小児臨床試験で 3 年間までの期間で実施されており、これらの期間を超えた本剤の長期投与時の安全性は確立していない。

- (5) 特発性の慢性蕁麻疹患者を対象とした本剤の臨床試験は、日本人の成人及び 12 歳以上の小児を含む臨床試験で 12 週間、海外の成人及び 12 歳以上の小児の臨床試験で最長 24 週間で実施されており、これらの期間を超えた本剤の長期投与時の安全性は確立していない。
- (6) 動物を用いた反復皮下投与毒性試験において、カニクイザルでは 15mg/kg/週以上（幼若動物）及び 30mg/kg/週以上（成熟動物）の群で、チンパンジーでは 250mg/kg/週の群で血小板数の減少が報告されている。
- (7) 本剤投与により、抗オマリズマブ抗体が発現することがある。

（下線部：一変申請に伴う改訂）

## 9.2 その他の注意の設定根拠

- (1)-(4)気管支喘息を対象とした臨床試験からのデータについて対象を明記した。
- (5)日本人慢性蕁麻疹を対象とした臨床試験においては 12 週間、海外臨床試験においても 24 週間を超える投与経験はないことから設定した。
- その他は、現行添付文書の変更を要する追加情報はないため、現行添付文書に基づき設定した。

## **1.9 一般的名称に係る文書**

**既承認医薬品に係る資料を参照**

## 1.10 毒薬・劇薬等の指定審査資料のまとめ

## &lt;現行&gt;

| 化学名・別名               | ヒト化マウス抗ヒトIgEモノクローナル抗体で1,338個のアミノ酸残基からなる糖たん白質(分子量:約149,000)(別名オマリズマブ(遺伝子組換え))及びその製剤  |                      |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
|----------------------|---|----------------------|------------|------------|------------|------------|------------|------------|-------------|--------------|--|--|------------|------------|------------|------------|------------|------------|------------|------------|-------------|--------------|---------|-------|-------|-------|--------|--------|--------|--------|--------|--------|--------|----------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|----------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--|----------|--------|--------|--------|--------|--------|--------|--------|--------|--|--|----------|--------|--------|--------|--------|--------|--------|--|--|--|--|----------|--------|--------|--------|--------|--------|--|--|--|--|--|----------|--------|--|--------|--------|--|--|--|--|--|--|----------|--|--|--|--|--|--|--|--|--|--|----------|--|--|--|--|--|--|--|--|--|--|------------|--|--|--|--|--|--|--|--|--|--|--------------|--|--|--|--|--|--|--|--|--|--|--------------|--|--|--|--|--|--|--|--|--|--|--------------|--|--|--|--|--|--|--|--|--|--|--------------|--|--|--|--|--|--|--|--|--|--|----------------------|--------|--|--|--|--|--|--|--|--|--|------------|------------|------------|------------|------------|------------|------------|------------|-------------|--------------|---------|--|--|--|--|--|--|--|--|--|--|----------|--|--|--|--|--|--|--|--|--|--|----------|--|--|--|--|--|--|--|--|--|--------|----------|--|--|--|--|--|--|--|--|--------|--------|----------|--|--|--|--|--|--|--------|--------|--------|--------|----------|--|--|--|--|--|--------|--------|--------|--------|--|----------|--|--------|--|--|--------|--------|--------|--------|--|--|----------|--------|--------|--------|--------|--------|--------|--------|--------|--|--|----------|--------|--------|--------|--------|--------|--------|--------|--|--|--|------------|--------|--------|--------|--------|--------|--------|--|--|--|--|--------------|--------|--------|--------|--------|--------|--|--|--|--|--|--------------|--------|--------|--------|--------|--------|--|--|--|--|--|--------------|--------|--------|--------|--------|--|--|--|--|--|--|--------------|--------|--------|--------|--------|--|--|--|--|--|--|
| 構造式                  | 省略  |                      |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| 効能・効果                | 気管支喘息(既存治療によっても喘息症状をコントロールできない難治の患者に限る)   |                      |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| 用法・用量                | <p>通常、オマリズマブ(遺伝子組換え)として1回75~600mgを2又は4週間毎に皮下に注射する。1回あたりの投与量並びに投与間隔は、初回投与前の血清中総IgE濃度及び体重に基づき、下記の投与量換算表により設定する。</p> <p>投与量換算表(1回投与量)</p> <p>4週間毎投与</p> <table border="1"> <thead> <tr> <th rowspan="2">投与前の血清中総IgE濃度(IU/mL)</th> <th colspan="10">体重(kg)</th> </tr> <tr> <th>≥20<br/>~25</th> <th>&gt;25<br/>~30</th> <th>&gt;30<br/>~40</th> <th>&gt;40<br/>~50</th> <th>&gt;50<br/>~60</th> <th>&gt;60<br/>~70</th> <th>&gt;70<br/>~80</th> <th>&gt;80<br/>~90</th> <th>&gt;90<br/>~125</th> <th>&gt;125<br/>~150</th> </tr> </thead> <tbody> <tr> <td>≥30~100</td> <td>75 mg</td> <td>75 mg</td> <td>75 mg</td> <td>150 mg</td> <td>150 mg</td> <td>150 mg</td> <td>150 mg</td> <td>150 mg</td> <td>300 mg</td> <td>300 mg</td> </tr> <tr> <td>&gt;100~200</td> <td>150 mg</td> <td>150 mg</td> <td>150 mg</td> <td>300 mg</td> <td>300 mg</td> <td>300 mg</td> <td>300 mg</td> <td>300 mg</td> <td>450 mg</td> <td>600 mg</td> </tr> <tr> <td>&gt;200~300</td> <td>150 mg</td> <td>150 mg</td> <td>225 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mg | 450 mg | 450 mg | 600 mg |  | >300~400 | 225 mg | 225 mg | 300 mg | 450 mg | 450 mg | 450 mg | 600 mg | 600 mg |  |  | >400~500 | 225 mg | 300 mg | 450 mg | 450 mg | 600 mg | 600 mg |  |  |  |  | >500~600 | 300 mg | 300 mg | 450 mg | 600 mg | 600 mg |  |  |  |  |  | >600~700 | 300 mg |  | 450 mg | 600 mg |  |  |  |  |  |  | >700~800 |  |  |  |  |  |  |  |  |  |  | >800~900 |  |  |  |  |  |  |  |  |  |  | >900~1,000 |  |  |  |  |  |  |  |  |  |  | >1,000~1,100 |  |  |  |  |  |  |  |  |  |  | >1,100~1,200 |  |  |  |  |  |  |  |  |  |  | >1,200~1,300 |  |  |  |  |  |  |  |  |  |  | >1,300~1,500 |  |  |  |  |  |  |  |  |  |  | 投与前の血清中総IgE濃度(IU/mL) | 体重(kg) |  |  |  |  |  |  |  |  |  | ≥20<br>~25 | >25<br>~30 | >30<br>~40 | >40<br>~50 | >50<br>~60 | >60<br>~70 | >70<br>~80 | >80<br>~90 | >90<br>~125 | >125<br>~150 | ≥30~100 |  |  |  |  |  |  |  |  |  |  | >100~200 |  |  |  |  |  |  |  |  |  |  | >200~300 |  |  |  |  |  |  |  |  |  | 375 mg | >300~400 |  |  |  |  |  |  |  |  | 450 mg | 525 mg | >400~500 |  |  |  |  |  |  | 375 mg | 375 mg | 525 mg | 600 mg | >500~600 |  |  |  |  |  | 375 mg | 450 mg | 450 mg | 600 mg |  | >600~700 |  | 225 mg |  |  | 375 mg | 450 mg | 450 mg | 525 mg |  |  | >700~800 | 225 mg | 225 mg | 300 mg | 375 mg | 450 mg | 450 mg | 525 mg | 600 mg |  |  | >800~900 | 225 mg | 225 mg | 300 mg | 375 mg | 450 mg | 525 mg | 600 mg |  |  |  | >900~1,000 | 225 mg | 300 mg | 375 mg | 450 mg | 525 mg | 600 mg |  |  |  |  | >1,000~1,100 | 225 mg | 300 mg | 375 mg | 450 mg | 600 mg |  |  |  |  |  | >1,100~1,200 | 300 mg | 300 mg | 450 mg | 525 mg | 600 mg |  |  |  |  |  | >1,200~1,300 | 300 mg | 375 mg | 450 mg | 525 mg |  |  |  |  |  |  | >1,300~1,500 | 300 mg | 375 mg | 525 mg | 600 mg |  |  |  |  |  |  |
| 投与前の血清中総IgE濃度(IU/mL) | 体重(kg)  |                      |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
|                      | ≥20<br>~25  | >25<br>~30           | >30<br>~40 | >40<br>~50 | >50<br>~60 | >60<br>~70 | >70<br>~80 | >80<br>~90 | >90<br>~125 | >125<br>~150 |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| ≥30~100              | 75 mg   | 75 mg                | 75 mg      | 150 mg     | 150 mg     | 150 mg     | 150 mg     | 150 mg     | 300 mg      | 300 mg       |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >100~200             | 150 mg  | 150 mg               | 150 mg     | 300 mg     | 300 mg     | 300 mg     | 300 mg     | 300 mg     | 450 mg      | 600 mg       |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >200~300             | 150 mg  | 150 mg               | 225 mg     | 300 mg     | 300 mg     | 450 mg     | 450 mg     | 450 mg     | 600 mg      |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >300~400             | 225 mg  | 225 mg               | 300 mg     | 450 mg     | 450 mg     | 450 mg     | 600 mg     | 600 mg     |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >400~500             | 225 mg  | 300 mg               | 450 mg     | 450 mg     | 600 mg     | 600 mg     |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >500~600             | 300 mg  | 300 mg               | 450 mg     | 600 mg     | 600 mg     |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >600~700             | 300 mg  |                      | 450 mg     | 600 mg     |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >700~800             |   |                      |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >800~900             |   |                      |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >900~1,000           |   |                      |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >1,000~1,100         |   |                      |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >1,100~1,200         |   |                      |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >1,200~1,300         |   |                      |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >1,300~1,500         |   |                      |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| 投与前の血清中総IgE濃度(IU/mL) | 体重(kg)  |                      |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
|                      | ≥20<br>~25  | >25<br>~30           | >30<br>~40 | >40<br>~50 | >50<br>~60 | >60<br>~70 | >70<br>~80 | >80<br>~90 | >90<br>~125 | >125<br>~150 |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| ≥30~100              |   |                      |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >100~200             |   |                      |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >200~300             |   |                      |            |            |            |            |            |            |             | 375 mg       |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >300~400             |   |                      |            |            |            |            |            |            | 450 mg      | 525 mg       |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >400~500             |   |                      |            |            |            |            | 375 mg     | 375 mg     | 525 mg      | 600 mg       |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >500~600             |   |                      |            |            |            | 375 mg     | 450 mg     | 450 mg     | 600 mg      |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >600~700             |   | 225 mg               |            |            | 375 mg     | 450 mg     | 450 mg     | 525 mg     |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >700~800             | 225 mg  | 225 mg               | 300 mg     | 375 mg     | 450 mg     | 450 mg     | 525 mg     | 600 mg     |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >800~900             | 225 mg  | 225 mg               | 300 mg     | 375 mg     | 450 mg     | 525 mg     | 600 mg     |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >900~1,000           | 225 mg  | 300 mg               | 375 mg     | 450 mg     | 525 mg     | 600 mg     |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >1,000~1,100         | 225 mg  | 300 mg               | 375 mg     | 450 mg     | 600 mg     |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >1,100~1,200         | 300 mg  | 300 mg               | 450 mg     | 525 mg     | 600 mg     |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >1,200~1,300         | 300 mg  | 375 mg               | 450 mg     | 525 mg     |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >1,300~1,500         | 300 mg  | 375 mg               | 525 mg     | 600 mg     |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                      |        |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |

|              | 投与量換算表では、本剤の臨床推奨用量である 0.008 mg/kg/[IU/mL]以上（2 週間間隔皮下投与時）又は 0.016 mg/kg/[IU/mL]以上（4 週間間隔皮下投与時）となるよう投与量が設定されている。   |               |              |              |   |               |            |        |                    |               |            |        |            |             |              |      |     |             |     |              |    |                     |        |             |         |              |   |        |   |         |              |   |          |              |    |            |      |   |
|--------------|--|---------------|--------------|--------------|---|---------------|------------|--------|--------------------|---------------|------------|--------|------------|-------------|--------------|------|-----|-------------|-----|--------------|----|---------------------|--------|-------------|---------|--------------|---|--------|---|---------|--------------|---|----------|--------------|----|------------|------|---|
| 劇薬等の指定       | 原体：劇薬，製剤：劇薬  |               |              |              |   |               |            |        |                    |               |            |        |            |             |              |      |     |             |     |              |    |                     |        |             |         |              |   |        |   |         |              |   |          |              |    |            |      |   |
| 市販名及び有効成分・分量 | 原体：オマリズマブ（遺伝子組換え）<br>製剤：ゾレア皮下注用 150 mg [1 バイアル中オマリズマブ（遺伝子組換え） 202.5 mg 含有]<br>ゾレア皮下注用 75 mg [1 バイアル中オマリズマブ（遺伝子組換え） 129.6 mg 含有]  |               |              |              |   |               |            |        |                    |               |            |        |            |             |              |      |     |             |     |              |    |                     |        |             |         |              |   |        |   |         |              |   |          |              |    |            |      |   |
| 毒性           | <p>単回投与毒性試験</p> <table border="1"> <thead> <tr> <th>投与量(mg/kg)</th> <th>静脈内</th> <th>皮下</th> </tr> </thead> <tbody> <tr> <td>マウス</td> <td>0, 1, 10, 100</td> <td>—</td> </tr> <tr> <td>カニクイザル</td> <td>0, 0.5, 5, 50, 200</td> <td>0, 0.5, 5, 50</td> </tr> </tbody> </table> <p>成績：いずれの投与量においても、オマリズマブに関連した毒性変化なし</p> <p>反復投与毒性試験</p> <table border="1"> <thead> <tr> <th>動物種</th> <th>投与期間</th> <th>投与経路</th> <th>投与量 (mg/kg)</th> <th>無毒性量 (mg/kg)</th> <th>主な所見</th> </tr> </thead> <tbody> <tr> <td>マウス</td> <td>週 1 回, 4 週間</td> <td>静脈内</td> <td>0, 1, 10, 50</td> <td>50</td> <td rowspan="3">オマリズマブ投与に関連した毒性変化なし</td> </tr> <tr> <td>カニクイザル</td> <td>週 3 回, 4 週間</td> <td>皮下及び静脈内</td> <td>0, 0.1, 1, 5</td> <td>5</td> </tr> <tr> <td>カニクイザル</td> <td>週 3 回, 6 ヶ月間, 又は試験 1~59 日及び試験 122~183 日</td> <td>皮下及び静脈内</td> <td>0, 0.1, 1, 5</td> <td>5</td> </tr> <tr> <td>幼若カニクイザル</td> <td>週 1 回, 26 週間</td> <td>皮下</td> <td>0, 50, 250</td> <td>&lt; 50</td> <td>50 mg/kg 以上の群：<br/>血小板数減少，巨核球数増加，投与部位／胃底腺粘膜固有層／十二指腸粘膜固有層／心臓心室内膜下／精囊周囲組織／子宮内膜の出血<br/>250 mg/kg 群：<br/>出血時間の延長</td> </tr> </tbody> </table> | 投与量(mg/kg)    | 静脈内          | 皮下           | マウス   | 0, 1, 10, 100 | —          | カニクイザル | 0, 0.5, 5, 50, 200 | 0, 0.5, 5, 50 | 動物種        | 投与期間   | 投与経路       | 投与量 (mg/kg) | 無毒性量 (mg/kg) | 主な所見 | マウス | 週 1 回, 4 週間 | 静脈内 | 0, 1, 10, 50 | 50 | オマリズマブ投与に関連した毒性変化なし | カニクイザル | 週 3 回, 4 週間 | 皮下及び静脈内 | 0, 0.1, 1, 5 | 5 | カニクイザル | 週 3 回, 6 ヶ月間, 又は試験 1~59 日及び試験 122~183 日 | 皮下及び静脈内 | 0, 0.1, 1, 5 | 5 | 幼若カニクイザル | 週 1 回, 26 週間 | 皮下 | 0, 50, 250 | < 50 | 50 mg/kg 以上の群：<br>血小板数減少，巨核球数増加，投与部位／胃底腺粘膜固有層／十二指腸粘膜固有層／心臓心室内膜下／精囊周囲組織／子宮内膜の出血<br>250 mg/kg 群：<br>出血時間の延長 |
|              | 投与量(mg/kg)   | 静脈内           | 皮下           |              |   |               |            |        |                    |               |            |        |            |             |              |      |     |             |     |              |    |                     |        |             |         |              |   |        |   |         |              |   |          |              |    |            |      |   |
| マウス          | 0, 1, 10, 100  | —             |              |              |   |               |            |        |                    |               |            |        |            |             |              |      |     |             |     |              |    |                     |        |             |         |              |   |        |   |         |              |   |          |              |    |            |      |   |
| カニクイザル       | 0, 0.5, 5, 50, 200   | 0, 0.5, 5, 50 |              |              |   |               |            |        |                    |               |            |        |            |             |              |      |     |             |     |              |    |                     |        |             |         |              |   |        |   |         |              |   |          |              |    |            |      |   |
| 動物種          | 投与期間   | 投与経路          | 投与量 (mg/kg)  | 無毒性量 (mg/kg) | 主な所見  |               |            |        |                    |               |            |        |            |             |              |      |     |             |     |              |    |                     |        |             |         |              |   |        |   |         |              |   |          |              |    |            |      |   |
| マウス          | 週 1 回, 4 週間  | 静脈内           | 0, 1, 10, 50 | 50           | オマリズマブ投与に関連した毒性変化なし   |               |            |        |                    |               |            |        |            |             |              |      |     |             |     |              |    |                     |        |             |         |              |   |        |   |         |              |   |          |              |    |            |      |   |
| カニクイザル       | 週 3 回, 4 週間  | 皮下及び静脈内       | 0, 0.1, 1, 5 | 5            |   |               |            |        |                    |               |            |        |            |             |              |      |     |             |     |              |    |                     |        |             |         |              |   |        |   |         |              |   |          |              |    |            |      |   |
| カニクイザル       | 週 3 回, 6 ヶ月間, 又は試験 1~59 日及び試験 122~183 日  | 皮下及び静脈内       | 0, 0.1, 1, 5 | 5            |   |               |            |        |                    |               |            |        |            |             |              |      |     |             |     |              |    |                     |        |             |         |              |   |        |   |         |              |   |          |              |    |            |      |   |
| 幼若カニクイザル     | 週 1 回, 26 週間   | 皮下            | 0, 50, 250   | < 50         | 50 mg/kg 以上の群：<br>血小板数減少，巨核球数増加，投与部位／胃底腺粘膜固有層／十二指腸粘膜固有層／心臓心室内膜下／精囊周囲組織／子宮内膜の出血<br>250 mg/kg 群：<br>出血時間の延長 |               |            |        |                    |               |            |        |            |             |              |      |     |             |     |              |    |                     |        |             |         |              |   |        |   |         |              |   |          |              |    |            |      |   |
| 副作用          | <p>副作用発現率（成人）<br/>47.2%（134 例／284 例）</p> <table border="1"> <thead> <tr> <th>副作用の種類</th> <th>例数</th> </tr> </thead> <tbody> <tr> <td>注射部位紅斑</td> <td>53 例（18.7%）</td> </tr> <tr> <td>注射部位そう痒感</td> <td>26 例（9.2%）</td> </tr> <tr> <td>注射部位腫脹</td> <td>24 例（8.5%）</td> </tr> <tr> <td>注射部位疼痛</td> <td>20 例（7.0%）</td> </tr> <tr> <td>注射部位熱感</td> <td>14 例（4.9%）</td> </tr> </tbody> </table>  | 副作用の種類        | 例数           | 注射部位紅斑       | 53 例（18.7%）   | 注射部位そう痒感      | 26 例（9.2%） | 注射部位腫脹 | 24 例（8.5%）         | 注射部位疼痛        | 20 例（7.0%） | 注射部位熱感 | 14 例（4.9%） |             |              |      |     |             |     |              |    |                     |        |             |         |              |   |        |   |         |              |   |          |              |    |            |      |   |
| 副作用の種類       | 例数   |               |              |              |   |               |            |        |                    |               |            |        |            |             |              |      |     |             |     |              |    |                     |        |             |         |              |   |        |   |         |              |   |          |              |    |            |      |   |
| 注射部位紅斑       | 53 例（18.7%）  |               |              |              |   |               |            |        |                    |               |            |        |            |             |              |      |     |             |     |              |    |                     |        |             |         |              |   |        |   |         |              |   |          |              |    |            |      |   |
| 注射部位そう痒感     | 26 例（9.2%）   |               |              |              |   |               |            |        |                    |               |            |        |            |             |              |      |     |             |     |              |    |                     |        |             |         |              |   |        |   |         |              |   |          |              |    |            |      |   |
| 注射部位腫脹       | 24 例（8.5%）   |               |              |              |   |               |            |        |                    |               |            |        |            |             |              |      |     |             |     |              |    |                     |        |             |         |              |   |        |   |         |              |   |          |              |    |            |      |   |
| 注射部位疼痛       | 20 例（7.0%）   |               |              |              |   |               |            |        |                    |               |            |        |            |             |              |      |     |             |     |              |    |                     |        |             |         |              |   |        |   |         |              |   |          |              |    |            |      |   |
| 注射部位熱感       | 14 例（4.9%）   |               |              |              |   |               |            |        |                    |               |            |        |            |             |              |      |     |             |     |              |    |                     |        |             |         |              |   |        |   |         |              |   |          |              |    |            |      |   |

|     |                              |              |
|-----|------------------------------|--------------|
|     | 注射部位硬結                       | 13 例 (4.6%)  |
|     | 注射部位出血                       | 12 例 (4.2%)  |
|     | 蕁麻疹                          | 5 例 (1.8%)   |
|     | けん怠感                         | 5 例 (1.8%) 等 |
|     | 副作用発現率 (小児)                  |              |
|     | 26.3% (10 例/38 例)            |              |
|     | 副作用の種類                       | 例数           |
|     | 頭痛                           | 4 例 (10.5%)  |
|     | 注射部位疼痛                       | 3 例 (7.9%)   |
|     | 注射部位紅斑                       | 2 例 (5.3%)   |
|     | 注射部位膨張                       | 2 例 (5.3%)   |
|     | 蕁麻疹                          | 2 例 (5.3%) 等 |
| 会 社 | ノバルティス ファーマ株式会社 製剤：製造販売 (輸入) |              |



<追加・変更> (下線部)

| 化学名・別名                |  |                       |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
|-----------------------|--|-----------------------|------------|------------|------------|------------|------------|------------|-------------|--------------|--|--|------------|------------|------------|------------|------------|------------|------------|------------|-------------|--------------|---------|-------|-------|-------|--------|--------|--------|--------|--------|--------|--------|----------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|----------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--|----------|--------|--------|--------|--------|--------|--------|--------|--------|--|--|----------|--------|--------|--------|--------|--------|--------|--|--|--|--|----------|--------|--------|--------|--------|--------|--|--|--|--|--|----------|--------|--|--------|--------|--|--|--|--|--|--|----------|--|--|--|--|--|--|--|--|--|--|----------|--|--|--|--|--|--|--|--|--|--|------------|--|--|--|--|--|--|--|--|--|--|--------------|--|--|--|--|--|--|--|--|--|--|--------------|--|--|--|--|--|--|--|--|--|--|--------------|--|--|--|--|--|--|--|--|--|--|--------------|--|--|--|--|--|--|--|--|--|--|-----------------------|---------|--|--|--|--|--|--|--|--|--|------------|------------|------------|------------|------------|------------|------------|------------|-------------|--------------|---------|--|--|--|--|--|--|--|--|--|--|----------|--|--|--|--|--|--|--|--|--|--|----------|--|--|--|--|--|--|--|--|--|--------|----------|--|--|--|--|--|--|--|--|--------|--------|----------|--|--|--|--|--|--|--------|--------|--------|--------|----------|--|--|--|--|--|--------|--------|--------|--------|--|----------|--|--------|--|--|--------|--------|--------|--------|--|--|----------|--------|--------|--------|--------|--------|--------|--------|--------|--|--|----------|--------|--------|--------|--------|--------|--------|--------|--|--|--|------------|--------|--------|--------|--------|--------|--------|--|--|--|--|--------------|--------|--------|--------|--------|--------|--|--|--|--|--|--------------|--------|--------|--------|--------|--------|--|--|--|--|--|--------------|--------|--------|--------|--------|--|--|--|--|--|--|--------------|--------|--------|--------|--------|--|--|--|--|--|--|
| 構造式                   |  |                       |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| 効能・効果                 | <p>1. 気管支喘息（既存治療によっても喘息症状をコントロールできない難治の患者に限る）</p> <p>2. 特発性の慢性蕁麻疹（既存治療で効果不十分な患者に限る）</p>  |                       |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| 用法・用量                 | <p>1. 気管支喘息</p> <p>通常、オマリズマブ（遺伝子組換え）として1回75～600 mgを2又は4週間毎に皮下に注射する。1回あたりの投与量並びに投与間隔は、初回投与前の血清中総IgE濃度及び体重に基づき、下記の投与量換算表により設定する。</p> <p>投与量換算表（1回投与量）</p> <p>4週間毎投与</p> <table border="1"> <thead> <tr> <th rowspan="2">投与前の血清中総IgE濃度 (IU/mL)</th> <th colspan="10">体重 (kg)</th> </tr> <tr> <th>≥20<br/>~25</th> <th>&gt;25<br/>~30</th> <th>&gt;30<br/>~40</th> <th>&gt;40<br/>~50</th> <th>&gt;50<br/>~60</th> <th>&gt;60<br/>~70</th> <th>&gt;70<br/>~80</th> <th>&gt;80<br/>~90</th> <th>&gt;90<br/>~125</th> <th>&gt;125<br/>~150</th> </tr> </thead> <tbody> <tr> <td>≥30~100</td> <td>75 mg</td> <td>75 mg</td> <td>75 mg</td> <td>150 mg</td> <td>150 mg</td> <td>150 mg</td> <td>150 mg</td> <td>150 mg</td> <td>300 mg</td> <td>300 mg</td> </tr> <tr> <td>&gt;100~200</td> <td>150 mg</td> <td>150 mg</td> <td>150 mg</td> <td>300 mg</td> <td>300 mg</td> <td>300 mg</td> <td>300 mg</td> <td>300 mg</td> <td>450 mg</td> <td>600 mg</td> </tr> <tr> <td>&gt;200~300</td> <td>150 mg</td> <td>150 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| 300 mg | 300 mg | 450 mg | 450 mg | 450 mg | 600 mg |  | >300~400 | 225 mg | 225 mg | 300 mg | 450 mg | 450 mg | 450 mg | 600 mg | 600 mg |  |  | >400~500 | 225 mg | 300 mg | 450 mg | 450 mg | 600 mg | 600 mg |  |  |  |  | >500~600 | 300 mg | 300 mg | 450 mg | 600 mg | 600 mg |  |  |  |  |  | >600~700 | 300 mg |  | 450 mg | 600 mg |  |  |  |  |  |  | >700~800 |  |  |  |  |  |  |  |  |  |  | >800~900 |  |  |  |  |  |  |  |  |  |  | >900~1,000 |  |  |  |  |  |  |  |  |  |  | >1,000~1,100 |  |  |  |  |  |  |  |  |  |  | >1,100~1,200 |  |  |  |  |  |  |  |  |  |  | >1,200~1,300 |  |  |  |  |  |  |  |  |  |  | >1,300~1,500 |  |  |  |  |  |  |  |  |  |  | 投与前の血清中総IgE濃度 (IU/mL) | 体重 (kg) |  |  |  |  |  |  |  |  |  | ≥20<br>~25 | >25<br>~30 | >30<br>~40 | >40<br>~50 | >50<br>~60 | >60<br>~70 | >70<br>~80 | >80<br>~90 | >90<br>~125 | >125<br>~150 | ≥30~100 |  |  |  |  |  |  |  |  |  |  | >100~200 |  |  |  |  |  |  |  |  |  |  | >200~300 |  |  |  |  |  |  |  |  |  | 375 mg | >300~400 |  |  |  |  |  |  |  |  | 450 mg | 525 mg | >400~500 |  |  |  |  |  |  | 375 mg | 375 mg | 525 mg | 600 mg | >500~600 |  |  |  |  |  | 375 mg | 450 mg | 450 mg | 600 mg |  | >600~700 |  | 225 mg |  |  | 375 mg | 450 mg | 450 mg | 525 mg |  |  | >700~800 | 225 mg | 225 mg | 300 mg | 375 mg | 450 mg | 450 mg | 525 mg | 600 mg |  |  | >800~900 | 225 mg | 225 mg | 300 mg | 375 mg | 450 mg | 525 mg | 600 mg |  |  |  | >900~1,000 | 225 mg | 300 mg | 375 mg | 450 mg | 525 mg | 600 mg |  |  |  |  | >1,000~1,100 | 225 mg | 300 mg | 375 mg | 450 mg | 600 mg |  |  |  |  |  | >1,100~1,200 | 300 mg | 300 mg | 450 mg | 525 mg | 600 mg |  |  |  |  |  | >1,200~1,300 | 300 mg | 375 mg | 450 mg | 525 mg |  |  |  |  |  |  | >1,300~1,500 | 300 mg | 375 mg | 525 mg | 600 mg |  |  |  |  |  |  |
| 投与前の血清中総IgE濃度 (IU/mL) | 体重 (kg)  |                       |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
|                       | ≥20<br>~25   | >25<br>~30            | >30<br>~40 | >40<br>~50 | >50<br>~60 | >60<br>~70 | >70<br>~80 | >80<br>~90 | >90<br>~125 | >125<br>~150 |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| ≥30~100               | 75 mg  | 75 mg                 | 75 mg      | 150 mg     | 150 mg     | 150 mg     | 150 mg     | 150 mg     | 300 mg      | 300 mg       |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >100~200              | 150 mg   | 150 mg                | 150 mg     | 300 mg     | 300 mg     | 300 mg     | 300 mg     | 300 mg     | 450 mg      | 600 mg       |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >200~300              | 150 mg   | 150 mg                | 225 mg     | 300 mg     | 300 mg     | 450 mg     | 450 mg     | 450 mg     | 600 mg      |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >300~400              | 225 mg   | 225 mg                | 300 mg     | 450 mg     | 450 mg     | 450 mg     | 600 mg     | 600 mg     |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >400~500              | 225 mg   | 300 mg                | 450 mg     | 450 mg     | 600 mg     | 600 mg     |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >500~600              | 300 mg   | 300 mg                | 450 mg     | 600 mg     | 600 mg     |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >600~700              | 300 mg   |                       | 450 mg     | 600 mg     |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >700~800              |  |                       |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >800~900              |  |                       |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >900~1,000            |  |                       |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >1,000~1,100          |  |                       |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >1,100~1,200          |  |                       |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >1,200~1,300          |  |                       |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >1,300~1,500          |  |                       |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| 投与前の血清中総IgE濃度 (IU/mL) | 体重 (kg)  |                       |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
|                       | ≥20<br>~25   | >25<br>~30            | >30<br>~40 | >40<br>~50 | >50<br>~60 | >60<br>~70 | >70<br>~80 | >80<br>~90 | >90<br>~125 | >125<br>~150 |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| ≥30~100               |  |                       |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >100~200              |  |                       |            |            |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >200~300              |  |                       |            |            |            |            |            |            |             | 375 mg       |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >300~400              |  |                       |            |            |            |            |            |            | 450 mg      | 525 mg       |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >400~500              |  |                       |            |            |            |            | 375 mg     | 375 mg     | 525 mg      | 600 mg       |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >500~600              |  |                       |            |            |            | 375 mg     | 450 mg     | 450 mg     | 600 mg      |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >600~700              |  | 225 mg                |            |            | 375 mg     | 450 mg     | 450 mg     | 525 mg     |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >700~800              | 225 mg   | 225 mg                | 300 mg     | 375 mg     | 450 mg     | 450 mg     | 525 mg     | 600 mg     |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >800~900              | 225 mg   | 225 mg                | 300 mg     | 375 mg     | 450 mg     | 525 mg     | 600 mg     |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >900~1,000            | 225 mg   | 300 mg                | 375 mg     | 450 mg     | 525 mg     | 600 mg     |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >1,000~1,100          | 225 mg   | 300 mg                | 375 mg     | 450 mg     | 600 mg     |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >1,100~1,200          | 300 mg   | 300 mg                | 450 mg     | 525 mg     | 600 mg     |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >1,200~1,300          | 300 mg   | 375 mg                | 450 mg     | 525 mg     |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |
| >1,300~1,500          | 300 mg   | 375 mg                | 525 mg     | 600 mg     |            |            |            |            |             |              |  |  |            |            |            |            |            |            |            |            |             |              |         |       |       |       |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |        |          |        |        |        |        |        |        |        |        |        |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |  |  |  |  |          |        |        |        |        |        |  |  |  |  |  |          |        |  |        |        |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |            |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |              |  |  |  |  |  |  |  |  |  |  |                       |         |  |  |  |  |  |  |  |  |  |            |            |            |            |            |            |            |            |             |              |         |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |  |          |  |  |  |  |  |  |  |  |  |        |          |  |  |  |  |  |  |  |  |        |        |          |  |  |  |  |  |  |        |        |        |        |          |  |  |  |  |  |        |        |        |        |  |          |  |        |  |  |        |        |        |        |  |  |          |        |        |        |        |        |        |        |        |  |  |          |        |        |        |        |        |        |        |  |  |  |            |        |        |        |        |        |        |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |        |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |              |        |        |        |        |  |  |  |  |  |  |

|              | <p>投与量換算表では、本剤の臨床推奨用量である 0.008 mg/kg/[IU/mL]以上（2 週間間隔皮下投与時）又は 0.016 mg/kg/[IU/mL]以上（4 週間間隔皮下投与時）となるよう投与量が設定されている。</p> <p>2. <u>特発性の慢性蕁麻疹</u><br/>通常、成人及び12歳以上の小児にはオマリズマブ（遺伝子組換え）として1回 300 mg を4週間毎に皮下に注射する。</p>  |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
|--------------|--|--------|----|--------|------------|----------|-----------|--------|-----------|--------|-----------|--------|-----------|--------|-----------|--------|-----------|-----|----------|------|-----------|--------|----|----|-----------|--------|----------|--------|----------|--------|----------|-----|-----------|--------|----|----|----------|------|-----------|
| 劇薬等の指定       |  |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 市販名及び有効成分・分量 |  |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 毒性           |  |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 副作用          | <p><u>気管支喘息</u></p> <p>副作用発現率（成人）<br/>47.2%（134例／284例）</p> <table> <thead> <tr> <th>副作用の種類</th> <th>例数</th> </tr> </thead> <tbody> <tr> <td>注射部位紅斑</td> <td>53例（18.7%）</td> </tr> <tr> <td>注射部位そう痒感</td> <td>26例（9.2%）</td> </tr> <tr> <td>注射部位腫脹</td> <td>24例（8.5%）</td> </tr> <tr> <td>注射部位疼痛</td> <td>20例（7.0%）</td> </tr> <tr> <td>注射部位熱感</td> <td>14例（4.9%）</td> </tr> <tr> <td>注射部位硬結</td> <td>13例（4.6%）</td> </tr> <tr> <td>注射部位出血</td> <td>12例（4.2%）</td> </tr> <tr> <td>蕁麻疹</td> <td>5例（1.8%）</td> </tr> <tr> <td>けん怠感</td> <td>5例（1.8%）等</td> </tr> </tbody> </table> <p>副作用発現率（小児）<br/>26.3%（10例／38例）</p> <table> <thead> <tr> <th>副作用の種類</th> <th>例数</th> </tr> </thead> <tbody> <tr> <td>頭痛</td> <td>4例（10.5%）</td> </tr> <tr> <td>注射部位疼痛</td> <td>3例（7.9%）</td> </tr> <tr> <td>注射部位紅斑</td> <td>2例（5.3%）</td> </tr> <tr> <td>注射部位膨張</td> <td>2例（5.3%）</td> </tr> <tr> <td>蕁麻疹</td> <td>2例（5.3%）等</td> </tr> </tbody> </table> <p><u>特発性の慢性蕁麻疹</u></p> <p>副作用発現率<br/>9.0%（13例／144例）</p> <table> <thead> <tr> <th>副作用の種類</th> <th>例数</th> </tr> </thead> <tbody> <tr> <td>頭痛</td> <td>3例（2.1%）</td> </tr> <tr> <td>鼻咽頭炎</td> <td>2例（1.4%）等</td> </tr> </tbody> </table> | 副作用の種類 | 例数 | 注射部位紅斑 | 53例（18.7%） | 注射部位そう痒感 | 26例（9.2%） | 注射部位腫脹 | 24例（8.5%） | 注射部位疼痛 | 20例（7.0%） | 注射部位熱感 | 14例（4.9%） | 注射部位硬結 | 13例（4.6%） | 注射部位出血 | 12例（4.2%） | 蕁麻疹 | 5例（1.8%） | けん怠感 | 5例（1.8%）等 | 副作用の種類 | 例数 | 頭痛 | 4例（10.5%） | 注射部位疼痛 | 3例（7.9%） | 注射部位紅斑 | 2例（5.3%） | 注射部位膨張 | 2例（5.3%） | 蕁麻疹 | 2例（5.3%）等 | 副作用の種類 | 例数 | 頭痛 | 3例（2.1%） | 鼻咽頭炎 | 2例（1.4%）等 |
| 副作用の種類       | 例数   |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 注射部位紅斑       | 53例（18.7%）   |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 注射部位そう痒感     | 26例（9.2%）  |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 注射部位腫脹       | 24例（8.5%）  |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 注射部位疼痛       | 20例（7.0%）  |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 注射部位熱感       | 14例（4.9%）  |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 注射部位硬結       | 13例（4.6%）  |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 注射部位出血       | 12例（4.2%）  |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 蕁麻疹          | 5例（1.8%）   |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| けん怠感         | 5例（1.8%）等  |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 副作用の種類       | 例数   |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 頭痛           | 4例（10.5%）  |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 注射部位疼痛       | 3例（7.9%）   |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 注射部位紅斑       | 2例（5.3%）   |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 注射部位膨張       | 2例（5.3%）   |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 蕁麻疹          | 2例（5.3%）等  |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 副作用の種類       | 例数   |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 頭痛           | 3例（2.1%）   |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 鼻咽頭炎         | 2例（1.4%）等  |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |
| 会社           |  |        |    |        |            |          |           |        |           |        |           |        |           |        |           |        |           |     |          |      |           |        |    |    |           |        |          |        |          |        |          |     |           |        |    |    |          |      |           |

## 1.12 添付資料一覧

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## 1 第3部

該当資料なし

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|------------|---|----------------|
| 4.3        | 参考文献 (評価/参考の別: 参考資料)  |                |
| 4.3-1      | Hide M, Francis DM, Grattan CEH, et al. (1993) Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. N Engl J Med; 328(22):1599-604.  | 海外             |
| 4.3-2      | Kaplan AP and Greaves M (2009) Pathogenesis of chronic urticaria. Clin Exp Allergy; 39:777-87.  | 海外             |
| 4.3-3      | Lourenco FD, Azor MH, Santos JC, et al. (2008) Activated status of basophils in chronic urticaria leads to interleukin-3 hyper-responsiveness and enhancement of histamine release induced by anti-IgE stimulus. Br J Dermatol; 158:979-86. | 海外             |
| 4.3-4      | Saavedra MC and Sur S (2011) Down regulation of the high-affinity IgE receptor associated with successful treatment of chronic idiopathic urticaria with omalizumab. Clinical and Molecular Allergy; 9:2:p1-3.                              | 海外             |
| 4.3-5      | Sabroe RA and Greaves MW (2006) Chronic idiopathic urticaria with functional autoantibodies: 12 years on. Br J Dermatol; 154:813-9.   | 海外             |

| 添付資料番号                                    | 表題   | 著者       | 試験実施期間                    | 試験実施場所        | 報種類<br>(国内/海外) | 掲載誌   | 評価/参考 |
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| 5.3.3.5-1                                 | Population Pharmacokinetics/Pharmacodynamics of Omalizumab in Chronic Idiopathic Urticaria   | ジェネンテック社 | 2013年5月28日                | —             | 海外             | 社外報告書 | 評価    |
| 5.3.3.5-2                                 | Exposure-Response Analysis of Omalizumab in Chronic Idiopathic Urticaria   | ジェネンテック社 | 2013年5月28日                | —             | 海外             | 社外報告書 | 評価    |
| 5.3.3.5-3                                 | Population pharmacokinetics-efficacy time course analysis of omalizumab induced reduction of itch and hives symptoms in patients with chronic spontaneous urticaria (CSU)  | ノバルティス   | 2013年6月14日                | —             | 海外             | 社内報告書 | 評価    |
| 5.3.3.5-4                                 | Revision of Xolair dosing table for dosing every four instead of two weeks for specific ranges of bodyweight and baseline IgE  | ノバルティス   | 2011年7月15日                | —             | 海外             | 社内報告書 | 参考    |
| 5.3.4 臨床薬力学 (PD) 試験報告書                    |  |          |                           |               |                |       |       |
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| 5.3.4.2-1                                 | A phase II, multi-centre, randomized, double blind, placebo-controlled study to determine the mode of action of omalizumab in patients with chronic idiopathic urticaria (CIU) who remain symptomatic with antihistamine treatment (H1)                | ノバルティス   | 2012年4月17日～<br>2013年9月10日 | ドイツ, 計4施設     | 海外             | 社内報告書 | 参考    |
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| 5.3.5.1-1                                 | A multicenter, randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy and safety of omalizumab in patients with chronic spontaneous urticaria (CSU) who remain symptomatic despite H <sub>1</sub> antihistamine therapy | ノバルティス   | 2014年12月9日～<br>2015年12月3日 | 日本, 韓国, 計42施設 | 国際共同           | 社内報告書 | 評価    |

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|----------------------------|---|----------|----------------------------|--|----------------|-------|-------|
| 5.3.5.1-2                  | A PHASE II, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED DOSE-RANGING STUDY OF XOLAIR® (OMALIZUMAB) IN PATIENTS WITH CHRONIC IDIOPATHIC URTICARIA (CIU) WHO REMAIN SYMPTOMATIC WITH ANTIHISTAMINE TREATMENT (H1)   | ジェネンテック社 | 2009年3月26日～<br>2010年1月7日   | 米国, ドイツ, 計26<br>施設   | 海外             | 社外報告書 | 参考    |
|                            | CLINICAL STUDY REPORT ADDENDUM  | ジェネンテック社 | 2009年3月26日～<br>2010年1月7日   | —  | 海外             | 社外報告書 | 参考    |
|                            | errata list   |          |                            |  |                |       |       |
| 5.3.5.1-3                  | A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study To Evaluate The Efficacy and Safety of Xolair® (Omalizumab) in Patients With Chronic Idiopathic Urticaria (CIU) Who Remain Symptomatic Despite Antihistamine Treatment (H1)                    | ジェネンテック社 | 2011年2月16日～<br>2012年10月17日 | デンマーク, フラン<br>ス, ドイツ, イタリ<br>ア, ポーランド, ス<br>ペイン, トルコ, 米<br>国, 計54施設  | 海外             | 社外報告書 | 参考    |
|                            | errata list   |          |                            |  |                |       |       |
| 5.3.5.1-4                  | A Phase III, Multicenter, Randomized, Double-Blind, Dose-Ranging, Placebo-Controlled Study To Evaluate The Efficacy, Response Duration And Safety of Xolair® (Omalizumab) in Patients With Chronic Idiopathic Urticaria (CIU) Who Remain Symptomatic Despite Antihistamine Treatment (H1) | ジェネンテック社 | 2011年3月10日～<br>2012年6月27日  | デンマーク, フラン<br>ス, ドイツ, イタリ<br>ア, ポーランド, ス<br>ペイン, トルコ, 米<br>国, 計60施設  | 海外             | 社外報告書 | 参考    |
| 5.3.5.1-5                  | A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Safety Study of Xolair (Omalizumab) in Patients with Chronic Idiopathic Urticaria (CIU) Who Remain Symptomatic Despite Treatment With H1 Antihistamines, H2 Blockers, and/or Leukotriene Receptor Antagonists      | ジェネンテック社 | 2011年2月21日～<br>2012年11月22日 | 米国, ドイツ, ポー<br>ランド, 英国, オー<br>ストラリア, ニュー<br>ジーランド, シンガ<br>ポール, 計65施設 | 海外             | 社外報告書 | 参考    |
|                            | errata list   |          |                            |  |                |       |       |
| 5.3.5.2 非対照試験報告書【該当資料なし】   |   |          |                            |  |                |       |       |
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| 5.3.5.3-1                  | SCS Appendix 1 (Integrated Summary of Safety, data analyses)  | ノバルティス   | —                          | —  | 海外             | 社内報告書 | 参考    |
| 5.3.5.3-2                  | SCS Appendix 3 (Clinical summary of suspected anaphylaxis events)   | ノバルティス   | —                          | —  | 海外             | 社内報告書 | 参考    |
| 5.3.5.3-3                  | SCE Appendix for Japan submission (Integrated Summary of Efficacy, data analyses)   | ノバルティス   | —                          | —  | 国内             | 社内報告書 | 参考    |



| 添付資料<br>番号            | 表 題   | 著者     | 試験実施期間                                       | 試験実施場所     | 報種類<br>(国内/海外) | 掲載誌   | 評価/参考 |
|-----------------------|---|--------|--|------------|----------------|-------|-------|
| 5.3.5.3-4             | SCS and PI Appendix for Japan submission<br>(Integrated Summary of Safety, data analyses)   | ノバルティス | —  | —          | 国内             | 社内報告書 | 参考    |
| 5.3.5.4 その他の臨床試験報告書   |   |        |  |            |                |       |       |
| 5.3.5.4-1             | An extension study to CIGE025B1301 to evaluate the long-term safety, tolerability and efficacy of omalizumab in Japanese children (6 – 15 years) with inadequately controlled allergic asthma despite current recommended treatment | ノバルティス | 2011年3月18日～<br>2013年12月26日                   | 日本, 計15施設  | 国内             | 社内報告書 | 参考    |
| 5.3.5.4-2             | A randomized, 24 week, double-blind, placebo-controlled, parallel-group, multicenter study to assess the efficacy and safety of Omalizumab in adult patients with chronic urticaria who exhibit IgE against thyreoperoxidase        | ノバルティス | 2007年5月11日～<br>2009年4月30日                    | ドイツ, 計17施設 | 海外             | 社内報告書 | 参考    |
|                       | Addendum 1 to Clinical Study Report CIGE025ADE05<br>(Patient narratives, Protocol Amendment 1 and additional administrative information)  | ノバルティス | 2007年5月11日～<br>2009年4月30日                    | —          | 海外             | 社内報告書 | 参考    |
| 5.3.6 市販後の使用経験に関する報告書 |   |        |  |            |                |       |       |
| 5.3.6-1               | PERIODIC SAFETY UPDATE REPORT 21 (PSUR 21)  | ノバルティス | Period covered:<br>2015年1月1日～<br>2015年12月31日 | —          | 海外             | 社内報告書 | 参考    |
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| 5.3.7-3               | 重篤な有害事象一覧表  |        |  |            |                |       |       |
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| 添付資料<br>番号 | 著者・表題・掲載誌  | 報種類<br>(国内/海外) |
|------------|--|----------------|
| 5.4 参考文献   | (評価/参考の別: 参考資料)  |                |
| 5.4-1      | Study Q4458g Pharmacovigilance data repository of patients with and without history of anaphylactic reactions subsequent to Xolair® dosing (report date: June 2014)  | 海外             |
| 5.4-2      | Study Q2952g THE XOLAIR® PREGNANCY REGISTRY: AN OBSERVATIONAL STUDY OF THE USE AND SAFETY OF XOLAIR (OMALIZUMAB) DURING PREGNANCY (EXPECT) (report date: 27Mar2015)  | 海外             |
| 5.4-3      | Fedorowicz Z, van Zuuren EJ, Hu N (2012) Histamine H2-receptor antagonists for urticaria (Review). Cochrane Database Syst Rev; 3:1-37.   | 海外             |
| 5.4-4      | Finlay AY and Khan GK (1994) Dermatology Life Quality Index (DLQI) - a simple practical measure for routine clinical use. Clin Exp Dermatol; 19(3):210-6.  | 海外             |
| 5.4-5      | Gober LM, Sterba PM, Eckman JA, et al. (2008) Effect of Anti-IgE (Omalizumab) in Chronic Idiopathic Urticaria (CIU) Patients[abstract]. J ALLERGY CLIN IMMUNOL; 121(2):S147.   | 海外             |
| 5.4-6      | Hide M and Hiragun T (2012) Japanese Guidelines for Diagnosis and Treatment of Urticaria in Comparison with Other Countries. Allergol Int; 61(4):517-27.   | 海外             |
| 5.4-7      | Hongbo Y, Thomas CL, Harrison MA, et al. (2005) Translating the science of quality of life into practice: What do dermatology life quality index scores mean? J Invest Dermatol; 125(4):659-64.                                | 海外             |
| 5.4-8      | Kaplan AP (2012) Treatment of Chronic Spontaneous Urticaria. Allergy Asthma Immunol Res; 4(6):326-31.  | 海外             |
| 5.4-9      | Kaplan AP, Joseph K, Maykut RJ, et al. (2008) Treatment of chronic autoimmune urticaria with omalizumab. J Allergy Clin Immunol; 122(3):569-73.  | 海外             |
| 5.4-10     | Khan DA (2013) Alternative Agents in Refractory Chronic Urticaria: Evidence and Considerations on Their Selection and Use. J Allergy Clin Immunol Pract; 1(5):433-40.  | 海外             |
| 5.4-11     | Lewis V and Finlay AY (2004) 10 years experience of the Dermatology Life Quality Index (DLQI). J Investig Dermatol Symp Proc; 9(2):169-80.   | 海外             |
| 5.4-12     | Manson SC, Brown RE, Cerulli A, et al. (2009) The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. Respir Med; 103(7):975-94.   | 海外             |
| 5.4-13     | Maurer M, Weller K, Bindslev-Jensen C, et al. (2011) Unmet clinical needs in chronic spontaneous urticaria. A GA <sup>2</sup> LEN task force report. Allergy; 66(3):317-30.  | 海外             |
| 5.4-14     | O'Donnell BF, Lawlor F, Simpson J, et al. (1997) The impact of chronic urticaria on the quality of life. Br J Dermatol; 136(2):197-201.  | 海外             |
| 5.4-15     | Saavedra MC and Sur S (2011) Down regulation of the high-affinity IgE receptor associated with successful treatment of chronic idiopathic urticaria with omalizumab. Clin Mol Allergy; 9(1):2.                                 | 海外             |
| 5.4-16     | Sánchez-Borges M, Ansotegui I, Jimenez JM, et al. (2014) Comparative efficacy of non-sedating antihistamine uposing in patients with chronic urticaria. World Allergy Organ J; 7(1):33.  | 海外             |
| 5.4-17     | Shikhar R, Harding G, Leahy M, et al. (2005) Minimal important difference (MID) of the Dermatology Life Quality Index (DLQI): results from patients with chronic idiopathic urticaria. Health Qual Life Outcomes; 3:36.        | 海外             |
| 5.4-18     | Spector SL and Tan RA (2007) Effect of omalizumab on patients with chronic urticaria. Ann Allergy Asthma Immunol; 99(2):190-3.   | 海外             |
| 5.4-19     | Zuberbier T, Aberer W, Asero R, et al. (2014) The EAACI/GA <sup>2</sup> LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy; 69(7):868-87. | 海外             |