# ゾレア皮下注用75 mg,
# ゾレア皮下注用150 mg,
# ゾレア皮下注75 mgシリンジ,
# ゾレア皮下注150 mgシリンジに関する資料

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# 「起源又は発見の経緯及び開発の経緯」等の資料

## 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 | 略していない表現 (英) | 略していない表現 (日) |
|---|---|---|
| AdNCS | adjusted nasal congestion score | 調整した鼻閉の重症度スコア |
| ADR | adverse drug reaction | 医薬品副作用 |
| ALP | alkaline phosphatase | アルカリホスファターゼ |
| ALT | alanine aminotransferase | アラニンアミノトランスフェラーゼ |
| AST | aspartate aminotransferase | アスパラギン酸アミノトランスフェラーゼ |
| bid | bis in die | 1 日 2 回 |
| BMI | body mass index | 体格指数［体重 kg/(身長 m)$^2$］ |
| CABG | coronary artery bypass graft | 冠動脈バイパス術 |
| CCDS | company core data sheet | 企業中核データシート |
| CI | confidence interval | 信頼区間 |
| CMQ | custom MedDRA queries | - |
| eCRF | electronic case report form | 電子症例報告書 |
| FAS | full analysis set | 最大の解析対象集団 |
| HLGT | high level group term | 高位グループ用語 |
| HLT | high level term | 高位用語 |
| IgE | immunoglobulin E | 免疫グロブリン E |

| 略号 | 略していない表現 (英) | 略していない表現 (日) |
|---|---|---|
| IgG | immunoglobulin G | 免疫グロブリン G |
| INR | international normalized ratio | 国際標準比 |
| IRT | Interactive Response Technology | 双方向自動応答技術 |
| ITT | intention-to-treat | - |
| IU | international unit | 国際単位 |
| IUD | intrauterine device | 子宮内避妊器具 |
| IUS | intrauterine system | 子宮内避妊システム |
| JRQLQ | Japanese Rhinoconjunctivitis Quality of Life Questionnaire | 日本アレルギー性鼻炎標準 QOL 調査票 |
| LSM | least squares mean | 最小二乗平均 |
| LTs | leukotriene | ロイコトリエン |
| MAR | missing at random | ランダムな欠損 |
| MedDRA | Medical Dictionary for Regulatory Activities | ICH 国際医薬用語集 |
| MedDRA/J | Medical Dictionary for Regulatory Activities /Japanese edition | MedDRA 日本語版 |
| NCS | nasal congestion score | 鼻閉の重症度スコア |
| NMQ | Novartis MedDRA queries | - |
| NR | not reported here | 報告せず |
| PD | pharmacodynamics | 薬力学 |
| $PGD_2$ | prostaglandin $D_2$ | プロスタグランジン $D_2$ |
| PK | pharmacokinetics | 薬物動態 |
| PPS | per protocol set | 治験実施計画書に適合した対象集団 |
| PSUR | periodic safety update report | 定期的安全性最新報告 |
| PT | preferred term | 基本語 |
| QOL | quality of life | 生活の質 |
| RAN | randomized population | ランダム化解析対象集団 |
| RMP | risk management plan | 医薬品リスク管理計画 |
| SAF | safety analysis population | 安全性解析対象集団 |
| SD | standard deviation | 標準偏差 |
| SE | standard error | 標準誤差 |
| SMQ | standardised MedDRA queries | MedDRA 標準検索式 |
| SOC | system organ class | 器官別大分類 |
| TBL | total bilirubin | 総ビリルビン |
| $TXA_2$ | thromboxane $A_2$ | トロンボキサン $A_2$ |
| UA | uric acid | 尿酸 |
| ULN | upper limit normal | 基準値上限 |
| WPAI-AS | Work Productivity and Activity Impairment Questionnaire-Allergy Specific | 日常生活に及ぼす影響の調査 アレルギー編 |

# 1 起原又は発見の経緯

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 $IgG_1$ 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，国内では成人の気管支喘息治療剤として 2009 年 1 月（150 mg 凍結乾燥製剤）及び 2012 年 9 月（75 mg 凍結乾燥製剤）に，小児の気管支喘息治療剤として 2013 年 8 月に，また，慢性蕁麻疹治療剤として 2017 年 3 月に承認を取得している。2019 年 4 月現在，世界 90 ヵ国以上で気管支喘息の治療薬として，また，世界 80 ヵ国以上で慢性蕁麻疹の治療薬として承認されている。

# 2 花粉症について

## 2.1 定義，診断基準及び患者数

花粉症は，植物花粉によって誘因される季節性アレルギー性鼻炎で，IgE を介する I 型アレルギー疾患である。花粉症の主な症状は，発作・反復性のくしゃみ，水様性鼻漏，鼻閉（3 主徴）で，これに加えてしばしば目のかゆみ，涙目が伴う。花粉症及びその原因抗原の診断は，前述 3 主徴を持ち，鼻汁好酸球検査，皮膚テスト，血清特異的 IgE 抗体検査及び誘発テストが陽性であれば確実である（鼻アレルギー診療ガイドライン 2016）。花粉症の重症度は，3 主徴である鼻症状の程度によって，軽度，中等症，重症，最重症の 4 つに分類される。2011 年春シーズンに花粉症又はアレルギー性鼻炎の治療のために医療機関を受診し，薬剤を処方された患者（1634 名）を対象として実施されたインターネット調査によると，治療前の重症度別の患者割合は，成人では最重症が 50.1%，重症が 29.0%，小児では最重症が 34.8%，重症が 32.8%であった（大久保，奥田 2012）。

国内の花粉症の有病率は，2008 年に全国の耳鼻咽頭科医及びその家族に対して実施した疫学調査によると 29.8%であり，主因植物であるスギ及びヒノキのうち，特にスギ花粉症は有病率が 26.5%と花粉症患者の大部分を占めている。花粉症の有病率は，同一の方法で実施した 1998 年と上記 2008 年の調査によると，10 年間で約 10%増加している。この増加は主にスギ花粉症有病率が約 10%増加したことによるものであり，近年のスギ花粉飛散量増加に加え，スギに対する感作・発症の若年化及び自然寛解が少ないことが原因と推定されている（鼻アレルギー診療ガイド

ライン 2016 年版）。さらに，花粉症患者の多くが上述のとおり重症又は最重症であるため，花粉症の有病率の増加に伴いこれらの患者も増加していると推察される。

## 2.2 花粉症に対する治療の現状

花粉症に対する治療は，抗原の除去と回避を基本とし，対症療法として薬物療法，長期寛解の可能性があるアレルゲン免疫療法，又は手術療法が行われる。

花粉症治療の主力である薬物治療に関して，鼻アレルギー診療ガイドライン 2016 年版では，病型（鼻症状の種類による分類）と重症度に基づく治療法の選択を推奨している。重症又は最重症では，鼻噴霧用ステロイド薬と第二世代抗ヒスタミン薬が基本の治療とされ，症状に応じて抗ロイコトリエン薬や点眼用第二世代抗ヒスタミン薬等を組み合わせることとされている。しかし，2011 年春シーズンの調査では，花粉症又はアレルギー性鼻炎の治療のために医療機関を受診し，薬剤を処方された患者（1634 名）の約 25%は何らかの治療を受けた後も重症度は重症又は最重症であったと報告されている。加えて，重症又は最重症の患者では，基本治療に加えて作用機序・投与経路が異なる数種類の薬剤が必要になることも多く，眼症状を合併する場合は点眼薬も必要となる上に，これらの薬剤は毎日複数回投与しなければならないことから，治療が煩雑であるという問題もある。結果として治療全般に対する満足度も低い（大久保，奥田 2012）。

アレルゲン免疫療法は，長期寛解の可能性がある治療法として期待されているものの，利便性・安全性の問題で適応されない患者も存在する（鼻アレルギー診療ガイドライン2016年版）。

このように，花粉症に対してはさまざまな治療法が市場に供されているものの，これらの既存治療によって症状が十分に管理できない重症又は最重症患者が一定数存在すると考えられる。これらの重症又は最重症患者では症状が非常に強く，全身性の症状も認められることから，患者の QOL や労働生産性が顕著に低下する。花粉症の有病率が高いこともあり，ひいては社会全体が経済的にも多大な損失を被ることになる。このことから，既存治療で効果不十分な重症又は最重症の花粉症患者に対し新たな治療法を開発することは，臨床上の重要な課題である。

## 2.3 本剤の治療上の位置付け

1 章のとおり，オマリズマブは IgE と FcεRI の結合を競合的に阻害し，IgE の肥満細胞，好塩基球等の炎症細胞への結合を阻害する。これら炎症細胞での抗原抗体反応を抑制することで，IgE を介する疾患に対して薬効を示す。また，オマリズマブの結合部位である Cε3 は IgE の定常領域にあり，IgE の抗原特異性にかかわらず結合することができる。加えて，オマリズマブは既存治療とは異なり，アレルギーカスケードの初期反応を阻害する作用機序を有することから，既存治療で効果不十分な重症又は最重症の花粉症患者の治療選択肢になり得ると考えた。

国内第 III 相試験（F1301 試験）の結果から，既存治療で効果不十分な重症又は最重症のスギ花粉症患者に対し，オマリズマブ群は鼻症状，眼症状，QOL，労働生産性のいずれもプラセボ群に比べて改善させ，忍容性も良好であることが明らかになった。また，既存の特定されているオマリズマブのリスク以外に，新たに特定されたリスクはなかった。

以上より，オマリズマブは既存治療で効果不十分な重症又は最重症の花粉症患者に対する新たな治療選択肢となり得ると考える。

# 3 開発の経緯

## 3.1 海外における開発

オマリズマブのアレルギー性鼻炎に対する開発は，海外で先行して開始された。第 I 相，第 IIa 相試験で初期の検討が行われた後，1997 年～1999 年にかけてブタクサ花粉による季節性アレルギー性鼻炎（花粉症）を対象に，第 IIb 相試験として 006，006E 試験を実施し，1998 年にカバノキ花粉による季節性アレルギー性鼻炎（花粉症）を対象に 007 試験を実施した[redacted]また，1999 年以降に[redacted]季節性アレルギー性鼻炎又は通年性アレルギー性鼻炎を対象に第 III 相の 3 試験［0114（ダニ，イヌ，ネコによる通年性），D-01（カバノキ花粉及びイネ花粉），2304（アレルギー性喘息と通年性アレルギー性鼻炎の合併）］を実施した[1.13.1-1-気管支喘息 150 mg-CTD 2.7.6]。

なお，現在米国及び EU では，慢性副鼻腔炎患者を対象とした第 III 相試験を実施中である。

## 3.2 国内における開発

国内においては，2[redacted]年に[redacted]相談（医機治発第[redacted]号，平成[redacted]年[redacted]月[redacted]日）にて[redacted]について助言を得て，2002 年のシーズンに第 II 相試験としてプラセボ対照試験（A1303 試験），2003 年のシーズンに第 III 相試験としてトシル酸スプラタスト対照試験（A1305 試験）を実施した。また，本剤再投与時の有効性及び安全性を検討するため，A1303 試験患者を対象とした 2 シーズン目の再投与試験（A1306 試験）を実施した。試験終了後の 2[redacted]年に[redacted]相談（医機治発第[redacted]号，平成[redacted]年[redacted]月[redacted]日）を実施したところ，[redacted]という理由から，[redacted]とされた。

その後，Ethnic sensitivity 試験（A2206 試験，2005 年実施）により日本人と外国人の PK/PD（血清中遊離 IgE 濃度）が同様であることが確認できたこと，及び主にアレルギー性喘息を対象に実施した臨床試験及び市販後の使用経験から豊富な安全性データが蓄積された。そこで，[redacted]2[redacted]年に[redacted]相談（薬機審長発第[redacted]号，平成[redacted]年[redacted]月[redacted]日）及び事後相談（#後[redacted]号，平成[redacted]年[redacted]月[redacted]日）にて[redacted]

[redacted]について助言を求めた。その際に，オマリズマブの有効性及び安全性を評価するのに適切な患者集団として既存治療で効果不十分な重症又は最重症のスギ花粉症患者を想定し，F1301 試験を計画・実施した。

F1301 試験では，既存治療でコントロール不十分な重症又は最重症スギ花粉症の成人及び青少年患者を対象に，オマリズマブの有効性及び安全性を評価した。その結果，オマリズマブ群のプラセボ群に対する優越性が検証された。また，オマリズマブの安全性及び忍容性は良好で，既存の特定されているオマリズマブのリスク以外に，新たに特定されたリスクはなかった。

本申請では，F1301 試験を評価資料，過去に実施した国内試験を参考資料として提出する（Figure 3-1）。これらの参考資料は，成人の気管支喘息に対する承認申請時に提出済みである。本申請で提出する品質及び非臨床試験の資料はない。

**Figure 3-1　　開発の経緯図**

| 試験項目 ＼ 年 | | | 2000 (H12) | 2001 (H13) | 2002 (H14) | 2003 (H15) | 2004 (H16) | …(中略)… | 2017 (H29) | 2018 (H30) |
|---|---|---|---|---|---|---|---|---|---|---|
| | 比較対照試験 | 国内/A1303試験:<br>季節性アレルギー性鼻炎(スギ)に対するプラセボを対照とした比較試験 | | 10●—● | 6 | | | | | |
| | 比較対照試験 | 国内/A1305試験:<br>季節性アレルギー性鼻炎(スギ)に対するトシル酸スプラタストを対照とした比較試験 | | | 11●—● | 8 | | | | |
| | 非比較対照試験 | 国内/A1306試験:<br>季節性アレルギー性鼻炎(スギ)に対するA1303試験患者への2シーズン目再投与，オープン試験 | | | 11●—● | 6 | | | | |
| | 比較対照試験 | 国内/F1301試験:<br>スギ花粉症に対する抗ヒスタミン薬＋鼻噴霧用ステロイドへの上乗せ効果を見たプラセボ対照比較試験 | | | | | | | 12●—● | 5 |
| 治験相談 | | [redacted] | | | | | | | | |

なお，現在国内では凍結乾燥製剤である「ゾレア皮下注用 75 mg」，「ゾレア皮下注用 150 mg」が販売されている。さらに，投与前の注射用水による溶解が不要となるプレフィルドシリンジ製剤の「ゾレア皮下注 75 mg シリンジ」，「ゾレア皮下注 150 mg シリンジ」については 2019 年 3 月 26 日に承認された。本承認申請は，いずれの剤形についても花粉症を効能又は効果として追加することを目的としている。

# 4　特徴及び有用性

### オマリズマブは新規作用機序の花粉症治療薬である

オマリズマブは，血清中の遊離 IgE に結合し，肥満細胞や好塩基球表面に発現している FcεRI と IgE との結合を競合的に阻害する。オマリズマブの結合部位である Cε3 は IgE の定常領域にあり，オマリズマブは IgE の抗原特異性にかかわらず結合することができる。

花粉症は，IgE がマスト細胞，好塩基球等の炎症細胞上の受容体に結合し抗原抗体反応が起こることで，ヒスタミンやロイコトリエン等の化学伝達物質が放出された結果，症状を呈する疾患である。オマリズマブは既存治療とは異なり，放出された化学伝達物質を阻害するのではなく，

アレルギーカスケードの初期反応を阻害する作用機序を有することから，既存治療で効果不十分な重症又は最重症花粉症患者の治療選択肢になり得ると考える。

**オマリズマブは花粉症による鼻症状及び眼症状を改善させる**

F1301 試験において，鼻症状については，症状ピーク期の Nasal Symptom Score の平均値，症状ピーク期のくしゃみ，鼻汁，鼻閉の重症度スコアの平均値，症状ピーク期のすべての鼻症状が軽度以下であった日数の中央値，症状ピーク期に完全にすべての鼻症状が軽度以下であった被験者の割合，及び鼻症状レスキュー薬（トラマゾリン塩酸塩）不使用日数の結果に基づき多角的に評価され，オマリズマブ群の鼻症状改善効果はプラセボ群に比べて高いことが示された。

眼症状については，症状ピーク期の Ocular Symptom Score の平均値，症状ピーク期の眼のかゆみ，涙目の重症度スコアの平均値の結果から，鼻症状と同様に，オマリズマブ群の眼症状改善効果はプラセボ群より高いことが示された。

以上より，オマリズマブは，花粉症の主症状である鼻症状及び眼症状を改善させることが期待できる。

**オマリズマブは花粉症患者の QOL 及び労働生産性を改善する**

F1301 試験において，アレルギー性鼻炎の標準的な QOL 調査票である JRQLQ No.1 を用いた結果から，オマリズマブ群の QOL 改善効果はプラセボ群より高いことが示された。

また，症状ピーク期の日常生活の支障度スコアの平均値の結果から，日常生活の支障に対するオマリズマブの改善効果はプラセボより高いことが示された。加えて，評価来院時の WPAI-AS スコアを用いた結果から，労働生産性低下や日常の諸活動への支障に対するオマリズマブの改善効果はプラセボよりも高いことが示された。

以上より，オマリズマブは花粉症罹患により大きく損なわれる QOL 及び労働生産性を改善させることが期待できる。

**オマリズマブの花粉症患者における安全性及び忍容性は良好である**

F1301 試験において，オマリズマブ群の有害事象発現率は，プラセボ群と同程度であり，高度の有害事象の発現はなかった。また，本試験期間中に発現した重篤あるいは投与中止に至った有害事象は，すべて治験薬との関連を否定され，既存の特定されているオマリズマブのリスク以外に，新たに特定されたリスクはなかった。

以上より，花粉症患者におけるオマリズマブの安全性及び忍容性は良好であることが示唆された。

# 5 まとめ

花粉症は，植物花粉によって誘因される季節性アレルギー性鼻炎で，国内の花粉症の有病率は 29.8%と高い。重症又は最重症の花粉症患者の中には，既存治療により十分な治療効果が認めら

れないことにより，鼻症状・眼症状・全身症状に悩まされ，QOL や労働生産性が著しく低下する患者が一定数存在する。花粉症の有病率が高いこともあり，ひいては社会全体が経済的にも多大な損失を被ることになる。したがって，これらの患者で花粉症の鼻症状及び眼症状を改善することにより，QOL や労働生産性も改善することができる新たな治療法が望まれている IgE の定常領域に結合するオマリズマブは，抗原特異性にかかわらずアレルギーカスケードの初期反応を阻害する新規作用機序を有することから，花粉抗原によらず既存治療により十分な治療効果が認められない患者の新たな治療選択肢となることが期待される。

ノバルティス社は，既存治療でコントロール不十分な重症又は最重症スギ花粉症の成人及び青少年患者を対象に，標準治療にオマリズマブを上乗せ投与したときの有効性及び安全性を検証することを目的とした，国内第 III 相試験（F1301 試験）を計画・実施した。F1301 試験の結果，既存治療で効果不十分な重症又は最重症のスギ花粉症患者に対して，オマリズマブ群は，鼻症状，眼症状，QOL，労働生産性のいずれもプラセボ群に比べて改善させ，安全性及び忍容性も良好であることが明らかになった。また，F1301 試験の成績から，これまでに特定されているリスク以外に新たに特定されたオマリズマブのリスクはなかった。

以上より，既存治療で効果不十分な重症又は最重症の花粉症患者に対するオマリズマブのベネフィットはリスクを上回り，新たな作用機序を有する治療選択肢として臨床的，社会的に意義が高い薬剤であると考え，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
ゾレア皮下注 75 mg シリンジ，ゾレア皮下注 150 mg シリンジ

**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. <u>花粉症（既存治療で効果不十分な重症又は最重症患者に限る）</u>
3. 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）

**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。

2. 花粉症

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 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）

3. 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 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，審査中の医薬品医療機器総合機構との協議内容を踏まえ，効能又は効果（案），及び用法及び用量（案）を以下の通り変更した。

**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. 季節性アレルギー性鼻炎（既存治療で効果不十分な重症又は最重症患者に限る）
3. 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）

**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。

2. 季節性アレルギー性鼻炎

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 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）

3. 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 300 mg を 4 週間毎に皮下に注射する。

（訂正線及び下線部：本申請に伴う変更箇所）

# 6 参考文献

[大久保公裕，奥田稔 (2012)] インターネットを用いたアレルギー性鼻炎患者に対する アンケート調査 2011. アレルギー・免疫; 19(1):113-24.

# 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

2019 年 8 月現在，オマリズマブはアレルギー性喘息の適応として EU，米国等世界 90 ヵ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 80 ヵ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 75 mg, 150 mg powder and solvent for solution for injection | 75 mg 及び 150 mg：<br>アレルギー性喘息：成人及び青少年（12 歳以上）<br>2005 年 10 月 25 日<br><br>アレルギー性喘息：小児（6 歳以上 12 歳未満）<br>2009 年 7 月 27 日<br><br>150 mg：<br>慢性特発性蕁麻疹<br>2014 年 2 月 28 日 | 凍結乾燥注射剤及び注射用溶解液<br>75 mg：溶解後 0.6 mL 溶液中にオマリズマブ 75 mg を含有<br><br>150 mg：溶解後 1.2 mL 溶液中にオマリズマブ 150 mg を含有 | 75 mg 及び 150 mg：<br>**アレルギー性喘息**<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>成人及び青少年（12 歳以上）<br>ゾレアは，通年性空中アレルゲンに対して皮膚試験陽性または *in vitro* 反応性であり，肺機能が低下し（$FEV_1$ <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 β2 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。<br><br>小児（6 歳以上 12 歳未満）<br>ゾレアは，通年性空中アレルゲンに対して皮膚試験陽性または *in vitro* 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 β2 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。<br><br>150 mg：<br>**慢性特発性蕁麻疹**<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。 |
| | Xolair 75 mg, 150 mg solution for injection in pre-filled syringe | 75 mg 及び 150 mg：<br>アレルギー性喘息：成人及び青少年（12 歳以上）<br>2009 年 2 月 10 日<br><br>アレルギー性喘息：小児（6 歳以上 12 歳未満）<br>2009 年 7 月 27 日<br><br>150 mg：<br>慢性特発性蕁麻疹<br>2014 年 2 月 28 日 | シリンジ充填済み注射剤<br>75 mg：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<br><br>150 mg：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 | |

| | | | | |
|---|---|---|---|---|
| 米国 | XOLAIR (omalizumab) for injection, for subcutaneous 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 1.2 mL 溶液中にオマリズマブ 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 150 mg 製剤のみ | **喘息**<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 *in vitro* 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>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>**慢性特発性蕁麻疹**<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（2019 年 7 月改訂）の概略を Table 2-1 に，米国の添付文書（2019 年 5 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 in pre-filled syringe<br>Xolair 150 mg solution for injection in pre-filled syringe |
| 剤型・含量 | **Xolair 75 mg powder and solvent for solution for injection**<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>**Xolair 150 mg powder and solvent for solution for injection**<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>**Xolair 75 mg solution for injection in pre-filled syringe**<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>**Xolair 150 mg solution for injection in pre-filled syringe**<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・効果注) | アレルギー性喘息<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>成人及び青少年（12 歳以上） |

| | |
|---|---|
| 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 in pre-filled syringe<br>Xolair 150 mg solution for injection in pre-filled syringe |
| | ゾレアは，通年性空中アレルゲンに対して皮膚試験陽性または *in vitro* 反応性であり，肺機能が低下し（$FEV_1$ <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 β2 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。<br><br><u>小児（6 歳以上 12 歳未満）</u><br>ゾレアは，通年性空中アレルゲンに対して皮膚試験陽性または *in vitro* 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 β2 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。<br><br><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。 |
| 用法・用量[注)] | 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。<br><br><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。<br><br>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ゲンに対する *in vitro* 反応性（RAST）が明らかに陽性であることを確認すること。<br><br>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。<br><br>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。<br><br>最大推奨用量はオマリズマブ 600 mg を 2 週間ごとである。 |

| | |
|---|---|
| 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 in pre-filled syringe<br>Xolair 150 mg solution for injection in pre-filled syringe |

**表 1：各投与時における投与量からバイアル数，注射回数及び総投与液量への換算**

| 投与量（mg） | バイアル数 75 mg [a] | バイアル数 150 mg [b] | 注射回数 | 総投与液量（ml） |
|---|---|---|---|---|
| 75 | 1[c] | 0 | 1 | 0.6 |
| 150 | 0 | 1 | 1 | 1.2 |
| 225 | 1[c] | 1 | 2 | 1.8 |
| 300 | 0 | 2 | 2 | 2.4 |
| 375 | 1[c] | 2 | 3 | 3.0 |
| 450 | 0 | 3 | 3 | 3.6 |
| 525 | 1[c] | 3 | 4 | 4.2 |
| 600 | 0 | 4 | 4 | 4.8 |

[a] 0.6 ml = 1 バイアル（ゾレア 75 mg）あたりの最大投与液量。

[b] 1.2 ml = 1 バイアル（ゾレア 150 mg）あたりの最大投与液量。

[c] あるいは 150 mg バイアルから 0.6 ml を取って使用する。

**表 2：4 週間ごとの投与。4 週間ごとに皮下注射で投与するゾレアの投与量（mg／投与）**

| | 体重（kg） | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ベースライン IgE (IU/ml) | ≥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 | 2 週間ごとの投与は表 3 を参照 | | | | | | | | | |
| >800-900 | | | | | | | | | | |
| >900-1000 | | | | | | | | | | |
| >1000-1100 | | | | | | | | | | |

| | |
|---|---|
| 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 in pre-filled syringe<br>Xolair 150 mg solution for injection in pre-filled syringe |

**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）**

| | 体重（kg） | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ベースライン IgE (IU/ml) | ≥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 | | | | | | |

*投与期間，モニタリング及び用量調節*

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。

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。

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）。

慢性特発性蕁麻疹（CSU）

*用量*

推奨用量は 300 mg であり，4 週間ごとに皮下投与する。

処方医は治療継続の必要性を定期的に再評価すること。

本適応症に対する 6 ヵ月を超える長期治療の臨床試験データは限られている。

特別な集団

*高齢者（65 歳以上）*

| | |
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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 in pre-filled syringe<br>Xolair 150 mg solution for injection in pre-filled syringe |
| | 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。<br><br>*腎機能障害又は肝機能障害*<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。<br><br>*小児患者集団*<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。<br><br>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。<br><br>用法<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。<br><br>150 mg を超えた用量（表 1）は 2 箇所以上の注射部位に分けて投与する。<br><br>ゾレア凍結乾燥製剤の自己注射の経験は限られている。したがって凍結乾燥製剤については医療関係者による投与に限定する。<br><br>投与前の製剤の溶解法は本剤の使用方法の項，及び添付文書の医療従事者向け情報を参照する。<br><br>シリンジ製剤について，アナフィラキシーの既往がない患者において医師が適切であると判断した場合には，4 回目以降の投与について自己投与もしくは介護者による投与が可能である。患者もしくは介護者は正しい注射手技を訓練し，重篤なアレルギー反応の早期の兆候や症状について認知すること。<br><br>患者もしくは介護者には，リーフレットの指示に従ってゾレアの全量を注射するよう指導すること。 |
| 使用上の注意[注)] | **禁忌**<br>有効成分又は添加物に対する過敏症。<br><br>**警告及び使用上の注意**<br>全般<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。<br><br>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。 |

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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 in pre-filled syringe<br>Xolair 150 mg solution for injection in pre-filled syringe |
| | 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。<br><br>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。<br><br>免疫系異常<br>*I 型アレルギー反応*<br>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。アナフィラキシー反応の大部分はゾレア投与の最初の 3 回のうちに発現した。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。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。もしもアナフィラキシー反応もしくは重篤なアレルギー反応が発現した場合には，ゾレアの投与を速やかに止め，適切な治療を始めるべきである。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。<br><br>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。<br><br>*血清病*<br>オマリズマブを含めヒト化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。<br><br>*Churg-Strauss 症候群及び好酸球増加症候群*<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。<br><br>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。<br><br>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。<br><br>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。 |

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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 in pre-filled syringe<br>Xolair 150 mg solution for injection in pre-filled syringe |
| | 寄生虫（蠕虫）感染症<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。<br><br>ラテックス過敏症者（Xolair 75 mg, 150 mg solution for injection のみ該当）<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。<br><br>**薬物相互作用及びその他の形の相互作用**<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。<br><br>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。<br><br>アレルギー性喘息<br>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。<br><br>慢性特発性蕁麻疹（CSU）<br>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。<br><br>*小児患者集団*<br>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。<br><br>**生殖能，妊娠及び授乳** |

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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 in pre-filled syringe<br>Xolair 150 mg solution for injection in pre-filled syringe |
| | 妊娠<br>妊婦を対象としたレジストリーまたは市販後の自発報告に基づく一定量の妊婦のデータ（300 から 1000 の妊婦における結果）から奇形性や胎児，新生児への毒性は示されなかった。ゾレアを投与された喘息を有する妊婦 250 名を対象とした前向きレジストリー試験（EXPECT）から，主な先天性異常の有病率は，EXPECT と同様の疾患（中等症又は重症喘息）の患者において同程度であった（それぞれ 8.1%，8.9%）。当該データの解釈には症例数が少ないことやランダム化をしないデザインであったことを含め，方法論的な限界があると思われる。<br><br>オマリズマブは胎盤関門を通過するが，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。<br><br>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。<br><br>臨床的に必要な場合には，妊娠中のゾレアの投与を検討すること。<br><br>授乳<br>免疫グロブリン G（IgG）はヒト乳汁中に存在するため，オマリズマブがヒト乳汁中に存在することが想定される。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。<br><br>EXPECT 試験では 154 名の乳児がゾレアを投与している妊婦からの授乳を介して曝露したが，母乳で育てられた乳児において有害事象は示されなかった。当該データの解釈には症例数が少ないことやランダム化をしないデザインであったことを含め，方法論的な限界があると思われる。<br><br>経口投与では，免疫グロブリン G タンパクは腸管内でタンパク分解されるため，バイオアベイラビリティは低い。母乳で育てられた新生児／乳児に対して影響はないことが想定される。よって，臨床的に必要な場合には，授乳中のゾレアの投与を検討すること。<br><br>生殖能<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。<br><br>**自動車運転及び機械操作に対する影響**<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。<br><br>**副作用**<br>アレルギー性喘息<br>*安全性プロファイルの要約* |

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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 in pre-filled syringe<br>Xolair 150 mg solution for injection in pre-filled syringe |

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。

*副作用の一覧*

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。

**表 4：アレルギー性喘息における副作用**

| | |
|---|---|
| **感染症および寄生虫症** | |
| 少ない | 咽頭炎 |
| まれ | 寄生虫感染 |
| **血液およびリンパ系障害** | |
| 不明 | 特発性血小板減少症（重症例を含む） |
| **免疫系障害** | |
| 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） |
| **神経系障害** | |
| 多い | 頭痛* |
| 少ない | 失神，錯感覚，傾眠，浮動性めまい |
| **血管障害** | |
| 少ない | 体位性低血圧，潮紅 |
| **呼吸器，胸郭および縦隔障害** | |
| 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） |
| **胃腸障害** | |
| 多い | 上腹部痛** |
| 少ない | 消化不良徴候及び症状，下痢，悪心 |
| **皮膚および皮下組織障害** | |
| 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 |
| **筋骨格系および結合組織障害** | |
| 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 |
| **一般・全身障害および投与部位の状態** | |
| 非常に多い | 発熱** |

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| | |
|---|---|
| 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 |

*：6 歳以上 12 歳未満の小児においては非常に多い

**：6 歳以上 12 歳未満の小児において

慢性特発性蕁麻疹（CSU）

*安全性プロファイルの要約*

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 週まで 300 mg 投与を受けた。

*副作用の一覧*

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。

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。

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）。

**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）**

| **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 | |
| **感染症および寄生虫症** | | | |
| 副鼻腔炎 | 5 (2.1%) | 20 (4.9%) | 多い |
| **神経系障害** | | | |
| 頭痛 | 7 (2.9%) | 25 (6.1%) | 多い |
| **筋骨格系および結合組織障害** | | | |
| 関節痛 | 1 (0.4%) | 12 (2.9%) | 多い |
| **一般・全身障害および投与部位の状態** | | | |
| 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 | |

| | |
|---|---|
| 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 in pre-filled syringe<br>Xolair 150 mg solution for injection in pre-filled syringe |
| | **感染症および寄生虫症**<br>上気道感染 5 (3.1%) 19 (5.7%) 多い<br>*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。<br><br>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<br>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。<br><br>*免疫系障害*<br>より詳細な情報は警告及び使用上の注意の項を参照。<br><br>*アナフィラキシー*<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，推定曝露 566,923 患者治療・年とした時，約 0.20%の報告率となる。<br><br>*動脈血栓塞栓事象（ATE）*<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）。<br><br>*血小板*<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。<br><br>*寄生虫感染*<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。<br><br>*全身性エリテマトーデス*<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ない。<br><br>副作用疑いの報告 |

| | |
|---|---|
| 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 in pre-filled syringe<br>Xolair 150 mg solution for injection in pre-filled syringe |
| | 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。<br><br>**過量投与**<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。<br><br>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。 |
| 改訂年月日 | 2019 年 7 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) injection, for subcutaneous use<br>XOLAIR (omalizumab) for injection, for subcutaneous use |
| 剤型・含量 | 注射剤：ゾレア注射剤は澄明又はわずかに混濁した，無色から微黄褐色の液体である。<br>• 青色のニードルシールドのプレフィルドシリンジ製剤は 75 mg/0.5 mL<br>• 紫色のニードルシールドのプレフィルドシリンジ製剤は 150 mg/mL<br>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，単回投与用のバイアルに充填されている。 |
| 効能・効果 | **喘息**<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 *in vitro* 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>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>使用に関する制限事項：<br>● 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。<br>● 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。<br><br>**慢性特発性蕁麻疹（CIU）**<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。<br>使用に関する制限事項：<br>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。 |
| 用法・用量 | **喘息患者への投与**<br>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。<br>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）。<br>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。 |

| 販売名 | XOLAIR (omalizumab) injection, for subcutaneous use<br>XOLAIR (omalizumab) for injection, for subcutaneous use |
|---|---|

- 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。
- 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。

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。

成人及び 12 歳以上の青少年患者：表 1 に従い投与を開始する。

**表 1.　12 歳以上の喘息患者に対するゾレアの 2 又は 4 週間隔*皮下投与量**

| 投与開始前の血清中 IgE 濃度 (IU/mL) | 投与間隔 | 体重 | | | |
|---|---|---|---|---|---|
| | | 30～60 kg | >60～70 kg | >70～90 kg | >90～150 kg |
| | | 用量 (mg) | | | |
| ≥ 30～100 | 4 週間隔 | 150 | 150 | 150 | 300 |
| > 100～200 | | 300 | 300 | 300 | 225 |
| > 200～300 | | 300 | 225 | 225 | 300 |
| > 300～400 | 2 週間隔 | 225 | 225 | 300 | 用量を推奨するのに十分なデータがない |
| > 400～500 | | 300 | 300 | 375 | |
| > 500～600 | | 300 | 375 | | |
| > 600～700 | | 375 | | | |

*投与間隔
- 4 週間隔で皮下注投与
- 2 週間隔で皮下注投与

6 歳以上 12 歳未満の小児患者：表 2 に従い投与を開始する。

**表 2.　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**

| 投与開始前の血清中 IgE 濃度 (IU/mL) | 投与間隔 | 体重 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ≥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 |
| | | 用量（mg） | | | | | | | | | |
| 30-100 | | 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 |

| 販売名 | XOLAIR (omalizumab) injection, for subcutaneous use<br>XOLAIR (omalizumab) for injection, for subcutaneous use |
|---|---|

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| >300-400 | 4 週間隔 | 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 週間隔 | 225 | 225 | 300 | 375 | 用量を推奨するのに十分なデータがない | | | |
| >800-900 | | 225 | 225 | 300 | 375 | | | | |
| >900-1000 | | 225 | 300 | 375 | | | | | |
| >1000-1100 | | 225 | 300 | 375 | | | | | |
| >1100-1200 | | 300 | 300 | | | | | | |
| >1200-1300 | | 300 | 375 | | | | | | |

*投与間隔
- 4 週間隔で皮下注投与
- 2 週間隔で皮下注投与

**慢性特発性蕁麻疹患者への投与**

ゾレア 150 mg 又は 300 mg を 4 週間隔で皮下投与する。

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。

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。

**投与時**

ゾレアはプレフィルドシリンジ製剤とバイアル入り凍結乾燥粉末製剤がある。ゾレアのプレフィルドシリンジ製剤と凍結乾燥粉末製剤の両製剤とも医療従事者によって投与されること。ゾレアは皮下注射する。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 1 回を超えて投与しないこと。（表 3，表 4）。

**表 3.　シリンジ数，注射回数及び総投与液量**

| ゾレアの投与量* | 75 mg シリンジ | 150 mg シリンジ | 総投与液量 |
|---|---|---|---|
| 75 mg | 1 | 0 | 0.5 mL |
| 150 mg | 0 | 1 | 1 mL |
| 225 mg | 1 | 1 | 1.5 mL |
| 300 mg | 0 | 2 | 2 mL |
| 375 mg | 1 | 2 | 2.5 mL |

* 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。

**表 4.　バイアル数，注射回数及び総投与液量**

| ゾレアの投与量* | バイアル数 | 注射回数 | 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 |

| 販売名 | XOLAIR (omalizumab) injection, for subcutaneous use<br>XOLAIR (omalizumab) for injection, for subcutaneous use |
|---|---|

| | | | |
|---|---|---|---|
| 300 mg | 2 | 2 | 2.4 mL |
| 375 mg | 3 | 3 | 3.0 mL |

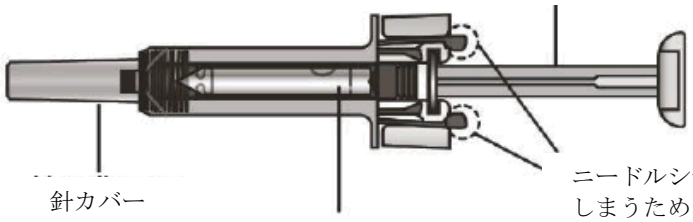
* 本表に記載している投与量は，いずれも喘息患者への投与が承認されている。ゾレア 150 mg 及び 300 mg は CIU 患者に対する投与量である。

**ゾレアのプレフィルドシリンジ製剤の使用準備**

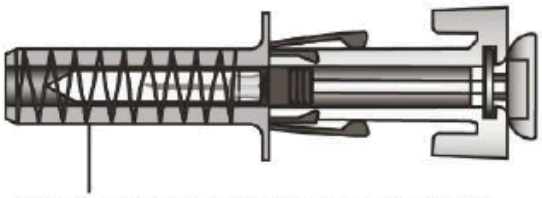
ゾレアの皮下投与用のプレフィルドシリンジ製剤の準備について，これらの使用ガイドを注意深く読み遵守すること

プレフィルドシリンジのパーツ

使用前：



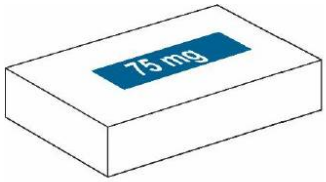

使用後：

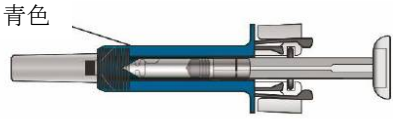


ニードルシールド（伸びて固定される）

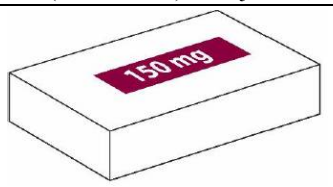
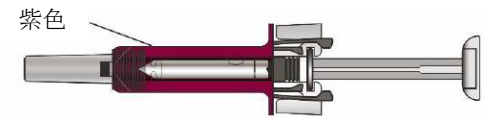
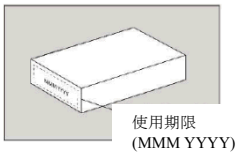
ゾレアのプレフィルドシリンジ製剤は 2 用量ある。これらのインストラクションはどちらの用量にも適用される。用量が正しいことを確認するためにゾレアのプレフィルドシリンジ製剤の外箱のラベルを確認すること。

- 青色のニードルシールドのゾレア 75 mg プレフィルドシリンジ




- 紫色のニードルシールドのゾレア 150 mg プレフィルドシリンジ

| | |
|---|---|
| 販売名 | XOLAIR (omalizumab) injection, for subcutaneous use<br>XOLAIR (omalizumab) for injection, for subcutaneous use |
| |  <br>  <br>保管のインストラクション<br>• 未使用のシリンジは元の外箱に入った状態を保ち，36°F～46°F（2°C～8°C）で冷蔵保管すること。<br>• 直射日光を避けること。<br>• 冷凍しないこと。<br>• 凍っていた場合には使用しないこと。<br>• 常に乾燥を保つこと。<br>プレフィルドシリンジに関する重要な情報<br>• ゾレアの注射用のプレフィルドシリンジ製剤の取り外し可能な針カバーには天然ゴムラッテクス由来物質を含んでいる。<br>• ゾレア投与の準備が完了するまで，外箱を開封しないこと。<br>• ゾレア投与の準備が完了するまで，針カバーを外さないこと。<br>• どんなときもシリンジを解体しないこと。<br>• 同じシリンジを再使用しないこと。<br>• シリンジを落としたり傷つけたりした場合には使用しないこと。<br>• パッケージが傷ついているもしくは異変がある場合には使用しないこと。<br>• シリンジを放置しないこと。<br>• シリンジに子どもの手の届かないようにすること。<br>注射前の準備<br>1. 清潔で平らな作業面を見つける。<br>　• それぞれのゾレアの箱に 1 つのシリンジが入っている。<br>　• 冷蔵庫からシリンジの入った箱を取り出す。<br>2. ゾレア外箱の使用期限を確認する。<br>　• 使用するには安全でない可能性があるため，使用期限を超えている場合には使用しないこと。使用期限を超えている場合には，シリンジを安全に専用の容器で処分すること（Step 14 を参照）。<br>  <br>3. 清潔で平らな作業面に箱を置く。<br>　• 少なくとも 15～30 分間箱を置いておき室温にする（光から守るためにシリンジは箱の中のままとすること）。<br>　• もしもシリンジが室温に満たなかった場合，注射により不快に感じたりプランジャーが押しにくくなったりすることとなる。<br>　• シリンジが熱くならないようにすること。<br>　• どんな場合にもこの温度管理のプロセスを簡素化せず，シリンジを電子レンジやお湯の中に入れないこと。<br>4. 箱を開ける。<br>　• 石鹸と水で手を洗う。 |

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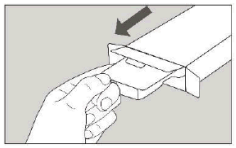
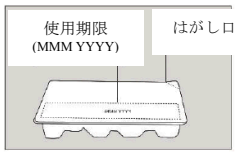
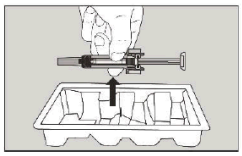
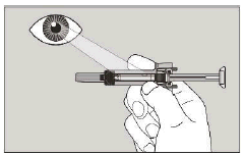
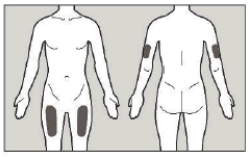
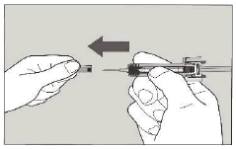
| | • 箱からブリスターパックを取り出す。<br>• ブリスターパックの使用期限を確認する。<br>• 使用するには安全でない可能性があるため，使用期限を超えている場合には使用しないこと。使用期限を超えている場合には，シリンジを安全に専用の容器で処分すること（Step 14 を参照）。<br>• シリンジを取り出すときには注意すること。シリンジを取り出すのにブリスターパックを逆さまにひっくり返さず，シリンジの後ろ部分を触らないこと。これがシリンジを傷つけることとなる。<br>• ブリスターパックのカバーをはがす。シリンジの真ん中部分を持ってシリンジを取り出す。シリンジを持つときには，図のとおり常に掴むようにすること<br>• プランジャーや針カバーを押さえてシリンジを掴まないこと。<br>  <br>  <br><br>  <br>5. シリンジを近くで目視する。<br>• シリンジを確認する。シリンジ中の液体は澄明又はわずかに混濁した，無色から微黄褐色である。液体が濁っていたり変色していたり異物が混入している場合にはシリンジを使用しないこと。<br>• シリンジの使用期限を確認する。使用するには安全でない可能性があるため，使用期限を超えている場合には使用しないこと。<br>• もしも薬剤が記載されているように見えなかったり，使用期限を超えていたりする場合には，シリンジを安全に専用の容器で処分すること（Step 14 を参照）。<br>  <br>6. 注射部位を選ぶ。<br>• 推奨する注射部位は上腕と大腿部である。<br>• ほくろ，傷痕，あざ，或いは肌が柔らかい，赤い，かたい若しくはひび割れている部位には注射しないこと。<br>• 新たに注射する際には前に注射した部位から少なくとも 1 インチ以上離れた異なる部位を選ぶ。<br>  <br><br>7. アルコール綿で注射部位を拭き，10 秒間空気で自然乾燥する。<br>• 注射前に注射部位に触れないこと。<br>• 清潔にした部位に扇いだり風を吹いたりしたいこと。<br>注射時<br>8. 片手でしっかりとシリンジを掴み，もう片方の手で針カバーをまっすぐ外す。<br>• 針カバーを外している間にプランジャーは掴まないこと<br>• 針カバーを外した後に針を触らないこと。<br>• 針カバーは専用の容器に捨てる。<br>• シリンジ内に小さな気泡がある場合がある。これは通常のことであるため，気泡を取り除こうとしないこと。<br>• 針の先端に水滴が見える場合がある。これも通常のことであり，用量に影響を与えない。<br>  |

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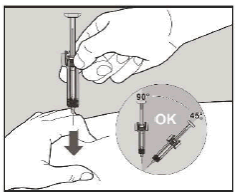
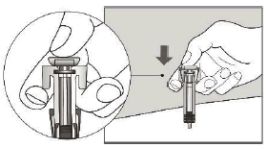
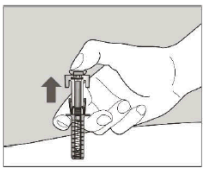
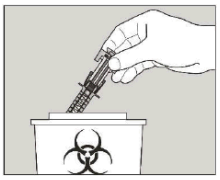
| | 9. もう片方の手を使って，清潔にした肌の部位をそっと摘む。しっかりと摘んだままにする。<br>• 肌を摘むのは，より深い場所（筋肉内）ではなく皮下（脂肪領域）に確実に注射するために重要である。<br>10. シリンジの中心部を掴んだまま，素早く，ダーツのような動きで摘んだ肌に 45°～90°で刺す。薬剤が皮下（脂肪領域）に到達するために，正しい角度で使うことが重要であり，さもないと，注射で不快に感じ，薬剤が作用しない可能性がある。<br>  <br><br>• 針を肌に指す間，プランジャーに触れないこと。<br>• 衣類の上から針を刺さないこと。一度針を刺したら，その場所でシリンジをしっかりと掴み，注射の角度を変えたり刺し直したりしないこと。患者は動くべきではないため，注射の間は突然の移動を防ぐようにする。<br>11. プランジャーをそっと押して全ての薬剤をゆっくりと注射する。<br>  <br>• 確実に薬剤の全用量が注射されるように，必ずプランジャーを押す必要がある。プランジャーを完全に押し切らなかった場合，針を取り出したときに針カバーが針を覆うために伸びない。<br>12. そっとプランジャーを離して針カバーで針が覆われるようにする。<br>  <br>• 針が覆われない場合，注意深くシリンジを廃棄する（Step 14 を参照）。<br>注射後<br>13. 注射部位は若干の出血をすることがある。綿棒やガーゼで注射部位を圧迫してよい。<br>• 注射部位をこすらないこと。<br>• 必要に応じて絆創膏で注射部位を覆ってもよい。<br>• 肌に薬剤が触れてしまった場合，薬剤と触れた部分を水洗いすること。<br>14. ゾレアのプレフィルドシリンジ製剤は一回量のシリンジで再使用すべきではない。<br>  <br>• 使用したゾレアのプレフィルドシリンジ製剤は FDA が許可した専用の廃棄用の容器に捨てる。ごみ箱にプレフィルドシリンジを捨ててはいけない。<br>• 針カバーを針に戻さないこと。<br><br>**ゾレアの凍結乾燥粉末製剤の使用準備**<br>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：<br><br>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］。<br>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。<br>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。<br>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。 |

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| | 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。**凍結乾燥粉末の溶解には 15～20 分かかる。**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。<br>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。<br>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。<br>8) **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。**溶解後のバイアルは遮光すること。<br>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**溶液をすべて吸引する**。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。<br>10) 18 ゲージ針を皮下注用の 25 ゲージ針に交換する。<br>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。<br>12) 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。 |
| 使用上の注意 | **警告：アナフィラキシー**<br>**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*］。**<br><br>**禁忌**<br>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*］。<br><br>**警告及び使用上の注意**<br>**アナフィラキシー** |

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| | 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。<br>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］。<br>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。<br>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。<br>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*］。<br><br>**悪性腫瘍**<br>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。<br>通年性吸入抗原に対する皮膚テスト陽性又は *in vitro* 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%）。<br><br>**急性喘息症状**<br>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。<br><br>**ステロイド薬の減量**<br>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。 |

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| 販売名 | XOLAIR (omalizumab) injection, for subcutaneous use<br>XOLAIR (omalizumab) for injection, for subcutaneous use |
| | **好酸球性疾患**<br>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ーグ・ストラウス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。<br>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。<br><br>**発熱，関節痛及び発疹**<br>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*］。<br><br>**寄生虫感染症**<br>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。<br>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。<br><br>**臨床検査値**<br>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*］<br><br>**副作用**<br>ゾレアの投与により次の副作用が発現している：<br>● 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*］<br>● 悪性腫瘍［*警告及び使用上の注意を参照*］<br><br>**臨床試験における経験**<br>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。<br><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> |

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| 販売名 | XOLAIR (omalizumab) injection, for subcutaneous use<br>XOLAIR (omalizumab) for injection, for subcutaneous use |

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 150 mg～375 mg 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。

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。

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。

**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**

| 副作用 | ゾレア<br>738 例 | プラセボ<br>717 例 |
|---|---|---|
| 全身障害 | | |
| 疼痛 | 7% | 5% |
| 疲労 | 3% | 2% |
| 筋骨格系障害 | | |
| 関節痛 | 8% | 6% |
| 骨折 | 2% | 1% |
| 下肢痛 | 4% | 2% |
| 上肢痛 | 2% | 1% |
| 神経系障害 | | |
| 浮動性めまい | 3% | 2% |
| 皮膚付属器状態 | | |
| そう痒症 | 2% | 1% |
| 皮膚炎 | 2% | 1% |
| 特殊感覚異常 | | |
| 耳痛 | 2% | 1% |

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。

*アナフィラキシーの症例対照研究*

| 販売名 | XOLAIR (omalizumab) injection, for subcutaneous use<br>XOLAIR (omalizumab) for injection, for subcutaneous use |
|---|---|
| | 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*］。<br><br>*注射部位反応*<br>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，注射部位腫瘤及び注射部位炎症であった。<br>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%）。<br>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。<br><br><u>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</u><br>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 75 mg～375 mg 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。<br>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。<br>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。<br><br><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><br>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 75 mg，150 mg，300 mg 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 300 mg 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 300 mg 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 150 mg 及び 75 mg 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。 |

| 販売名 | XOLAIR (omalizumab) injection, for subcutaneous use<br>XOLAIR (omalizumab) for injection, for subcutaneous use |
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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。

**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）**

| 副作用* | CIU の Trials 1，2 及び 3 を併合 | | |
|---|---|---|---|
| | 150 mg (175 例) | 300 mg (412 例) | プラセボ (242 例) |
| 胃腸障害 | | | |
| 悪心 | 2 (1.1%) | 11 (2.7%) | 6 (2.5%) |
| 感染症および寄生虫症 | | | |
| 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%) |
| 筋骨格系および結合組織障害 | | | |
| 関節痛 | 5 (2.9%) | 12 (2.9%) | 1 (0.4%) |
| 神経系障害 | | | |
| 頭痛 | 21 (12.0%) | 25 (6.1%) | 7 (2.9%) |
| 呼吸器，胸郭および縦隔障害 | | | |
| 咳嗽 | 2 (1.1%) | 9 (2.2%) | 3 (1.2%) |

* MedDRA（15.1）の器官別大分類及び基本語に従って分類

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。

*注射部位反応*

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。

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

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| 販売名 | XOLAIR (omalizumab) injection, for subcutaneous use<br>XOLAIR (omalizumab) for injection, for subcutaneous use |
| | 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 ヵ月間あった。<br>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，未測定の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。<br>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 ヵ月であった。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。<br><br>**免疫原性**<br>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（＜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，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。<br><br>**市販後の使用経験**<br>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。 |

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| 販売名 | XOLAIR (omalizumab) injection, for subcutaneous use<br>XOLAIR (omalizumab) for injection, for subcutaneous use |
| | アナフィラキシー：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。<br>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。<br>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。<br>好酸球性疾患：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*］。<br>発熱，関節痛及び発疹：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*］。<br>血液疾患：重度の血小板減少症が報告されている。<br>皮膚疾患：毛髪脱落が報告されている。<br><br>**薬物相互作用**<br>ゾレアの正式な薬物相互作用試験は実施していない。<br>喘息患者では，ゾレアとアレルゲン免疫療法の併用は評価していない。<br>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。<br><br>**特別な集団における使用**<br>**妊婦**<br>リスクの要約<br>妊娠中にゾレアを投与したレジストリー試験では大奇形や流産の割合の増加は見られなかった。レジストリーの乳児において，出生までの妊娠期間は平均的であったにもかかわらず，他のコホートに比べて低出生体重の割合の増加傾向が見られた。しかしながら，ゾレアが投与された女性はより重症の喘息であるため，低出生体重が薬剤によって引き起こされたのか，或いは疾患重篤性によるものなのか結論づけることは困難である。*[データ参照]*　コントロール不良又は不十分な喘息妊婦においてリスクがある。*[臨床的考察参照]*<br><br>ヒト IgG 抗体は胎盤関門を通過することが知られており，ゾレアは母体から発達段階の胎児に移行する可能性がある。 |

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| | 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。［*データ参照*］<br><br>適応となる患者集団における大奇形や流産の推定背景リスクは不明である。すべての妊婦は，先天性異常や欠損，その他望ましくない結果の背景リスクを有する。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。<br><br>臨床的考察<br>*疾患関連の母体，胎児のリスク*<br>コントロール不良又は不十分な喘息女性において，母体の子癇前症リスク，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。<br><br>*データ*<br>*ヒトデータ*<br>2006 年から 2018 年にかけて US において，ゾレアを投与された喘息を有する妊婦 250 名を含む前向きコホートレジストリー試験が実施された。このうち 246 名において妊娠初期にゾレアが投与され，平均曝露期間は 8.7 ヵ月であった。<br>対象となった母体及び乳児に関するレジストリーサブグループにおける調査結果を，（ゾレアの曝露がない）喘息を有する同様の疾患の妊婦 1153 名の外部コホートにおける年齢で補正した頻度と比較した。外部コホートは，Quebec External Comparator Cohort を参照して，カナダ ケベック州の居住者の医療データベースから特定した。<br>レジストリーの対象となった乳児における主な先天性異常の有病率（8.1%）は乳児に関して比較したコホート（8.9%）と同様であった。レジストリーの対象となった妊婦において 99.1%が生児出生であり，比較したコホートの 99.3%と同様であった。レジストリーの乳児において低出生体重の割合（13.7%）が比較したコホート（9.8%）よりも多かった。しかしながら，妊娠中にゾレアを投与している女性はより重症の喘息であるため，低出生体重が薬剤によって引き起こされたのか，或いは疾患重篤性によるものなのか結論づけることは困難である。<br>このレジストリー試験は，観察的であること，症例数が少ないこと，レジストリー集団と比較コホートの潜在的な違いを含む方法論的な限界により，何等かのリスクがないことを決定的に証明することはできない。<br><br>*動物実験データ*<br>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。<br><br>**授乳**<br>リスクの要約<br>ヒト乳汁中へのオマリズマブの移行，及び乳汁産生への影響に関する情報はない。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。 |

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| | レジストリーで曝露していた妊婦において大部分の乳児（80.9%，186/230）は母乳で育てられた。“感染及び侵入”に分類されたイベントについて，授乳を介してゾレアに曝露された乳児は，ゾレアを投与している妊婦の母乳で育っていない乳児或いはゾレアを投与していない妊婦の母乳で育った乳児と比較して，意義のある増加は見られなかった。<br><br>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の必要性と，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。<br><br>**小児への投与**<br><u>喘息</u><br>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 *in vitro* 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 の用量の倍増を必要とする喘息増悪と定義）。［*臨床試験を参照*］<br>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。<br><br><u>慢性特発性蕁麻疹</u><br>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。<br>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。<br><br>**高齢者への投与**<br>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。<br><br>**過量投与**<br>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。 |
| 改訂年月日 | 2019 年 5 月 |

[redacted]

# XOLAIR® (omalizumab)

75 mg, 150 mg Powder and solvent for solution for injection
75 mg, 150 mg Solution for injection in pre-filled syringe

## Core Data Sheet (CDS)

[redacted]

以下，非公開のため省略

## 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) injection, for subcutaneous use**
**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----------**

Dosage and Administration (2.1, 2.3, 2.4, 2.5) 09/2018

**----------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----------**

- Injection: 75 mg/0.5 mL and 150 mg/mL solution in a single-dose prefilled syringe (3)
- For Injection: 150 mg lyophilized powder in a single-dose vial for reconstitution (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)
- Eosinophilic Conditions: Be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy, especially upon reduction of oral corticosteroids. (5.5)
- Fever, Arthralgia, and Rash: Stop XOLAIR if patients develop signs and symptoms similar to serum sickness. (5.6)

**----------ADVERSE REACTIONS----------**

- Asthma: The most common adverse reactions in clinical studies with adult and adolescent patients ≥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 (≥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.**

**----------DRUG INTERACTIONS----------**

No formal drug interaction studies have been performed. (7)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 05/2019**

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* Sections or subsections omitted from the full prescribing information are not listed.



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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 mg 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 Tables 1 and 2).

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.



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- Interruptions lasting one year or more: Re-test total serum IgE levels for dose determination using Table 1 or 2, 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.

**Table 1. Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Patients 12 Years of Age and Older with Asthma**

| Pretreatment Serum IgE (IU/mL) | Dosing Freq. | Body Weight | | | |
|---|---|---|---|---|---|
| | | 30−60 kg | >60−70 kg | >70−90 kg | >90−150 kg |
| | | Dose (mg) | | | |
| ≥30−100 | Every 4 weeks | 150 | 150 | 150 | 300 |
| >100−200 | | 300 | 300 | 300 | 225 |
| >200−300 | | 300 | 225 | 225 | 300 |
| >300−400 | Every 2 weeks | 225 | 225 | 300 | |
| >400−500 | | 300 | 300 | 375 | |
| >500−600 | | 300 | 375 | **Insufficient Data to Recommend a Dose** | |
| >600−700 | | 375 | | | |

***Dosing frequency:**

- Subcutaneous doses to be administered every 4 weeks
- Subcutaneous doses to be administered every 2 weeks



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Pediatric patients 6 to <12 years of age: Initiate dosing according to Table 2.

**Table 2. 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 | Insufficient Data to Recommend a Dose | | | | | | |
| >1000-1100 | | 225 | 300 | 375 | | | | | | | |
| >1100-1200 | | 300 | 300 | | | | | | | | |
| >1200-1300 | | 300 | 375 | | | | | | | | |

***Dosing frequency:**

- Subcutaneous doses to be administered every 4 weeks
- Subcutaneous doses to be administered every 2 weeks

## 2.2 Dosage for Chronic Idiopathic Urticaria

Administer XOLAIR 150 mg 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 Administration

XOLAIR is available as a prefilled syringe and as a lyophilized powder in vial for reconstitution. Both XOLAIR prefilled syringe and lyophilized powder should be administered by a healthcare professional. Administer XOLAIR by subcutaneous injection. The injection may take 5-10 seconds to administer. Do not administer more than one injection per site. (Table 3, Table 4).



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**Table 3. Number of Prefilled Syringes, Injections and Total Injection Volumes**

| XOLAIR Dose* | 75 mg Syringes | 150 mg Syringes | Total Volume Injected |
|---|---|---|---|
| 75 mg | 1 | 0 | 0.5 mL |
| 150 mg | 0 | 1 | 1 mL |
| 225 mg | 1 | 1 | 1.5 mL |
| 300 mg | 0 | 2 | 2 mL |
| 375 mg | 1 | 2 | 2.5 mL |

* All doses in the table are approved for use in asthma patients. The 150 mg and 300 mg XOLAIR doses are also approved for use in CIU patients.

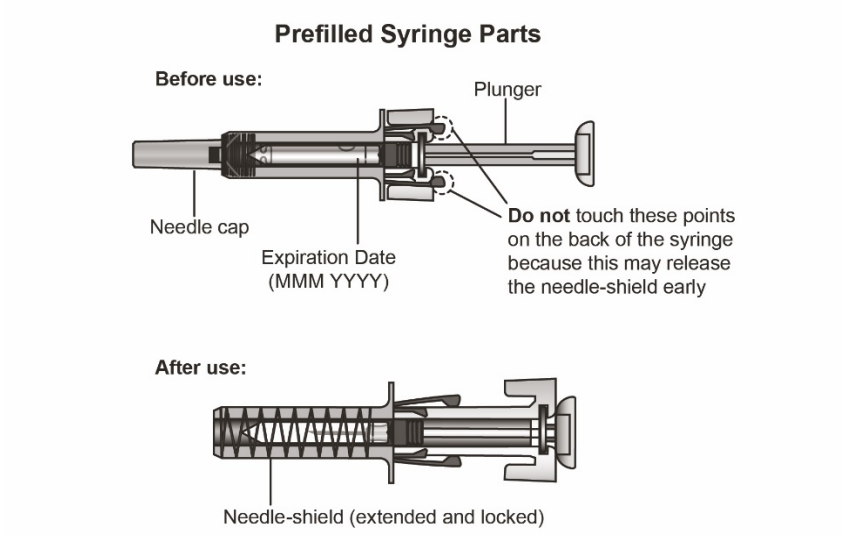
**Table 4. Number of Vials, Injections and Total Injection Volumes**

| 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 |
| 375 mg | 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 also approved for use in CIU patients.

## 2.4 Preparation for Use and Injection of XOLAIR Prefilled Syringe

To prepare XOLAIR prefilled syringes for subcutaneous administration, please carefully read and adhere to these instructions for use.



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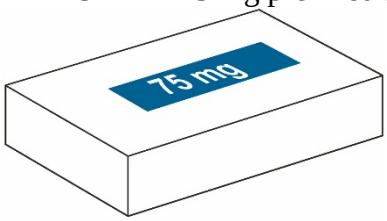
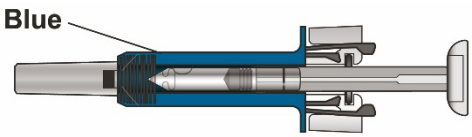
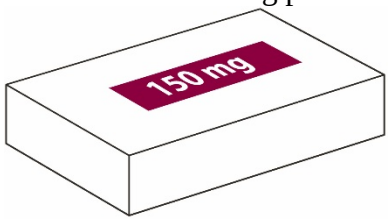
XOLAIR prefilled syringes are available in 2 dose strengths. These instructions are to be used for both dose strengths. You should check the label on the carton that comes with the XOLAIR prefilled syringe to make sure that the dose is correct.

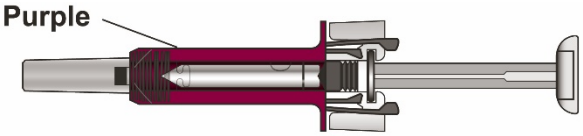
- XOLAIR 75 mg prefilled syringe with a blue needle shield




- XOLAIR 150 mg prefilled syringe with a purple needle shield




**Storage Instructions**

- Keep the unused syringe in the original carton and store the carton in a refrigerator at 36˚F to 46˚F (2˚C to 8˚C). **Do not** remove the syringe from its original carton during storage.
- Keep the XOLAIR syringe out of direct sunlight.
- **Do not** freeze.
- **Do not** use if the syringe has been frozen.
- Always keep the syringe dry.

**Important Information about the Prefilled Syringe**

- The removable needle cap of XOLAIR solution for injection in prefilled syringe contains a derivative of natural rubber latex *[see Description (11)]*.
- **Do not** open the sealed outer carton until you are ready to inject XOLAIR.
- **Do not** take the needle cap off until you are ready to inject XOLAIR.
- **Do not** try to take the syringe apart at any time.
- **Do not** reuse the same syringe.
- **Do not** use if the syringe has been dropped or damaged.
- **Do not** use if the packaging is damaged or appears to be tampered with.
- **Do not** leave the syringe unattended.
- Keep the syringe out of the reach of children.

**<u>Preparing for the Injection</u>**

**1** Find a clean, flat, working surface.

- Each XOLAIR carton contains 1 syringe.
- Take the carton containing the syringe out of the refrigerator.



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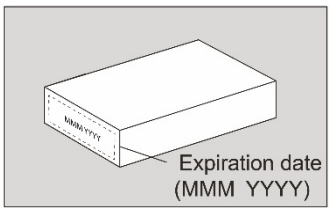
**2** Check the expiration date on the XOLAIR carton.

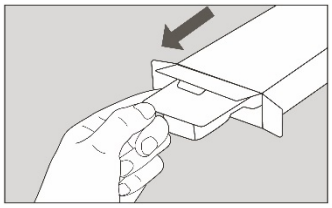



- Do not use it if the expiration date has passed because it may not be safe to use. If the expiration date has passed, safely dispose of the syringe in a sharps container (see step 14 at the end of these instructions for use).

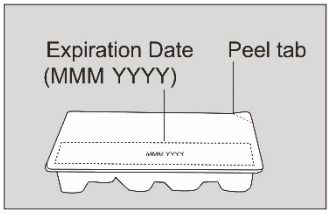
**3** Place the carton on a clean flat, surface.

- Set aside the carton for at least 15-30 minutes so the syringe can warm up on its own to room temperature (leave the syringe in the carton to protect it from light).
- If the syringe does not reach room temperature, this could cause the injection to feel uncomfortable and make it hard to push the plunger.
- **Do not** allow the syringe to become hot.
- **Do not** speed up the warming process in any way, and do not put the syringe in a microwave or in warm water.

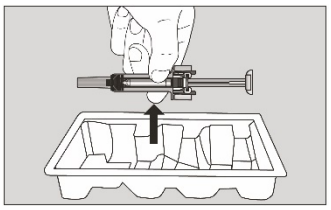
**4** Open the carton.



- Wash your hands with soap and water.
- Take the blister pack out of the carton.



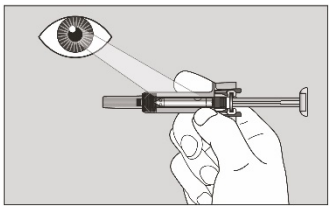

- Check the expiration date on blister pack.
- Do not use it if the expiration date has passed because it may not be safe to use. If the expiration date has passed, safely dispose of the syringe in a sharps container (see step 14 at the end of these instructions for use).



- Be careful when taking out the syringe. **Do not** flip the blister pack upside down to take out the syringe, and **do not** touch the back of the syringe. This may damage the syringe.
- Peel off the blister pack cover. Take the syringe out of the blister pack by holding the middle part of the syringe. When holding the syringe, make sure you always hold the syringe as shown.
- **Do not** handle the syringe by holding the plunger or needle cap.

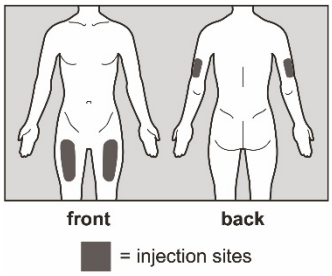
**5** Inspect the syringe closely.

- Check the syringe. The liquid in the syringe should be clear to slightly opalescent and colorless to pale brownish-yellow. **Do not** use the syringe if the liquid is cloudy, discolored, or contains foreign particles.
- Check the expiration date on the syringe. **Do not** use the syringe if the expiration date has passed because it may not be safe to use.
- If the medicine does not look as described or if the expiration date has passed, safely dispose of the syringe in a sharps container (see step 14 at the end of these instructions for use).



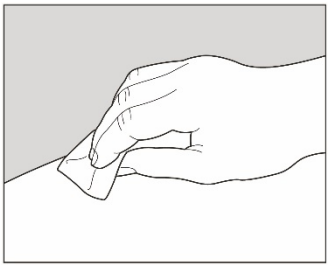
**6** Choose an injection site.

- The recommended injection sites are the upper arm and the front and middle of the thighs.
- **Do not** inject into moles, scars, bruises, or areas where the skin is tender, red, hard, or if there are breaks in the skin.
- Choose a different injection site for each new injection at least 1 inch from the area used for the last injection.




**7** Wipe the injection site with an alcohol pad in a circular motion and let it air dry for 10 seconds.

- **Do not** touch the injection site again before giving the injection.
- **Do not** fan or blow on the cleaned area.





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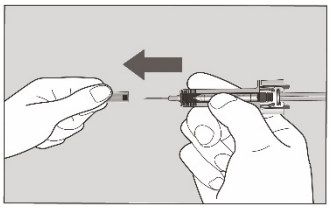
## Administering the Injection

**8** Hold the syringe firmly with 1 hand and pull the needle cap straight off with your other hand.

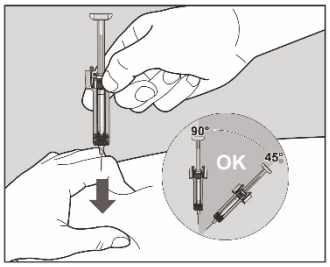


- **Do not** hold the plunger while you remove the needle cap.
- **Do not** touch the needle after removing the needle cap.
- Throw away the needle cap in a sharps container right away.
- There may be a small air bubble in the syringe. This is normal and you should not try to remove the air bubble.
- You may also see a drop of liquid at the end of the needle. This is also normal and will not affect the dose.

**9** Use your other hand and gently pinch the area of skin that was cleaned. Hold the pinched skin tight.

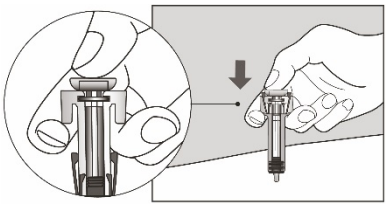
- Pinching the skin is important to make sure that you inject under the skin (into the fatty area) but not any deeper (into muscle).

**10** Continue holding the syringe by the center and use a quick, dart-like motion to insert the needle all the way into the pinched skin at an angle between 45° to 90°. It is important to use the correct angle to make sure the medicine is delivered under the skin (into the fatty area), or the injection could be uncomfortable and the medicine may not work.




- **Do not** touch the plunger while inserting the needle into the skin.
- **Do not** insert the needle through clothing. Once the needle is inserted, hold the syringe tightly in place and **do not** change the angle of injection or insert the needle again. The patient should not move and should avoid sudden movements throughout the injection.

**11** Slowly inject all of the medicine by gently pushing the plunger all the way down.



- You must press the plunger all the way down to make sure that the full dose of medicine gets injected. If the plunger is not fully pressed, the needle shield will not extend to cover the needle when it is removed.



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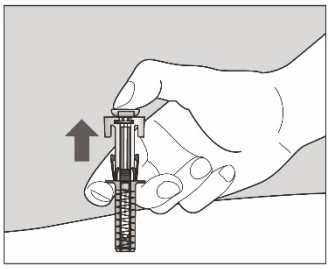
**12** Gently release the plunger and allow the needle to be covered by the needle-shield.

- If the needle is not covered, proceed carefully to dispose of the syringe (see step 14 at the end of these instructions for use).



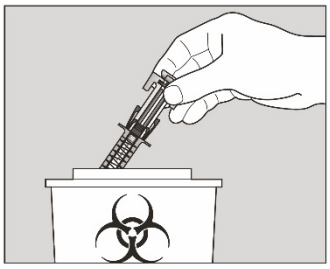
**After the Injection**

**13** There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site.

- **Do not** rub the injection site.
- If needed, you may cover the injection site with a small bandage.
- In case of skin contact with medicine, wash the area that touched the medicine with water.

**14** The XOLAIR prefilled syringe is a single-dose syringe and should not be used again.

- Put the used XOLAIR prefilled syringe in a FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) the prefilled syringe in the trash.
- **Do not** put the needle cap back on the needle.



### 2.5 Preparation for Use and Injection of XOLAIR Lyophilized Powder

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.



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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 2ºC to 8ºC (36ºF to 46ºF), 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

12) 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.

## 3 DOSAGE FORMS AND STRENGTHS

Injection:
XOLAIR injection is a clear to slightly opalescent and colorless to pale brownish-yellow solution available as:

- 75 mg/0.5 mL in a single-dose prefilled syringe with blue needle shield
- 150 mg/mL in a single-dose prefilled syringe with purple needle shield

For injection: 150 mg white lyophilized powder in a single-dose vial for reconstitution.

## 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



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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 ≥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.



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### 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)]*.



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## 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.

<u>Adverse Reactions from Clinical Studies in Adult and Adolescent Patients 12 Years of Age and Older with Asthma</u>

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 mg 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 ≥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.



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**Table 5. Adverse Reactions ≥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 n=738 | Placebo n=717 |
|---|---|---|
| Body as a whole | | |
| Pain | 7% | 5% |
| Fatigue | 3% | 2% |
| Musculoskeletal system | | |
| Arthralgia | 8% | 6% |
| Fracture | 2% | 1% |
| Leg pain | 4% | 2% |
| Arm pain | 2% | 1% |
| Nervous system | | |
| Dizziness | 3% | 2% |
| Skin and appendages | | |
| Pruritus | 2% | 1% |
| Dermatitis | 2% | 1% |
| Special senses | | |
| 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%).



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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 ≥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 mg, 150 mg, 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 ≥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.



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**Table 6. Adverse Reactions Occurring in ≥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 (n=175) | 300mg (n=412) | Placebo (n=242) |
| Gastrointestinal disorders | | | |
| Nausea | 2 (1.1%) | 11 (2.7%) | 6 (2.5%) |
| Infections and infestations | | | |
| 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%) |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | 5 (2.9%) | 12 (2.9%) | 1 (0.4%) |
| Nervous system disorders | | | |
| Headache | 21 (12.0%) | 25 (6.1%) | 7 (2.9%) |
| Respiratory, thoracic, and mediastinal disorders | | | |
| 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 [≥2% of patients receiving XOLAIR (150 mg 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 ≥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



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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

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to omalizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading

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.



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### 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.



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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

A registry study of XOLAIR exposure during pregnancy showed no increase in the rate of major birth defects or miscarriage. There was an increased rate of low birth weight among registry infants compared to infants in the other cohorts, despite average gestational age at birth; however, women taking XOLAIR during pregnancy also had more severe asthma, which makes it difficult to determine whether the low birth weight is due to the drug or the disease severity [*see Data*]. There are risks associated with poorly or moderately controlled asthma in pregnancy [*see Clinical Considerations*].

Human IgG antibodies-are known to cross the placental barrier; therefore, XOLAIR may be transmitted from the mother to the developing fetus.

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 Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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

*Human Data*

A prospective cohort pregnancy exposure registry study conducted in the US from 2006 to 2018, included 250 pregnant women with asthma treated with XOLAIR. Of these, 246 patients were exposed to XOLAIR in the first trimester of pregnancy, and the median exposure duration was 8.7 months.

The registry findings for applicable mother and infant subgroups were compared to age-adjusted frequencies in a disease matched external cohort of 1,153 pregnant women with asthma (without exposure to XOLAIR) identified from healthcare databases of residents in the Canadian province of Quebec, and referred to as the Quebec External Comparator Cohort (“comparator cohort”).

Among applicable registry infants, the prevalence of major congenital anomalies (8.1%) was similar to that for infants in the comparator cohort (8.9%). Among applicable registry pregnancies, 99.1% led to live births, similar to 99.3% for the comparator cohort. There



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was an increased rate of low birth weight among registry infants (13.7%) as compared to the comparator cohort (9.8%); however, women taking XOLAIR during pregnancy also had more severe asthma, which makes it difficult to determine whether the low birth weight is due to the drug or the disease severity.

The registry study cannot definitively establish the absence of any risk because of methodological limitations, including the observational nature of the registry, small sample size, and potential differences between the registry population and the comparator cohort.

*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, 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.

The majority of infants (80.9%, 186/230) in the pregnancy exposure registry were breastfed. Events categorized as “infections and infestations” were not significantly increased in infants who were exposed to XOLAIR through breastfeeding compared with infants who were not breastfed, or infants who were breastfed without exposure to XOLAIR.

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.



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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

Omalizumab is a recombinant DNA-derived humanized IgG1κ 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 that may contain the antibiotic gentamicin. Gentamicin is not detectable in the final product.

XOLAIR (omalizumab) is administered as a subcutaneous (SC) injection and is available in prefilled syringes and in vials.

Prefilled Syringe

XOLAIR (omalizumab) injection is supplied as a sterile, preservative-free, clear to slightly opalescent and colorless to pale brownish-yellow solution for subcutaneous injection. XOLAIR (omalizumab) injection is available as a single-dose prefilled syringe.

Each 75 mg prefilled syringe delivers 75 mg omalizumab in 0.5 mL and contains L-arginine hydrochloride (21.05 mg), L-histidine (0.68 mg), L-histidine hydrochloride monohydrate (1.17 mg), and polysorbate 20 (0.2 mg) in Sterile Water for Injection (SWFI), USP.

Each 150 mg prefilled syringe delivers 150 mg omalizumab in 1 mL and contains L-arginine hydrochloride (42.1 mg), L-histidine (1.37 mg), L-histidine hydrochloride monohydrate (2.34 mg), and polysorbate 20 (0.4 mg) in SWFI, USP.

The needle cap contains a derivative of natural rubber latex which may cause allergic reactions in latex sensitive individuals.

Vial

XOLAIR (omalizumab) for injection is a sterile, white, preservative free, lyophilized powder in a single-dose vial. After reconstitution with 1.4 mL of Sterile Water for Injection, USP,



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the vial contains 150 mg of omalizumab per 1.2 mL of reconstituted solution for subcutaneous injection. Each 1.2 mL of reconstituted solution also contains L-histidine (1.3 mg), L-histidine hydrochloride monohydrate (2.1 mg), polysorbate 20 (0.4 mg) and sucrose (108 mg).

# 12 CLINICAL PHARMACOLOGY

## 12.1 Mechanism of Action

Asthma

Omalizumab inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Reduction in surface-bound IgE on FcεRI-bearing cells limits the degree of release of mediators of the allergic response. Treatment with XOLAIR also reduces the number of FcεRI receptors on basophils in atopic patients.

Chronic Idiopathic Urticaria

Omalizumab binds to IgE and lowers free IgE levels. Subsequently, IgE receptors (FcεRI) 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.



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## 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 $^{125}$I-omalizumab by any organ or tissue. The apparent volume of distribution of omalizumab in patients with asthma following SC administration was 78 ± 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 Fcγ 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 ± 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.



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# 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 outpatient 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 ($FEV_1$) between 40% and 80% predicted. All patients had a $FEV_1$ improvement of at least 12% following $beta_2$-agonist administration. All patients were symptomatic and were being treated with inhaled corticosteroids (ICS) and short acting $beta_2$-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.



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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 ($FEV_1$) 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) | | | | |
|---|---|---|---|---|
| | Asthma Trial 1 | | Asthma Trial 2 | |
| Exacerbations per patient | XOLAIR N=268 | Placebo N=257 | XOLAIR N=274 | Placebo 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 | XOLAIR N=268 | Placebo N=257 | XOLAIR N=274 | Placebo 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 |



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**Table 8. Asthma Symptoms and Pulmonary Function During Stable Steroid Phase of Trial 1**

| | XOLAIR N=268* | | Placebo N=257* | |
|---|---|---|---|---|
| Endpoint | Mean Baseline | Median Change (Baseline to Wk 16) | Mean Baseline | Median Change (Baseline to Wk 16) |
| Total asthma symptom score | 4.3 | –1.5† | 4.2 | –1.1† |
| Nocturnal asthma score | 1.2 | –0.4† | 1.1 | –0.2† |
| Daytime asthma score | 2.3 | –0.9† | 2.3 | –0.6† |
| $FEV_1$ % predicted | 68 | 3† | 68 | 0† |

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.

† Comparison of XOLAIR versus placebo ($p < 0.05$).

*Asthma Trial 3*

In Asthma Trial 3, there was no restriction on screening $FEV_1$, and unlike Asthma Trials 1 and 2, long-acting $beta_2$-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.



Reference ID: 4426905

**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 N=126 | Placebo N=120 | XOLAIR N=50 | Placebo N=45 |
| % Patients with ≥1 exacerbations | 15.9% | 15.0% | 32.0% | 22.2% |
| Difference (95% CI) | 0.9 (–9.7, 13.7) | | 9.8 (–10.5, 31.4) | |
| | Steroid Reduction Phase (16 wks) | | | |
| | XOLAIR N=126 | Placebo N=120 | XOLAIR N=50 | Placebo N=45 |
| % Patients with ≥1 exacerbations | 22.2% | 26.7% | 42.0% | 42.2% |
| Difference (95% CI) | –4.4 (–17.6, 7.4) | | –0.2 (–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 $FEV_1$>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 ≥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 night-time 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).



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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 mg, 150 mg, 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 ≥16, and a weekly itch severity score of ≥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.



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**Table 10. Change from Baseline to Week 12 in Weekly Itch Severity Score and Weekly Hive Count Score in CIU Trial 1 [*]**

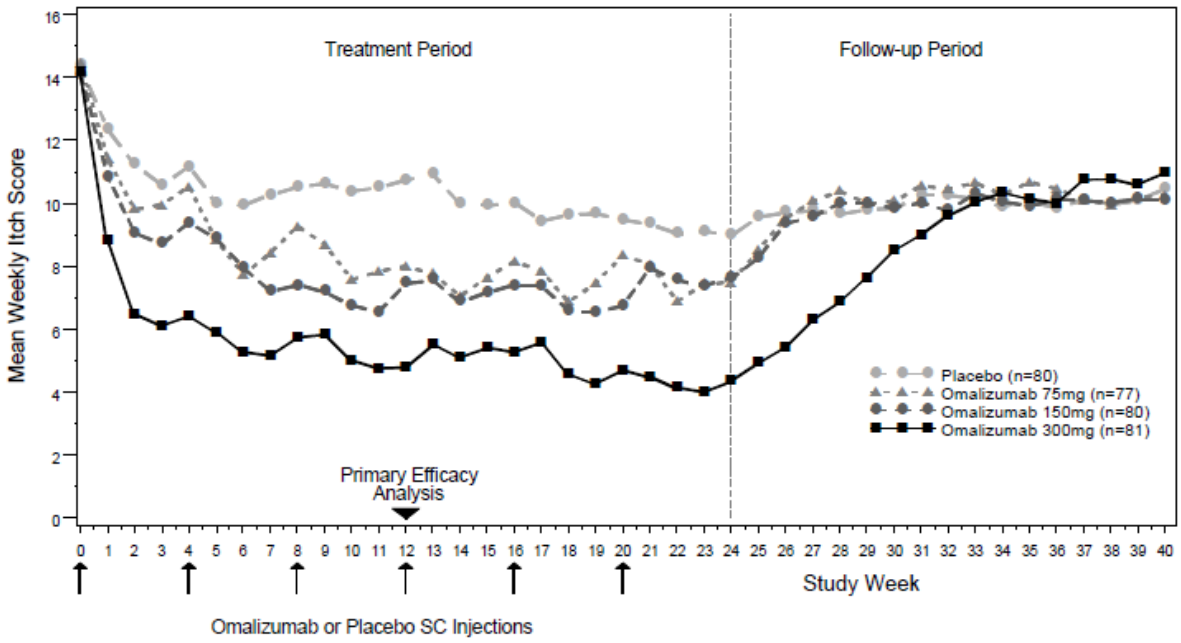
| | XOLAIR 75mg | XOLAIR 150mg | XOLAIR 300mg | Placebo |
|---|---|---|---|---|
| n | 77 | 80 | 81 | 80 |
| Weekly Itch Severity Score | | | | |
| Mean Baseline Score (SD) | 14.5 (3.6) | 14.1 (3.8) | 14.2 (3.3) | 14.4 (3.5) |
| Mean Change Week 12 (SD) | −6.46 (6.14) | −6.66 (6.28) | −9.40 (5.73) | −3.63 (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 [†] | | | | |
| 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.

[†] 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**



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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

Prefilled Syringe

XOLAIR (omalizumab) injection is a clear to slightly opalescent and colorless to pale brownish-yellow solution in a single-dose prefilled glass syringe with a 26 gauge staked needle, rigid needle cap, and needle shield. Each carton contains one prefilled syringe.

Each XOLAIR 75 mg carton contains one single-dose 75 mg prefilled syringe with a blue needle shield (NDC 50242-214-01).

Each XOLAIR 150 mg carton contains one single-dose 150 mg prefilled syringe with a purple needle shield (NDC 50242-215-01).

XOLAIR prefilled syringe should be shipped and stored under refrigerated conditions 2°C to 8°C (36°F to 46°F) in the original carton. Protect from direct sunlight.

Do not freeze. Do not use if the syringe has been frozen.

Vial

XOLAIR is supplied as a lyophilized, white, sterile powder in a single-dose vial without preservatives. Each carton contains one 150 mg single-dose vial of XOLAIR® (omalizumab) for injection NDC 50242-040-62.

XOLAIR should be shipped at controlled ambient temperature (≤30°C [≤86°F]). Store XOLAIR under refrigerated conditions 2°C to 8°C (36°F to 46°F) in the original carton. Do not use beyond the expiration date stamped on carton.

## 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



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that they may not see immediate improvement in their asthma or CIU symptoms after beginning XOLAIR therapy.

Inform patients the needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex

Manufactured by:
**Genentech, Inc.**
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
U.S. License No.:1048



Reference ID: 4426905

**MEDICATION GUIDE**

| **XOLAIR® (ZOHL-air)**<br>(omalizumab)<br>injection, for subcutaneous use | **XOLAIR® (ZOHL-air)**<br>(omalizumab)<br>for 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 a latex allergy or any other allergies (such as food allergy or seasonal allergies). The needle cap on the XOLAIR prefilled syringe may contain latex.
- 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.



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- 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
  - shortness of breath
  - chest pain
  - 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 or call 1-866-4XOLAIR (1-866-496-5247).

**What are the ingredients in XOLAIR?**

**Active ingredient**: omalizumab

**Inactive ingredients**:

Prefilled syringe: L-arginine hydrochloride, L-histidine, L-histidine hydrochloride monohydrate, and polysorbate 20

Vial: 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. U.S. License No.: 1048

**Jointly marketed by**:

**Genentech USA, Inc.**, A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990



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This Medication Guide has been approved by the U.S. Food and Drug Administration
Revised:xx/2019

**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).

<u>Adults and adolescents (12 years of age and older)</u>

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 ($FEV_1$ <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.

<u>Children (6 to <12 years of age)</u>

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 [a] | 150 mg [b] | | |
| 75 | 1[c] | 0 | 1 | 0.6 |
| 150 | 0 | 1 | 1 | 1.2 |
| 225 | 1[c] | 1 | 2 | 1.8 |
| 300 | 0 | 2 | 2 | 2.4 |
| 375 | 1[c] | 2 | 3 | 3.0 |
| 450 | 0 | 3 | 3 | 3.6 |
| 525 | 1[c] | 3 | 4 | 4.2 |
| 600 | 0 | 4 | 4 | 4.8 |

[a] 0.6 ml = maximum delivered volume per vial (Xolair 75 mg).
[b] 1.2 ml = maximum delivered volume per vial (Xolair 150 mg).
[c] 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**

| | **Body weight (kg)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Baseline IgE (IU/ml)** | ≥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 SEE TABLE 3 | | | | | | | | | |
| >800-900 | | | | | | | | | | |
| >900-1000 | | | | | | | | | | |
| >1000-1100 | | | | | | | | | | |

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

| | Body weight (kg) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Baseline IgE (IU/ml)** | ≥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 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. Xolair must not be administered by the intravenous or intramuscular route.

Doses of more than 150 mg (Table 1) should be divided across two or more injection sites.

There is limited experience with self-administration of Xolair powder and solvent for solution for injection. Therefore treatment with this formulation 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, even after a long duration of treatment. However, 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. The majority of anaphylactic reactions occurred within the first 3 doses of Xolair. A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following Xolair administration. Therefore medicinal products for the treatment of anaphylactic reactions should always be available for immediate use following administration of Xolair. If an anaphylactic or other serious allergic reaction occurs, administration of Xolair must be discontinued immediately and appropriate therapy initiated. Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur.

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

A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) based on pregnancy registry and post-marketing spontaneous reports, indicates no malformative or foeto/neonatal toxicity. A prospective pregnancy registry study (EXPECT) in 250 pregnant women with asthma exposed to Xolair showed the prevalence of major congenital anomalies was similar (8.1% vs. 8.9%) between EXPECT and disease-matched (moderate and severe asthma) patients. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomised design.

Omalizumab crosses the placental barrier. However, animal studies do not indicate either direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

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).

If clinically needed, the use of Xolair may be considered during pregnancy.

Breast-feeding

Immunoglobulins G (IgGs) are present in human milk and therefore it is expected that omalizumab will be present in human milk. Available data in non-human primates have shown excretion of omalizumab into milk (see section 5.3).

The EXPECT study, with 154 infants who had been exposed to Xolair during pregnancy and through breast-feeding did not indicate adverse effects on the breast-fed infant. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomised design.

Given orally, immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability. No effects on the breast-fed newborns/infants are anticipated. Consequently, if clinically needed, the use of Xolair may be considered 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 a separate non-clinical genotoxicity study.

## 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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**

| | |
|---|---|
| **Infections and infestations** | |
| Uncommon<br>Rare | Pharyngitis<br>Parasitic infection |
| **Blood and lymphatic system disorders** | |
| Not known | Idiopathic thrombocytopenia, including severe cases |
| **Immune system disorders** | |
| Rare<br><br>Not known | Anaphylactic reaction, other serious allergic conditions, anti-omalizumab antibody development<br>Serum sickness, may include fever and lymphadenopathy |
| **Nervous system disorders** | |
| Common<br>Uncommon | Headache*<br>Syncope, paraesthesia, somnolence, dizziness |
| **Vascular disorders** | |
| Uncommon | Postural hypotension, flushing |
| **Respiratory, thoracic and mediastinal disorders** | |
| Uncommon<br>Rare<br>Not known | Allergic bronchospasm, coughing<br>Laryngoedema<br>Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome) |

| | |
|---|---|
| **Gastrointestinal disorders** | |
| Common<br>Uncommon | Abdominal pain upper**<br>Dyspeptic signs and symptoms, diarrhoea, nausea |
| **Skin and subcutaneous tissue disorders** | |
| Uncommon<br>Rare<br>Not known | Photosensitivity, urticaria, rash, pruritus<br>Angioedema<br>Alopecia |
| **Musculoskeletal and connective tissue disorders** | |
| Rare | Systemic lupus erythematosus (SLE) |
| Not known | Arthralgia, myalgia, joint swelling |
| **General disorders and administration site conditions** | |
| Very common<br>Common<br>Uncommon | Pyrexia**<br>Injection site reactions such as swelling, erythema, pain, pruritus<br>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 ($FEV_1$ 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 ≥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 ≥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 N=209 | Placebo N=210 |
| **Asthma exacerbations** | | |
| Rate per 28-week period | 0.74 | 0.92 |
| % reduction, p-value for rate ratio | 19.4%, p = 0.153 | |
| **Severe asthma exacerbations** | | |
| Rate per 28-week period | 0.24 | 0.48 |
| % reduction, p-value for rate ratio | 50.1%, p = 0.002 | |
| **Emergency visits** | | |
| Rate per 28-week period | 0.24 | 0.43 |
| % reduction, p-value for rate ratio | 43.9%, p = 0.038 | |
| **Physician's overall assessment** | | |
| % responders* | 60.5% | 42.8% |
| p-value** | <0.001 | |
| **AQL improvement** | | |
| % of patients ≥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 ≤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 (≥500 µg/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

<u>Powder</u>

Sucrose
L-histidine
L-histidine hydrochloride monohydrate
Polysorbate 20

<u>Solvent</u>

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

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).

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.

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

## 7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 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 ($FEV_1$ <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 [a] | 150 mg [b] | | |
| 75 | 1[c] | 0 | 1 | 0.6 |
| 150 | 0 | 1 | 1 | 1.2 |
| 225 | 1[c] | 1 | 2 | 1.8 |
| 300 | 0 | 2 | 2 | 2.4 |
| 375 | 1[c] | 2 | 3 | 3.0 |
| 450 | 0 | 3 | 3 | 3.6 |
| 525 | 1[c] | 3 | 4 | 4.2 |
| 600 | 0 | 4 | 4 | 4.8 |

[a] 0.6 ml = maximum delivered volume per vial (Xolair 75 mg).
[b] 1.2 ml = maximum delivered volume per vial (Xolair 150 mg).
[c] 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**

| | **Body weight (kg)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Baseline IgE (IU/ml)** | ≥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 SEE TABLE 3 | | | | | | | | | |
| >800-900 | | | | | | | | | | |
| >900-1000 | | | | | | | | | | |
| >1000-1100 | | | | | | | | | | |

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

| | Body weight (kg) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Baseline IgE (IU/ml)** | ≥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 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).

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. Xolair must not be administered by the intravenous or intramuscular route.

Doses of more than 150 mg (Table 1) should be divided across two or more injection sites.

There is limited experience with self-administration of Xolair powder and solvent for solution for injection. Therefore treatment with this formulation 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, even after a long duration of treatment. However, 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. The majority of anaphylactic reactions occurred within the first 3 doses of Xolair. A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following Xolair administration. Therefore medicinal products for the treatment of anaphylactic reactions should always be available for immediate use following administration of Xolair. If an anaphylactic or other serious allergic reaction occurs, administration of Xolair must be discontinued immediately and appropriate therapy initiated. Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur.

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 helmith 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

A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) based on pregnancy registry and post-marketing spontaneous reports, indicates no malformative or foeto/neonatal toxicity. A prospective pregnancy registry study (EXPECT) in 250 pregnant women with asthma exposed to Xolair showed the prevalence of major congenital anomalies was similar (8.1% vs. 8.9%) between EXPECT and disease-matched (moderate and severe asthma) patients. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomised design.

Omalizumab crosses the placental barrier. However, animal studies do not indicate either direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

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).

If clinically needed, the use of Xolair may be considered during pregnancy.

Breast-feeding

Immunoglobulins G (IgGs) are present in human milk and therefore it is expected that omalizumab will be present in human milk. Available data in non-human primates have shown excretion of omalizumab into milk (see section 5.3).

The EXPECT study, with 154 infants who had been exposed to Xolair during pregnancy and through breast-feeding did not indicate adverse effects on the breast-fed infant. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomised design.

Given orally, immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability. No effects on the breast-fed newborns/infants are anticipated. Consequently, if clinically needed, the use of Xolair may be considered 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 a separate non-clinical genotoxicity study.

## 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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**

| | |
|---|---|
| **Infections and infestations** | |
| Uncommon | Pharyngitis |
| Rare | Parasitic infection |
| **Blood and lymphatic system disorders** | |
| Not known | Idiopathic thrombocytopenia, including severe cases |
| **Immune system disorders** | |
| Rare<br><br>Not known | Anaphylactic reaction, other serious allergic conditions, anti-omalizumab antibody development<br>Serum sickness, may include fever and lymphadenopathy |
| **Nervous system disorders** | |
| Common<br>Uncommon | Headache*<br>Syncope, paraesthesia, somnolence, dizziness |
| **Vascular disorders** | |
| Uncommon | Postural hypotension, flushing |
| **Respiratory, thoracic and mediastinal disorders** | |
| Uncommon<br>Rare<br>Not known | Allergic bronchospasm, coughing<br>Laryngoedema<br>Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome) |
| **Gastrointestinal disorders** | |
| Common<br>Uncommon | Abdominal pain upper**<br>Dyspeptic signs and symptoms, diarrhoea, nausea |
| **Skin and subcutaneous tissue disorders** | |
| Uncommon<br>Rare<br>Not known | Photosensitivity, urticaria, rash, pruritus<br>Angioedema<br>Alopecia |
| **Musculoskeletal and connective tissue disorders** | |
| Rare | Systemic lupus erythematosus (SLE) |
| Not known | Arthralgia, myalgia, joint swelling |
| **General disorders and administration site conditions** | |
| Very common<br>Common<br>Uncommon | Pyrexia**<br>Injection site reactions such as swelling, erythema, pain, pruritus<br>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 ≥1% of patients in any treatment group and ≥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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); 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 | |
| **Infections and infestations** | | | |
| Sinusitis | 5 (2.1%) | 20 (4.9%) | Common |
| **Nervous system disorders** | | | |
| Headache | 7 (2.9%) | 25 (6.1%) | Common |
| **Musculoskeletal and connective tissue disorders** | | | |
| Arthralgia | 1 (0.4%) | 12 (2.9%) | Common |
| **General disorder and administration site conditions** | | | |
| 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 | |
| **Infections and infestations** | | | |
| 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 ($FEV_1$ 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 ≥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 ≥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 N=209 | Placebo N=210 |
| **Asthma exacerbations** | | |
| Rate per 28-week period | 0.74 | 0.92 |
| % reduction, p-value for rate ratio | 19.4%, p = 0.153 | |
| **Severe asthma exacerbations** | | |
| Rate per 28-week period | 0.24 | 0.48 |
| % reduction, p-value for rate ratio | 50.1%, p = 0.002 | |
| **Emergency visits** | | |
| Rate per 28-week period | 0.24 | 0.43 |
| % reduction, p-value for rate ratio | 43.9%, p = 0.038 | |
| **Physician's overall assessment** | | |
| % responders* | 60.5% | 42.8% |
| p-value** | <0.001 | |
| **AQL improvement** | | |
| % of patients ≥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 ≤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 (≥500 µg/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 ≥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 ≥16, and a weekly itch severity score (which is a component of the UAS7; range 0-21) of ≥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≤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*)**

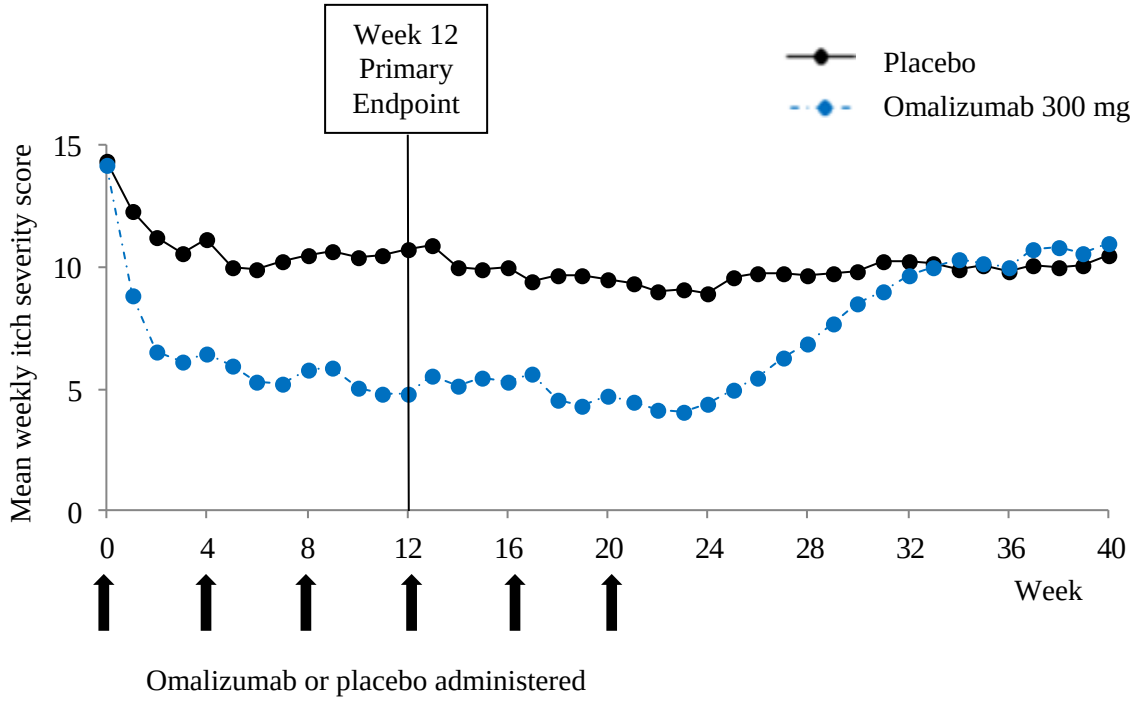
| | **Placebo** | **Omalizumab 300 mg** |
|---|---|---|
| **Study 1** | | |
| N | 80 | 81 |
| Mean (SD) | −3.63 (5.22) | −9.40 (5.73) |
| Difference in LS means vs. placebo[1] | - | −5.80 |
| 95% CI for difference | - | −7.49,−4.10 |
| P-value vs. placebo[2] | - | <0.0001 |
| **Study 2** | | |
| N |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

<u>Powder</u>

Sucrose
L-histidine
L-histidine hydrochloride monohydrate
Polysorbate 20

<u>Solvent</u>

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 x 1) vials of powder and 4 (4 x 1) ampoules of water for injections or 10 (10 x 1) vials of powder and 10 (10 x 1) ampoules of water for injections.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

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).

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.

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

## 7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 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 in pre-filled syringe

## 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 in pre-filled syringe (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 ($FEV_1$ <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**

| | **Body weight (kg)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Baseline IgE (IU/ml)** | ≥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 SEE TABLE 3 | | | | | | | | | |
| >800-900 | | | | | | | | | | |
| >900-1000 | | | | | | | | | | |
| >1000-1100 | | | | | | | | | | |

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

| | Body weight (kg) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Baseline IgE (IU/ml)** | ≥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 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. Xolair must not be administered by the intravenous or intramuscular route.

Doses of more than 150 mg (Table 1) should be divided across two or more injection sites.

Patients with no known history of anaphylaxis may self-inject Xolair or be injected by a caregiver from the 4th dose onwards if a physician determines that this is appropriate (see section 4.4). The patient or the caregiver must have been trained in the correct injection technique and the recognition of the early signs and symptoms of serious allergic reactions.

Patients or caregivers should be instructed to inject the full amount of Xolair according to the instructions provided in 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, even after a long duration of treatment. However, 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. The majority of anaphylactic reactions occurred within the first 3 doses of Xolair. Therefore, the first 3 doses must be administered either by or under the supervision of a healthcare professional. A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following Xolair administration. Therefore for patients with a known history of anaphylaxis, Xolair must be administered by a health care professional, who should always have medicinal products for the treatment of anaphylactic reactions available for immediate use following administration of Xolair. If an anaphylactic or other serious allergic reaction occurs, administration of Xolair must be discontinued immediately and appropriate therapy initiated. Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur.

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

A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) based on pregnancy registry and post-marketing spontaneous reports, indicates no malformative or foeto/neonatal toxicity. A prospective pregnancy registry study (EXPECT) in 250 pregnant women with asthma exposed to Xolair showed the prevalence of major congenital anomalies was similar (8.1% vs. 8.9%) between EXPECT and disease-matched (moderate and severe asthma) patients. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomised design.

Omalizumab crosses the placental barrier. However, animal studies do not indicate either direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

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).

If clinically needed, the use of Xolair may be considered during pregnancy.

Breast-feeding

Immunoglobulins G (IgGs) are present in human milk and therefore it is expected that omalizumab will be present in human milk. Available data in non-human primates have shown excretion of omalizumab into milk (see section 5.3).

The EXPECT study, with 154 infants who had been exposed to Xolair during pregnancy and through breast-feeding did not indicate adverse effects on the breast-fed infant. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomised design.

Given orally, immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability. No effects on the breast-fed newborns/infants are anticipated. Consequently, if clinically needed, the use of Xolair may be considered 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 a separate non-clinical genotoxicity study.

## 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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**

| | |
|---|---|
| **Infections and infestations** | |
| Uncommon<br>Rare | Pharyngitis<br>Parasitic infection |
| **Blood and lymphatic system disorders** | |
| Not known | Idiopathic thrombocytopenia, including severe cases |
| **Immune system disorders** | |
| Rare<br><br>Not known | Anaphylactic reaction, other serious allergic conditions, anti-omalizumab antibody development<br>Serum sickness, may include fever and lymphadenopathy |
| **Nervous system disorders** | |
| Common<br>Uncommon | Headache*<br>Syncope, paraesthesia, somnolence, dizziness |
| **Vascular disorders** | |
| Uncommon | Postural hypotension, flushing |
| **Respiratory, thoracic and mediastinal disorders** | |
| Uncommon<br>Rare<br>Not known | Allergic bronchospasm, coughing<br>Laryngoedema<br>Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome) |

| | |
|---|---|
| **Gastrointestinal disorders** | |
| Common<br>Uncommon | Abdominal pain upper**<br>Dyspeptic signs and symptoms, diarrhoea, nausea |
| **Skin and subcutaneous tissue disorders** | |
| Uncommon<br>Rare<br>Not known | Photosensitivity, urticaria, rash, pruritus<br>Angioedema<br>Alopecia |
| **Musculoskeletal and connective tissue disorders** | |
| Rare | Systemic lupus erythematosus (SLE) |
| Not known | Arthralgia, myalgia, joint swelling |
| **General disorders and administration site conditions** | |
| Very common<br>Common<br>Uncommon | Pyrexia**<br>Injection site reactions such as swelling, erythema, pain, pruritus<br>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 ($FEV_1$ 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 ≥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 ≥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 N=209 | Placebo N=210 |
| **Asthma exacerbations** | | |
| Rate per 28-week period | 0.74 | 0.92 |
| % reduction, p-value for rate ratio | 19.4%, p = 0.153 | |
| **Severe asthma exacerbations** | | |
| Rate per 28-week period | 0.24 | 0.48 |
| % reduction, p-value for rate ratio | 50.1%, p = 0.002 | |
| **Emergency visits** | | |
| Rate per 28-week period | 0.24 | 0.43 |
| % reduction, p-value for rate ratio | 43.9%, p = 0.038 | |
| **Physician's overall assessment** | | |
| % responders* | 60.5% | 42.8% |
| p-value** | <0.001 | |
| **AQL improvement** | | |
| % of patients ≥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 ≤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 (≥500 µg/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 ± 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 ± 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 x 1) or 10 (10 x 1) pre-filled syringes.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Xolair 75 mg solution for injection is supplied in a single-use pre-filled syringe for individual use. The syringe should be taken out of the refrigerator 20 minutes before injecting to allow it to reach room temperature.

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
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 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 in pre-filled syringe

## 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 in pre-filled syringe (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 ($FEV_1$ <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**

| | **Body weight (kg)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Baseline IgE (IU/ml)** | ≥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 SEE TABLE 3 | | | | | | | | | |
| >800-900 | | | | | | | | | | |
| >900-1000 | | | | | | | | | | |
| >1000-1100 | | | | | | | | | | |

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

| | Body weight (kg) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Baseline IgE (IU/ml)** | ≥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 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).

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. Xolair must not be administered by the intravenous or intramuscular route.

Doses of more than 150 mg (Table 1) should be divided across two or more injection sites.

Patients with no known history of anaphylaxis may self-inject Xolair or be injected by a caregiver from the 4th dose onwards if a physician determines that this is appropriate (see section 4.4). The patient or the caregiver must have been trained in the correct injection technique and the recognition of the early signs and symptoms of serious allergic reactions.

Patients or caregivers should be instructed to inject the full amount of Xolair according to the instructions provided in 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, even after a long duration of treatment. However, 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. The majority of anaphylactic reactions occurred within the first 3 doses of Xolair. Therefore, the first 3 doses must be administered either by or under the supervision of a healthcare professional. A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following Xolair administration. Therefore for patients with a known history of anaphylaxis, Xolair must be administered by a health care professional, who should always have medicinal products for the treatment of anaphylactic reactions available for immediate use following administration of Xolair. If an anaphylactic or other serious allergic reaction occurs, administration of Xolair must be discontinued immediately and appropriate therapy initiated. Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur.

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

A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) based on pregnancy registry and post-marketing spontaneous reports, indicates no malformative or foeto/neonatal toxicity. A prospective pregnancy registry study (EXPECT) in 250 pregnant women with asthma exposed to Xolair showed the prevalence of major congenital anomalies was similar (8.1% vs. 8.9%) between EXPECT and disease-matched (moderate and severe asthma) patients. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomised design.

Omalizumab crosses the placental barrier. However, animal studies do not indicate either direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

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).

If clinically needed, the use of Xolair may be considered during pregnancy.

Breast-feeding

Immunoglobulins G (IgGs) are present in human milk and therefore it is expected that omalizumab will be present in human milk. Available data in non-human primates have shown excretion of omalizumab into milk (see section 5.3).

The EXPECT study, with 154 infants who had been exposed to Xolair during pregnancy and through breast-feeding did not indicate adverse effects on the breast-fed infant. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomised design.

Given orally, immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability. No effects on the breast-fed newborns/infants are anticipated. Consequently, if clinically needed, the use of Xolair may be considered 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 a separate non-clinical genotoxicity study.

## 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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**

| | |
|---|---|
| **Infections and infestations** | |
| Uncommon<br>Rare | Pharyngitis<br>Parasitic infection |
| **Blood and lymphatic system disorders** | |
| Not known | Idiopathic thrombocytopenia, including severe cases |
| **Immune system disorders** | |
| Rare<br><br>Not known | Anaphylactic reaction, other serious allergic conditions, anti-omalizumab antibody development<br>Serum sickness, may include fever and lymphadenopathy |
| **Nervous system disorders** | |
| Common<br>Uncommon | Headache*<br>Syncope, paraesthesia, somnolence, dizziness |
| **Vascular disorders** | |
| Uncommon | Postural hypotension, flushing |
| **Respiratory, thoracic and mediastinal disorders** | |
| Uncommon<br>Rare<br>Not known | Allergic bronchospasm, coughing<br>Laryngoedema<br>Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome) |
| **Gastrointestinal disorders** | |
| Common<br>Uncommon | Abdominal pain upper**<br>Dyspeptic signs and symptoms, diarrhoea, nausea |
| **Skin and subcutaneous tissue disorders** | |
| Uncommon<br>Rare<br>Not known | Photosensitivity, urticaria, rash, pruritus<br>Angioedema<br>Alopecia |
| **Musculoskeletal and connective tissue disorders** | |
| Rare | Systemic lupus erythematosus (SLE) |
| Not known | Arthralgia, myalgia, joint swelling |
| **General disorders and administration site conditions** | |
| Very common<br>Common<br>Uncommon | Pyrexia**<br>Injection site reactions such as swelling, erythema, pain, pruritus<br>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 ≥1% of patients in any treatment group and ≥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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); 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 | |
| **Infections and infestations** | | | |
| Sinusitis | 5 (2.1%) | 20 (4.9%) | Common |
| **Nervous system disorders** | | | |
| Headache | 7 (2.9%) | 25 (6.1%) | Common |
| **Musculoskeletal and connective tissue disorders** | | | |
| Arthralgia | 1 (0.4%) | 12 (2.9%) | Common |
| **General disorder and administration site conditions** | | | |
| 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 | |
| **Infections and infestations** | | | |
| 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 ($FEV_1$ 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 ≥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 ≥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 N=209 | Placebo N=210 |
| **Asthma exacerbations** | | |
| Rate per 28-week period | 0.74 | 0.92 |
| % reduction, p-value for rate ratio | 19.4%, p = 0.153 | |
| **Severe asthma exacerbations** | | |
| Rate per 28-week period | 0.24 | 0.48 |
| % reduction, p-value for rate ratio | 50.1%, p = 0.002 | |
| **Emergency visits** | | |
| Rate per 28-week period | 0.24 | 0.43 |
| % reduction, p-value for rate ratio | 43.9%, p = 0.038 | |
| **Physician's overall assessment** | | |
| % responders* | 60.5% | 42.8% |
| p-value** | <0.001 | |
| **AQL improvement** | | |
| % of patients ≥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 ≤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 (≥500 µg/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 ≥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 ≥16, and a weekly itch severity score (which is a component of the UAS7; range 0-21) of ≥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≤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*)**

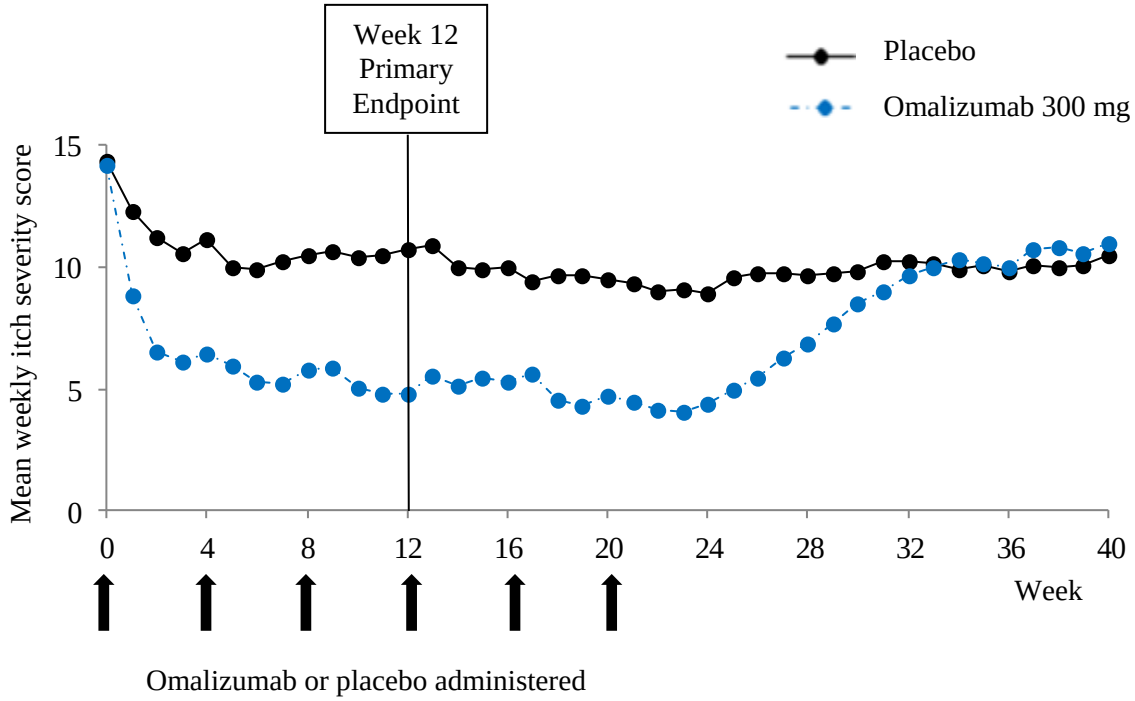
| | **Placebo** | **Omalizumab 300 mg** |
|---|---|---|
| **Study 1** | | |
| N | 80 | 81 |
| Mean (SD) | −3.63 (5.22) | −9.40 (5.73) |
| Difference in LS means vs. placebo[1] | - | −5.80 |
| 95% CI for difference | - | −7.49,−4.10 |
| P-value vs. placebo[2] | - | <0.0001 |
| **Study 2** | | |
| N | 79 | 79 |
| Mean (SD) | −5.14 (5.58) | −9.77 (5.95) |
| Difference in LS means vs. placebo[1] | - | −4.81 |
| 95% CI for difference | - | −6.49,−3.13 |
| P-value vs. placebo[2] | - | <0.0001 |
| **Study 3** | | |
| N | 83 | 252 |
| Mean (SD) | −4.01 (5.87) | −8.55 (6.01) |
| Difference in LS means vs. placebo[1] | - | -4.52 |
| 95% CI for difference | - | −5.97, −3.08 |
| P-value vs. placebo[2] | - | <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.
[1] 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).
[2] 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 ± 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 ± 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 x 1); 6 (6 x 1) or 10 (10 x 1) pre-filled syringes.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Xolair 150 mg solution for injection is supplied in a single-use pre-filled syringe for individual use. The syringe should be taken out of the refrigerator 20 minutes before injecting to allow it to reach room temperature.

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
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/008
EU/1/05/319/009
EU/1/05/319/010
EU/1/05/319/011

## 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

Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd.
BioProduction Operations Singapore
8 Tuas Bay Lane
Singapore 636986
Singapore

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.
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
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 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

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**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.

**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.
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
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 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

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**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.
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
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 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

## 17. UNIQUE IDENTIFIER – 2D BARCODE

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

**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 (4 x 1) vials and 4 (4 x 1) ampoules
Multipack: 10 (10 x 1) vials and 10 (10 x 1) ampoules

## 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.
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
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 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

## 17. UNIQUE IDENTIFIER – 2D BARCODE

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

**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.

**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 in pre-filled syringe
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 in pre-filled syringe

1 pre-filled syringe

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

Use only as directed by a doctor.
Read the package leaflet before use.
Subcutaneous use.
Single 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.
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 of the used syringe immediately in a sharps container.

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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/005 75 mg solution for injection in pre-filled syringe

## 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

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**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 in pre-filled syringe
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 in pre-filled syringe

Multipack: 4 (4 x 1) pre-filled syringes
Multipack: 10 (10 x 1) pre-filled syringes

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

Use only as directed by a doctor.
Read the package leaflet before use.
Subcutaneous use.
Single 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.
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 of the used syringe immediately in a sharps container.

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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

| | |
|---|---|
| EU/1/05/319/006 | 75 mg solution for injection in pre-filled syringe (4 x 1) |
| EU/1/05/319/007 | 75 mg solution for injection in pre-filled syringe (10 x 1) |

## 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

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**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 in pre-filled syringe
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 in pre-filled syringe

1 pre-filled syringe. 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.
Single 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.
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 of the used syringe immediately in a sharps container.

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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

| | |
|---|---|
| EU/1/05/319/006 | 75 mg solution for injection in pre-filled syringe (4 x 1) |
| EU/1/05/319/007 | 75 mg solution for injection in pre-filled syringe (10 x 1) |

## 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

## 17. UNIQUE IDENTIFIER – 2D BARCODE

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER OF PRE-FILLED SYRINGE**

## 1. NAME OF THE MEDICINAL PRODUCT

Xolair 75 mg injection
omalizumab
SC
Single 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 injection
omalizumab
SC

## 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 in pre-filled syringe
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 in pre-filled syringe

1 pre-filled syringe

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

Use only as directed by a doctor.
Read the package leaflet before use.
Subcutaneous use.
Single 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.
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 of the used syringe immediately in a sharps container.

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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/008 150 mg solution for injection in pre-filled syringe

## 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

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**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 in pre-filled syringe
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 in pre-filled syringe

Multipack: 4 (4 x 1) pre-filled syringes
Multipack: 6 (6 x 1) pre-filled syringes
Multipack: 10 (10 x 1) pre-filled syringes

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

Use only as directed by a doctor.
Read the package leaflet before use.
Subcutaneous use.
Single 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.
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 of the used syringe immediately in a sharps container.

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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

| | |
|---|---|
| EU/1/05/319/009 | 150 mg solution for injection in pre-filled syringe (4 x 1) |
| EU/1/05/319/010 | 150 mg solution for injection in pre-filled syringe (10 x 1) |
| EU/1/05/319/011 | 150 mg solution for injection in pre-filled syringe (6 x 1) |

## 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

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**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 in pre-filled syringe
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 in pre-filled syringe

1 pre-filled syringe. 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.
Single 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.
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 of the used syringe immediately in a sharps container.

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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

| | |
|---|---|
| EU/1/05/319/009 | 150 mg solution for injection in pre-filled syringe (4 x 1) |
| EU/1/05/319/010 | 150 mg solution for injection in pre-filled syringe (10 x 1) |
| EU/1/05/319/011 | 150 mg solution for injection in pre-filled syringe (6 x 1) |

## 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

## 17. UNIQUE IDENTIFIER – 2D BARCODE

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER OF PRE-FILLED SYRINGE**

## 1. NAME OF THE MEDICINAL PRODUCT

Xolair 150 mg injection
omalizumab
SC
Single 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 injection
omalizumab
SC

## 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

Xolair contains the active substance 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, adolescents and children (6 years of age and 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.

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**
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 are travelling to a region where infections caused by parasites are common - Xolair may weaken your resistance to such infections.
- if you have had a previous severe allergic reaction (anaphylaxis) for example resulting from a medicine, an insect bite or food.

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.

**Look out for signs of allergic reactions and other serious side effects**
Xolair can potentially cause serious side effects. You must look out for signs of these conditions while you use Xolair. Seek medical help immediately if you notice any signs indicating a possible serious side effect. Such signs are listed under "Serious side effects" in section 4. The majority of severe allergic reactions occur within the first 3 doses of Xolair.

**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**
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. 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.

Xolair may pass into breast milk. If you are breast-feeding or plan to breast-feed, ask your doctor for advice before using this medicine.

**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**
Your doctor will decide 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.

Keep 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 and 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:

Seek medical attention immediately if you notice any signs of the following side effects:
Rare (may affect up to 1 in 1,000 people)
- Severe allergic reactions (including anaphylaxis). Symptoms may include rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heartbeat, dizziness and light-headedness, confusion, shortness of breath, wheezing or trouble breathing, blue skin or lips, collapsing and losing consciousness. 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, rash, fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)
- Churg-Strauss syndrome or hypereosinophilic syndrome. 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 arms and legs.
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Serum sickness. Symptoms may include one or more of the following: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain.

Other side effects include:
Very common (may affect more than 1 in 10 people)
- fever (in children)

Common (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 (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 (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
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Dublin 4
Ireland

**Manufacturer**
Novartis Pharma GmbH
Roonstrasse 25
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Germany

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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 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, the lower abdomen (but not the area 5 centimetres around the navel) 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 contains the active substance 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 is used for the treatment of:
- allergic asthma
- chronic spontaneous urticaria (CSU)

Allergic asthma
This medicine is used to prevent asthma from getting worse by controlling symptoms of severe allergic asthma in adults, adolescents and children (6 years of age and 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.

Chronic spontaneous urticaria (CSU)
This medicine is used to treat chronic spontaneous urticaria in adults and adolescents (12 years of age and older) who are already receiving antihistamines but whose CSU symptoms are not well controlled by these medicines.

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.

## 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**
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 are travelling to a region where infections caused by parasites are common - Xolair may weaken your resistance to such infections.
- if you have had a previous severe allergic reaction (anaphylaxis) for example resulting from a medicine, an insect bite or food.

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.

**Look out for signs of allergic reactions and other serious side effects**
Xolair can potentially cause serious side effects. You must look out for signs of these conditions while you use Xolair. Seek medical help immediately if you notice any signs indicating a possible serious side effect. Such signs are listed under “Serious side effects” in section 4. The majority of severe allergic reactions occur within the first 3 doses of Xolair.

**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**
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. 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.

Xolair may pass into breast milk. If you are breast-feeding or plan to breast-feed, ask your doctor for advice before using this medicine.

**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 decide 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.

Keep 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.

Keep taking your current medicine for CSU during Xolair treatment. Do not stop taking any medicine without talking to your doctor.

**Use in children and adolescents**

Allergic asthma

Xolair can be given to children and adolescents aged 6 years and 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 and older, who are already receiving antihistamines but whose CSU symptoms are not well controlled by these medicines. The dose for adolescents aged 12 years and above is the same as for adults.

**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:

Seek medical attention immediately if you notice any signs of the following side effects:
Rare (may affect up to 1 in 1,000 people)
- Severe allergic reactions (including anaphylaxis). Symptoms may include rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heartbeat, dizziness and light-headedness, confusion, shortness of breath, wheezing or trouble breathing, blue skin or lips, collapsing and losing consciousness. 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, rash, fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)
- Churg-Strauss syndrome or hypereosinophilic syndrome. 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 arms and legs.
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Serum sickness. Symptoms may include one or more of the following: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain.

Other side effects include:
Very common (may affect more than 1 in 10 people)
- fever (in children)

Common (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 (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 (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 1 vial of powder and 1 ampoule of water for injections, and in multipacks containing 4 (4 x 1) vials of powder and 4 (4 x 1) ampoules of water for injections or 10 (10 x 1) vials of powder and 10 (10 x 1) ampoules of 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, the lower abdomen (but not the area 5 centimetres around the navel) or the thigh.

**Package leaflet: Information for the user**

**Xolair 75 mg solution for injection in pre-filled syringe**
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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- 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 use Xolair
3. How to use Xolair
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 contains the active substance 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, adolescents and children (6 years of age and 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.

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 use Xolair

**Do not use 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 use Xolair.

**Warnings and precautions**
Talk to your doctor before using 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 are travelling to region where infections caused by parasites are common - Xolair may weaken your resistance to such infections.
- if you have had a previous severe allergic reaction (anaphylaxis), for example resulting from a medicine, an insect bite or food.
- if you have ever had an allergic reaction to latex. The needle cap of the syringe may contain dry rubber (latex).

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.

**Look out for signs of allergic reactions and other serious side effects**
Xolair can potentially cause serious side effects. You must look out for signs of these conditions while you use Xolair. Seek medical help immediately if you notice any signs indicating a severe allergic reaction or other serious side effects. Such signs are listed under “Serious side effects” in section 4.

It is important that you receive training from your doctor in how to recognise early symptoms of severe allergic reactions, and how to manage these reactions if they occur, before you inject Xolair yourself or before a non-healthcare professional gives you a Xolair injection (see section 3, “How to use Xolair”). The majority of severe allergic reactions occur within the first 3 doses of Xolair.

**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**
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. 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.

Xolair may pass into breast milk. If you are breast-feeding or plan to breast-feed, ask your doctor for advice before using this medicine.

**Driving and using machines**
It is unlikely that Xolair will affect your ability to drive and use machines.

## 3. How to use Xolair

Always use this medicine exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure.

**How Xolair is used**
Xolair is used as an injection under your skin (known as a subcutaneous injection).

Injecting Xolair

- You and your doctor will decide if you should inject Xolair yourself. The first 3 doses are always given by or under the supervision of a healthcare professional (see section 2).
- It is important to be properly trained on how to inject the medicine before injecting yourself.
- A caregiver (for example a parent) may also give you your Xolair injection after he or she has received proper training.

For detailed instructions on how to inject Xolair, see "Instructions for use of Xolair pre-filled syringe" at the end of this leaflet.

Training to recognise serious allergic reactions

It is also important that you do not inject Xolair yourself until you have been trained by your doctor or nurse on:

- how to recognise the early signs and symptoms of serious allergic reactions.
- what to do if the symptoms occur.

For more information about the early signs and symptoms of serious allergic reactions, see section 4.

**How much to use**

Your doctor will decide how much Xolair you need and how often you will need 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 need 1 to 4 injections at a time. You will need the injections either every two weeks, or every four weeks.

Keep 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 treatment. It usually takes between 12 and 16 weeks to have the full effect.

**Use in children and adolescents**

Xolair can be used in children and adolescents aged 6 years and 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.

Children (6 to 11 years of age) are not expected to self-administer Xolair. However, if considered appropriate by their doctor, a caregiver may give them their Xolair injection after proper training.

**If a dose of Xolair is missed**

If you have missed an appointment, contact your doctor or hospital as soon as possible to re-schedule it.

If you have forgotten to give yourself a dose of Xolair, inject the dose as soon as you remember. Then talk to your doctor to discuss when you should inject the next dose.

**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:

Seek medical attention immediately if you notice any signs of the following side effects:
Rare (may affect up to 1 in 1,000 people)
- Severe allergic reactions (including anaphylaxis). Symptoms may include rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heartbeat, dizziness and light-headedness, confusion, shortness of breath, wheezing or trouble breathing, blue skin or lips, collapsing and losing consciousness. 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, rash, fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)
- Churg-Strauss syndrome or hypereosinophilic syndrome. 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 arms and legs.
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Serum sickness. Symptoms may include one or more of the following: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain.

Other side effects include:
Very common (may affect more than 1 in 10 people)
- fever (in children)

Common (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 (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 (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 containing 4 (4 x 1) or 10 (10 x 1) pre-filled syringes.

Not all pack sizes may be marketed in your country.

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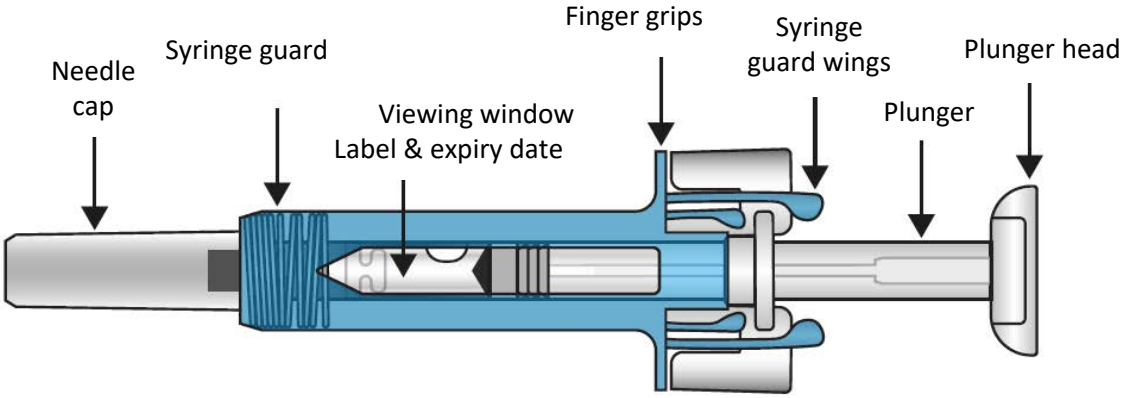
**This leaflet was last revised in**

**Other sources of information**
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

**INSTRUCTIONS FOR USE OF XOLAIR PRE-FILLED SYRINGE**

Read ALL the way through these instructions before injecting. If your doctor decides that you or a caregiver may be able to give your injections of Xolair at home, you need to be trained by your doctor, nurse or pharmacist before you inject yourself or others. Children (6 to less than 12 years of age) are not expected to inject Xolair themselves, however, if deemed appropriate by their doctor, a caregiver may give them their Xolair injection after proper training. The box contains Xolair pre-filled syringe(s) individually sealed in a plastic tray.

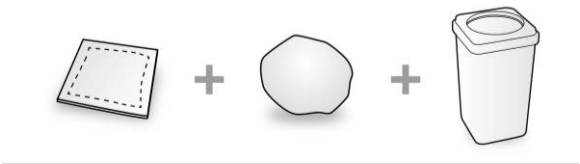
**Your Xolair 75 mg pre-filled syringe**




After the medicine has been injected, the syringe guard will be activated to cover the needle. This is intended to protect against accidental needlestick injuries.

**Other items you need for your injection:**

- Alcohol swab.
- Cotton ball or gauze.
- Sharps disposal container.



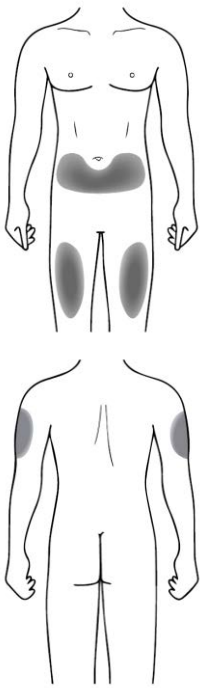
**Important safety information**
**Caution: Keep the syringe out of the sight and reach of children.**

- The needle cap of the syringe may contain dry rubber (latex), which should not be handled by anyone who is sensitive to this substance.
- Do not open the sealed outer box until you are ready to use this medicine.
- Do not use this medicine if either the seal on the outer box or the seal of the plastic tray is broken, as it may not be safe for you to use.
- Never leave the syringe where others might tamper with it.
- Do not shake the syringe.
- Be careful not to touch the syringe guard wings before use. If the wings are touched, the syringe guard may be activated too early.
- Do not remove the needle cap until just before you give the injection.
- The syringe cannot be re-used. Dispose of the used syringe immediately after use in a sharps container.

**Storage of the Xolair pre-filled syringe**

- Store this medicine sealed in its outer box to protect it from light. Store in the refrigerator between 2°C and 8°C. DO NOT FREEZE.
- Remember to take the syringe out of the refrigerator and allow it to reach room temperature (25°C) before preparing it for injection (it will take about 20 minutes). Leave the syringe in the box to protect it from light. The time that the syringe is kept at room temperature (25°C) before use must not exceed 4 hours.
- Do not use the syringe after the expiry date which is stated on the outer box and syringe label. If it has expired, return the entire pack to the pharmacy.

**The injection site**



The injection site is the place on the body where you are going to use the syringe.

- The recommended site is the front of the thighs. You may also use the lower abdomen, but **not** the area 5 centimetres around the navel (belly button).
- If you need to give more than one injection for the full dose, choose a different injection site each time you inject.
- Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks.

If a caregiver is giving the injection, the outer upper arms may also be used.

**Preparing the Xolair pre-filled syringe for use**

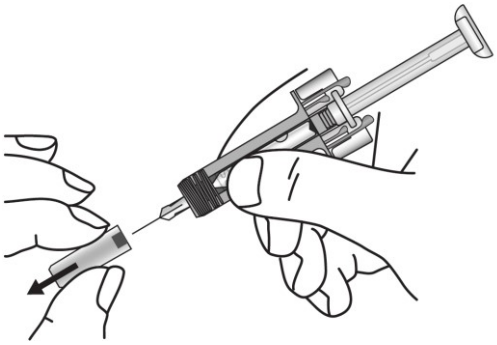
Note: Depending on the dose prescribed to you by your doctor, you may need to prepare one or more pre-filled syringes, and inject the contents of them all. The following table gives examples of how many injections of each dose strength you need for a given dose:

| Dose | Syringes needed for the dose | | | |
|---|---|---|---|---|
| 75 mg | 1 blue | | | |
| 150 mg | | | 1 purple (150 mg) | |
| 225 mg | 1 blue | + | 1 purple (150 mg) | |
| 300 mg | | | 2 purple (150 mg) | |
| 375 mg | 1 blue | + | 2 purple (150 mg) | |
| 450 mg | | | 3 purple (150 mg) | |
| 525 mg | 1 blue | + | 3 purple (150 mg) | |
| 600 mg | | | 4 purple (150 mg) | |

1. Take the box containing the syringe out of the refrigerator and leave it **unopened** for about 20 minutes so that it reaches room temperature (leave the syringe in the box to protect it from light).
2. When you are ready to use the syringe, wash your hands thoroughly with soap and water.
3. Clean the injection site with an alcohol swab.
4. Remove the plastic tray from the box, peel back the paper cover. Gripping the middle of the blue syringe guard, lift the syringe out of the tray.
5. Inspect the syringe. The liquid should be clear to slightly cloudy. Its colour may vary from colourless to pale brownish-yellow. You may see an air bubble, which is normal. DO NOT USE if the syringe is broken or if the liquid looks distinctly cloudy or distinctly brown, or contains particles. In all these cases, return the entire pack to the pharmacy.
6. Holding the syringe horizontally look into the viewing window to check the expiry date printed on the label. Note: It is possible to rotate the inner part of the syringe assembly so that the label can be read in the viewing window. DO NOT USE if the product has expired. If expired, return the entire pack to the pharmacy.

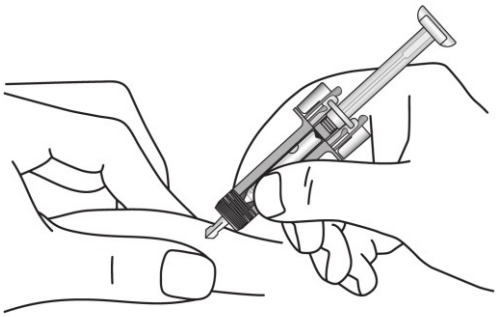
**How to use the Xolair pre-filled syringe**

1



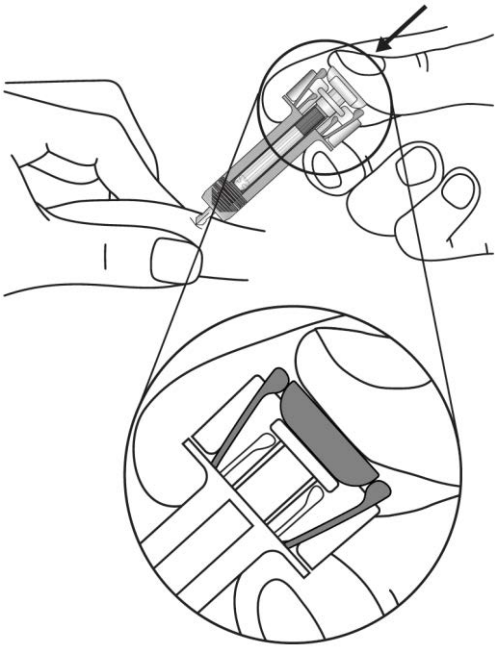
Carefully remove the needle cap from the syringe. Discard the needle cap. You may see a drop of liquid at the end of the needle. This is normal.

2



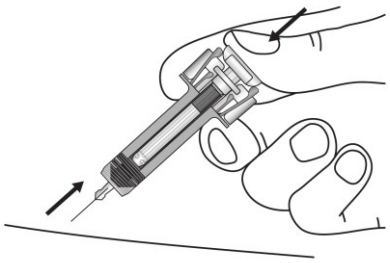
Gently pinch the skin at the injection site and insert the needle as shown. Push the needle all the way in to ensure that the medicine can be fully administered.

3



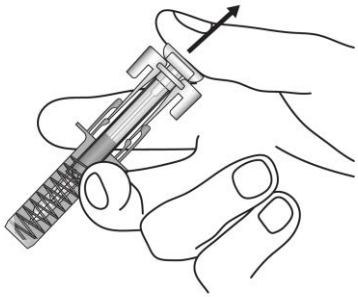
Hold the syringe as shown. **Slowly** depress the plunger **as far as it will go** so that the plunger head is completely between the syringe guard wings.

4



**Keep the plunger fully depressed** while you carefully lift the needle straight out from the injection site.

5



Slowly release the plunger and allow the syringe guard to automatically cover the exposed needle.

There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 30 seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

**Disposal instructions**

Dispose of the used syringe immediately in a sharps container (closable, puncture resistant container). For the safety and health of you and others, needles and used syringes **must never** be re-used. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

**Package leaflet: Information for the user**

**Xolair 150 mg solution for injection in pre-filled syringe**
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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- 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 use Xolair
3. How to use Xolair
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 contains the active substance 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 is used for the treatment of:
- allergic asthma
- chronic spontaneous urticaria (CSU)

Allergic asthma
This medicine is used to prevent asthma from getting worse by controlling symptoms of severe allergic asthma in adults, adolescents and children (6 years of age and 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.

Chronic spontaneous urticaria (CSU)
This medicine is used to treat chronic spontaneous urticaria in adults and adolescents (12 years of age and older) who are already receiving antihistamines but whose CSU symptoms are not well controlled by these medicines.

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.

## 2. What you need to know before you use Xolair

**Do not use 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 use Xolair.

**Warnings and precautions**
Talk to your doctor before using 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 are travelling to region where infections caused by parasites are common - Xolair may weaken your resistance to such infections.
- if you have had a previous severe allergic reaction (anaphylaxis), for example resulting from a medicine, an insect bite or food.
- if you have ever had an allergic reaction to latex. The needle cap of the syringe may contain dry rubber (latex).

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.

**Look out for signs of allergic reactions and other serious side effects**
Xolair can potentially cause serious side effects. You must look out for signs of these conditions while you use Xolair. Seek medical help immediately if you notice any signs indicating a severe allergic reaction or other serious side effects. Such signs are listed under “Serious side effects” in section 4.

It is important that you receive training from your doctor in how to recognise early symptoms of severe allergic reactions, and how to manage these reactions if they occur, before you inject Xolair yourself or before a non-healthcare professional gives you a Xolair injection (see section 3, “How to use Xolair”). The majority of severe allergic reactions occur within the first 3 doses of Xolair.

**Children and adolescents**
Allergic asthma
Xolair is not recommended for children under 6 years of age.

Chronic spontaneous urticaria (CSU)
Xolair should not be used in 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**
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. 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.

Xolair may pass into breast milk. If you are breast-feeding or plan to breast-feed, ask your doctor for advice before using this medicine.

**Driving and using machines**
It is unlikely that Xolair will affect your ability to drive and use machines.

## 3. How to use Xolair

Always use this medicine exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure

**How Xolair is used**
Xolair is used as an injection under your skin (known as a subcutaneous injection).

Injecting Xolair
- You and your doctor will decide if you should inject Xolair yourself. The first 3 doses are always given by or under the supervision of a healthcare professional (see section 2).
- It is important to be properly trained on how to inject the medicine before injecting yourself.
- A caregiver (for example a parent) may also give you your Xolair injection after he or she has received proper training.

For detailed instructions on how to inject Xolair, see "Instructions for use of Xolair pre-filled syringe" at the end of this leaflet.

Training to recognise serious allergic reactions
It is also important that you do not inject Xolair yourself until you have been trained by your doctor or nurse on:
- how to recognise the early signs and symptoms of serious allergic reactions
- what to do if the symptoms occur.

For more information about the early signs and symptoms of serious allergic reactions, see section 4.

**How much to use**
Allergic asthma
Your doctor will decide how much Xolair you need and how often you will need 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 need 1 to 4 injections at a time. You will need the injections either every two weeks, or every four weeks.

Keep 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 treatment. It usually takes between 12 and 16 weeks to have the full effect.

Chronic spontaneous urticaria (CSU)
You will need two 150 mg injections at a time every four weeks.

Keep taking your current medicine for CSU during Xolair treatment. Do not stop taking any medicine without talking to your doctor.

**Use in children and adolescents**
Allergic asthma
Xolair can be used in children and adolescents aged 6 years and 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.

Children (6 to 11 years of age) are not expected to self-administer Xolair. However, if considered appropriate by their doctor, a caregiver may give them their Xolair injection after proper training.

Chronic spontaneous urticaria (CSU)
Xolair can be used in adolescents aged 12 years of age and older, who are already receiving antihistamines but whose CSU symptoms are not well controlled by these medicines. The dose for adolescents aged 12 years and above is the same as for adults.

**If a dose of Xolair is missed**
If you have missed an appointment, contact your doctor or hospital as soon as possible to re-schedule it.

If you have forgotten to give yourself a dose of Xolair, inject the dose as soon as you remember. Then talk to your doctor to discuss when you should inject the next dose.

**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:

Seek medical attention immediately if you notice any signs of the following side effects:
Rare (may affect up to 1 in 1,000 people)
- Severe allergic reactions (including anaphylaxis). Symptoms may include rash, itching or hives on the skin, swelling of the face, lips, tongue, larynx (voice box), windpipe or other parts of the body, fast heartbeat, dizziness and light-headedness, confusion, shortness of breath, wheezing or trouble breathing, blue skin or lips, collapsing and losing consciousness. 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, rash, fever, weight loss, and fatigue.

Not known (frequency cannot be estimated from the available data)
- Churg-Strauss syndrome or hypereosinophilic syndrome. 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 arms and legs.
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.
- Serum sickness. Symptoms may include one or more of the following: joint pain with or without swelling or stiffness, rash, fever, swollen lymph nodes, muscle pain.

Other side effects include:
Very common (may affect more than 1 in 10 people)
- fever (in children)

Common (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 (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 (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 containing 4 (4 x 1), 6 (6 x 1) or 10 (10 x 1) pre-filled syringes.

Not all pack sizes may be marketed in your country.

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**Manufacturer**
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Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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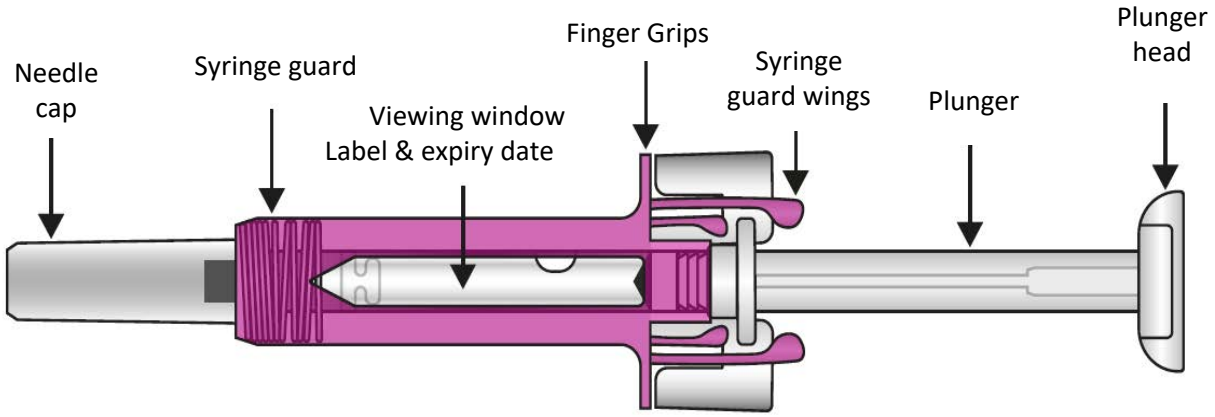
**This leaflet was last revised in**

**Other sources of information**
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

**INSTRUCTIONS FOR USE OF XOLAIR PRE-FILLED SYRINGE**

Read ALL the way through these instructions before injecting. If your doctor decides that you or a caregiver may be able to give your injections of Xolair at home, you need to be trained by your doctor, nurse or pharmacist before you inject yourself or others. Children (6 to less than 12 years of age) are not expected to inject Xolair themselves, however, if deemed appropriate by their doctor, a caregiver may give them their Xolair injection after proper training. The box contains Xolair pre-filled syringe(s) individually sealed in a plastic tray.

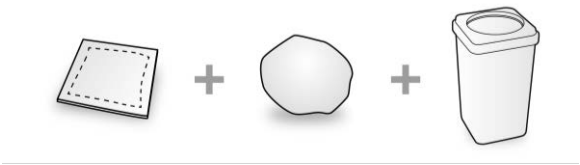
**Your Xolair 150 mg pre-filled syringe**




After the medicine has been injected, the syringe guard will be activated to cover the needle. This is intended to protect against accidental needlestick injuries.

**Other items you need for your injection:**

- Alcohol swab.
- Cotton ball or gauze.
- Sharps disposal container.



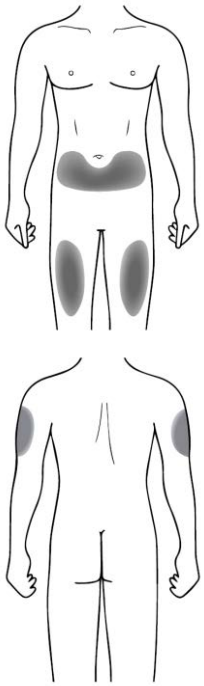
**Important safety information**
**Caution: Keep the syringe out of the sight and reach of children.**

- The needle cap of the syringe may contain dry rubber (latex), which should not be handled by anyone who is sensitive to this substance.
- Do not open the sealed outer box until you are ready to use this medicine.
- Do not use this medicine if either the seal on the outer box or the seal of the plastic tray is broken, as it may not be safe for you to use.
- Never leave the syringe where others might tamper with it.
- Do not shake the syringe.
- Be careful not to touch the syringe guard wings before use. If the wings are touched, the syringe guard may be activated too early.
- Do not remove the needle cap until just before you give the injection.
- The syringe cannot be re-used. Dispose of the used syringe immediately after use in a sharps container.

**Storage of the Xolair pre-filled syringe**

- Store this medicine sealed in its outer box to protect it from light. Store in the refrigerator between 2°C and 8°C. DO NOT FREEZE.
- Remember to take the syringe out of the refrigerator and allow it to reach room temperature (25°C) before preparing it for injection (it will take about 20 minutes). Leave the syringe in the box to protect it from light. The time that the syringe is kept at room temperature (25°C) before use must not exceed 4 hours.
- Do not use the syringe after the expiry date which is stated on the outer box and syringe label. If it has expired, return the entire pack to the pharmacy.

**The injection site**



The injection site is the place on the body where you are going to use the syringe.

- The recommended site is the front of the thighs. You may also use the lower abdomen, but **not** the area 5 centimetres around the navel (belly button).
- If you need to give more than one injection for the full dose, choose a different injection site each time you inject.
- Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks.

If a caregiver is giving the injection, the outer upper arms may also be used.

**Preparing the Xolair pre-filled syringe for use**

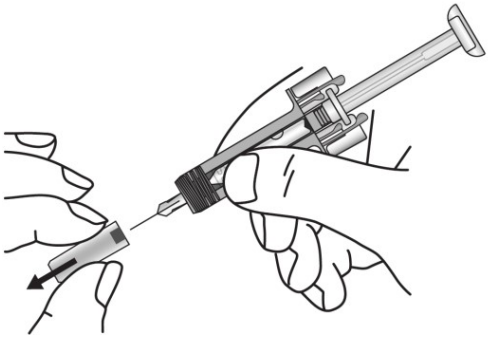
Note: Depending on the dose prescribed to you by your doctor, you may need to prepare one or more pre-filled syringes, and inject the contents of them all. The following table gives examples of how many injections of each dose strength you need for a given dose:

| Dose | Syringes needed for the dose | | | |
|---|---|---|---|---|
| 75 mg | 1 blue | | | |
| 150 mg | | | 1 purple (150 mg) | |
| 225 mg | 1 blue | + | 1 purple (150 mg) | |
| 300 mg | | | 2 purple (150 mg) | |
| 375 mg | 1 blue | + | 2 purple (150 mg) | |
| 450 mg | | | 3 purple (150 mg) | |
| 525 mg | 1 blue | + | 3 purple (150 mg) | |
| 600 mg | | | 4 purple (150 mg) | |

1. Take the box containing the syringe out of the refrigerator and leave it **unopened** for about 20 minutes so that it reaches room temperature (leave the syringe in the box to protect it from light).
2. When you are ready to use the syringe, wash your hands thoroughly with soap and water.
3. Clean the injection site with an alcohol swab.
4. Remove the plastic tray from the box and peel back the paper cover. Gripping the middle of the purple syringe guard, lift the syringe out of the tray.
5. Inspect the syringe. The liquid should be clear to slightly cloudy. Its colour may vary from colourless to pale brownish-yellow. You may see an air bubble, which is normal. DO NOT USE if the syringe is broken or if the liquid looks distinctly cloudy or distinctly brown, or contains particles. In all these cases, return the entire pack to the pharmacy.
6. Holding the syringe horizontally, look into the viewing window to check the expiry date printed on the label. Note: It is possible to rotate the inner part of the syringe assembly so that the label can be read in the viewing window. DO NOT USE if the product has expired. If expired, return the entire pack to the pharmacy.

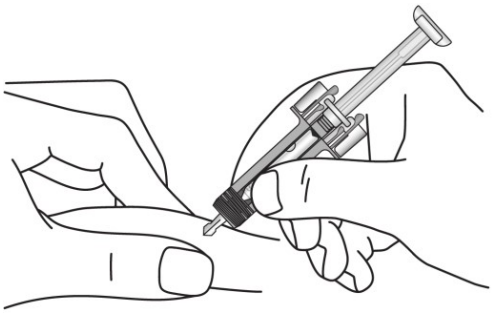
**How to use the Xolair pre-filled syringe**

1



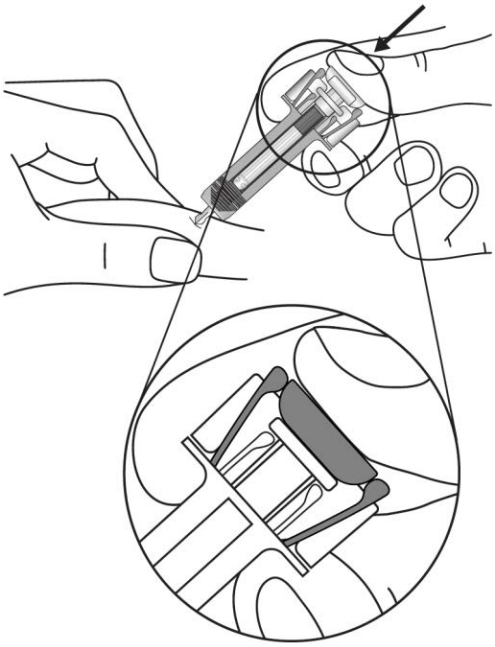
Carefully remove the needle cap from the syringe. Discard the needle cap. You may see a drop of liquid at the end of the needle. This is normal.

2



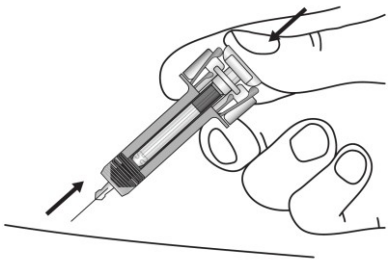
Gently pinch the skin at the injection site and insert the needle as shown. Push the needle all the way in to ensure that the medicine can be fully administered.

3



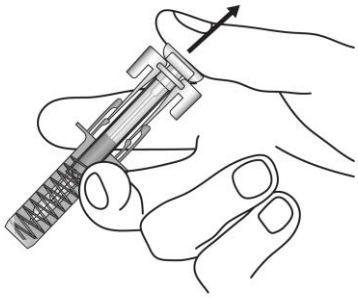
Hold the syringe as shown. **Slowly** depress the plunger **as far as it will go** so that the plunger head is completely between the syringe guard wings.

4



**Keep the plunger fully depressed** while you carefully lift the needle straight out from the injection site.

5



Slowly release the plunger and allow the syringe guard to automatically cover the exposed needle.

There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 30 seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

**Disposal instructions**

Dispose of the used syringe immediately in a sharps container (closable, puncture resistant container). For the safety and health of you and others, needles and used syringes **must never** be re-used. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 1.7 同種同効品一覧表

オマリズマブは，ヒト化抗ヒト IgE モノクローナル抗体製剤であり，薬理作用，効能・効果の観点から，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

20xx年xx月改訂（第1版）

貯法：2～8°Cに保存

有効期間：4年

| 日本標準商品分類番号 |
|---|
| 87229、87449 |

| | 75mg | 150mg |
|---|---|---|
| 承認番号 | 22400AMX 01381000 | 22300AMX 01262000 |
| 販売開始 | 2012年11月 | 2009年3月 |

**気管支喘息治療剤**
**季節性アレルギー性鼻炎治療剤**
**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）**
**オマリズマブ（遺伝子組換え）注射用凍結乾燥製剤**
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

NOVARTIS

**2.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

## 3.組成・性状
### 3.1組成

| 販売名 | ゾレア皮下注用75mg | ゾレア皮下注用150mg |
|---|---|---|
| 有効成分 | 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。※ | 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。※ |
| 添加剤 | 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 | 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 |

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。

### 3.2製剤の性状

| 販売名 | ゾレア皮下注用75mg | ゾレア皮下注用150mg |
|---|---|---|
| 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液 | |
| pH | 5.8～6.5（溶解後） | |
| 浸透圧 | 273～455mmol/kg（溶解後） | |

## 4.効能又は効果
**○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）**
**○季節性アレルギー性鼻炎（既存治療で効果不十分な重症又は最重症患者に限る）**
**○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）**

## 5.効能又は効果に関連する注意
**＜気管支喘息＞**
5.1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（$FEV_{1.0}$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

**＜季節性アレルギー性鼻炎＞**
5.2最新のガイドライン等を参考に、以下のいずれにも該当する患者に、ヒスタミン$H_1$受容体拮抗薬に追加して投与すること。［17.1.5参照］
・原因となる花粉抗原に対して血清特異的IgE抗体検査等で陽性を示す
・過去の治療において、花粉抗原の除去と回避を行ったうえで、鼻噴霧用ステロイド薬とケミカルメディエーター受容体拮抗薬を併用しても、重症又は最重症のアレルギー性鼻炎症状が認められた
・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

**＜特発性の慢性蕁麻疹＞**
5.3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$H_1$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。

## 6.用法及び用量
**＜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。

**＜季節性アレルギー性鼻炎＞**
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） | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ≥20～25 | >25～30 | >30～40 | >40～50 | >50～60 | >60～70 | >70～80 | >80～90 | >90～125 | >125～150 |
| ≥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 | 4週間毎投与の表に該当しない場合には<br>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<br>4週間毎投与の表に従い投与すること | | | | | | | | | |
| >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 | 投与不可 | | | | |
| >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0.008mg/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。

**＜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。

**7. 用法及び用量に関連する注意**

**＜気管支喘息、季節性アレルギー性鼻炎＞**

7.1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。

7.2本剤投与中に大幅に体重が~~増加~~変化した場合には、本剤の臨床推奨用量が投与されない可能性があるので、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。

7.3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るので、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。［12.参照］

7.4本剤投与中に喘息又は季節性アレルギー性鼻炎の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。

**＜気管支喘息＞**

7.5用法及び用量どおり、16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。

**＜季節性アレルギー性鼻炎＞**

7.6本剤投与が必要な季節性アレルギー性鼻炎に係る原因花粉抗原の飛散時期にのみ投与すること。なお、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。［15.1.5、17.1.5参照］また、症状発現初期に投与を開始することが望ましい。［18.2参照］

**＜特発性の慢性蕁麻疹＞**

7.7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。特に、用法及び用量どおり、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。［15.1.6、17.1.6参照］

**8. 重要な基本的注意**

**＜効能共通＞**

8.1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。

8.2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。［11.1.1、15.1.1参照］

8.3本剤投与中に、好酸球性多発血管炎性肉芽腫症（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。

8.4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。

8.5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。

8.6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。

8.7本剤の投与によって合併する他のアレルギー性疾患の症状が変化する可能性があり、当該アレルギー性疾患に対する適切な治療を怠った場合、症状が急激に悪化し、喘息等では死亡に至るおそれもある。本剤投与中止・終了後の疾患管理も含めて、本剤投与中から、合併するアレルギー性疾患を担当する医師と適切に連携すること。患者に対して、医師の指示なく、それらの疾患に対する治療内容を変更しないよう指導すること。

**＜気管支喘息＞**

8.8本剤は気管支拡張薬、ステロイド薬、~~抗ヒスタミン薬~~ヒスタミン$H_1$受容体拮抗薬等と異なり、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。

8.9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。

8.10長期ステロイド療法を受けている患者で、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。

## 9.特定の背景を有する患者に関する注意

### 9.5妊婦

妊婦又は妊娠している可能性のある女性には、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。

### 9.6授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。動物実験（サル）で乳汁中への移行が報告されている。

### 9.7小児等

**＜気管支喘息＞**

9.7.1低出生体重児、新生児、乳児又は6歳未満の幼児を対象とした臨床試験は実施していない。

9.7.2 6歳以上の小児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。

**＜季節性アレルギー性鼻炎、特発性の慢性蕁麻疹＞**

9.7.3低出生体重児、新生児、乳児、幼児又は12歳未満の小児を対象とした臨床試験は実施していない。

### 9.8高齢者

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。

## 11.副作用

次の副作用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するなど適切な処置を行うこと。

### 11.1重大な副作用

#### 11.1.1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・喉頭浮腫等があらわれることがある。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。[8.2、15.1.1参照]

### 11.2 その他の副作用

| | 5%以上 | 1%～5%未満 | 1%未満 | 頻度不明 |
|---|---|---|---|---|
| 感染症及び寄生虫症 | — | — | 鼻咽頭炎 | 上気道感染、咽頭炎、副鼻腔炎、寄生虫感染、尿路感染 |
| 血　液 | — | — | 血小板数減少 | 出血 |
| 神経系障害 | — | 頭痛 | 傾眠、めまい | 錯感覚、失神 |
| 血管障害 | — | — | 潮紅 | 起立性低血圧 |
| 呼吸器、胸郭及び縦隔障害 | — | — | — | 咳嗽、アレルギー性気管支痙攣、喉頭浮腫 |
| 胃腸障害 | — | — | 消化不良、悪心 | 下痢、上腹部痛 |
| 過敏症 | — | 蕁麻疹 | そう痒症、発疹 | 血管浮腫、血清病[注] |
| 皮　膚 | — | — | — | 光線過敏、脱毛 |
| 筋骨格系 | — | — | 四肢痛、筋骨格痛 | 関節痛、筋痛、関節腫脹 |
| 全身障害 | — | ~~けん怠感~~ — | 熱感、疲労、腕の腫脹、発熱、けん怠感 | 体重増加、インフルエンザ様疾患 |
| 注射部位 | 紅斑、腫脹~~、そう痒感、疼痛~~ | そう痒感、疼痛、出血、熱感、硬結 | 発疹、腫瘤、浮腫、蕁麻疹、しびれ感、不快感 | — |

注）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。

## 12.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、気管支喘息及び季節性アレルギー性鼻炎の用法・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。［7.3参照］

## 14.適用上の注意

### 14.1薬剤調製時の注意

#### 14.1.1調整前の準備

投与量が150mgを超える場合は投与液量一覧表を参考に、複数のバイアルを使用する。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。

#### 14.1.2調製方法

本剤の溶解には日局注射用水以外は使用しないこと。

(1)溶解時には以下の点に留意すること。

・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。

・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。

・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約5分毎に5～10秒間バイアルを回す操作を繰り返す。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。

(2)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。

**14.2薬剤投与時の注意**

14.2.1外観に異常を認めた場合には使用しないこと。

14.2.2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。

14.2.3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。

14.2.4 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（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 |

**15.その他の注意**

**15.1臨床使用に基づく情報**

15.1.1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。［8.2、11.1.1参照］

15.1.2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。

15.1.3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。

15.1.4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。

15.1.5スギ花粉症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歳以上の小児を対象として12週間の期間で実施されており、こ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。［7.6、17.1.5参照］

15.1.6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。［7.7、17.1.6参照］

15.1.7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。

**15.2非臨床試験に基づく情報**

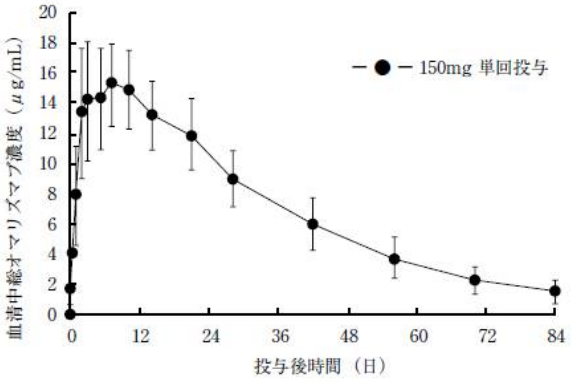
15.2.1動物を用いた反復皮下投与毒性試験において、カニクイザルでは15mg/kg/週以上（幼若動物）及び30mg/kg/週以上（成熟動物）の群で、チンパンジーでは250mg/kg/週の群で血小板数の減少が報告されている。

## 16. 薬物動態

### 16.1血中濃度

#### 16.1.1単回投与試験の成績

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[1)]。




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） | $T_{max}$（日） | $C_{max}$（μg/mL） | $T_{1/2}$（日） | $AUC_{0\text{-}inf}$（日·μg/mL） | $V_z/F$（L） | CL/F（mL/日） |
|---|---|---|---|---|---|---|
| 150 | 7 [2～14] | 16.7 ± 2.7 | 21.0 ± 3.5 | 642 ± 134 | 7.25 ± 1.33 | 242 ± 45.4 |

$T_{max}$は中央値[範囲]、その他は平均値±標準偏差

#### 16.1.2母集団解析の成績

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[2)]。

## 17. 臨床成績

### 17.1有効性及び安全性に関する試験

＜気管支喘息＞

#### 17.1.1国内第III相試験（成人）

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乗せ投与した。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、% $FEV_{1.0}$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ほぼ同様であった[3)]。

副作用発現頻度は本剤群で48.3%（73/151例）であった。主な副作用は、注射部位紅斑22.5%（34/151例）、注射部位そう痒感11.3%（17/151例）であった。

#### 17.1.2外国第III相試験（成人）

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$\beta_2$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、本剤を上乗せ投与した結果、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）[4)]。

副作用発現頻度は本剤群で11.8%（29/245例）であった。主な副作用は、悪心、注射部位紅斑、頭痛及びそう痒症各1.2%（3/245例）であった。

#### 17.1.3国内第III相試験（小児）

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週間上乗せ投与した。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。

副作用発現頻度は26.3%（10/38例）であった。主な副作用は、頭痛10.5%（4/38例）、注射部位疼痛7.9%（3/38例）、注射部位紅斑、注射部位腫脹及び蕁麻疹が各5.3%（2/38例）であった[5)]（小児承認時までの集計）。

#### 17.1.4外国第III相試験（小児）

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週間上乗せ投与した。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。
副作用発現頻度は、本剤群で6.9%（29/421例）であった。主な副作用は、頭痛1.7%（7/421例）、紅斑1.4%（6/421例）であった[6,7]。

＜季節性アレルギー性鼻炎＞

17.1.5国内第III相試験

既存治療で鼻症状が効果不十分な12歳以上のスギ花粉症患者（前スギ花粉シーズンに鼻噴霧用ステロイドに加え、経口アレルギー性鼻炎治療薬※1剤以上を投与してもくしゃみ、鼻汁及び鼻閉のすべての症状が発現し、そのうち1つ以上の鼻症状スコア※※が3点以上の重症又は最重症の患者）を対象としたプラセボ対照二重盲検比較試験において、161例に本剤をフェキソフェナジン塩酸塩に上乗せ投与した。本剤投与期間は12週間であり、フェキソフェナジン塩酸塩は12週間を通して投与し、このうち4週間では鼻噴霧用フルチカゾンプロピオン酸エステルも投与した。症状ピーク期※※※のNasal Symptom Score※※※※（平均値±標準偏差）は、本剤群が3.65±1.56、プラセボ群が4.70±2.18であり、プラセボ群に比べて本剤群で低かった。投与群間差（本剤群− プラセボ群、最小二乗平均値［95%CI］）は−1.03［−1.44、−0.62］であり、投与群間に有意な差が認められた（p＜0.001）。［7.6、15.1.5参照］

※第2世代ヒスタミン$H_1$受容体拮抗薬、ロイコトリエン受容体拮抗薬及びプロスタグランジン$D_2$・トロンボキサン$A_2$受容体拮抗薬
※※くしゃみ（0～4点）、鼻汁（0～4点）、及び鼻閉（0～4点）
※※※鼻噴霧用ステロイド併用期間の70%以上を含む、又は症状ピーク期の70%以上が鼻噴霧用ステロイド併用期間を含む、のいずれかを満たす1日のNasal symptom scoreの平均値の累積値が最大となる3週間以上の最短期間（2018年2月23日～3月24日）。
※※※※鼻症状スコアの合計（0～12点）

副作用発現頻度は本剤群で1.2%（2/161例）であった。主な副作用は、AST増加2例（1.2%）であった[8]。

＜特発性の慢性蕁麻疹＞

17.1.6国際共同第III相試験

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$H_1$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$H_1$受容体拮抗薬に上乗せ投与した。
プラセボ又は本剤150mg[注)]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※のベースラインからの変化量、週間膨疹スコア※※のベースラインからの変化量及びUAS7※※※が0（以下、UAS7=0）となった患者の割合を次表に示す。［7.7、15.1.6参照］

（注）本剤の承認された用法及び用量は1回300mgである。）
※1週間のそう痒スコア（1日0~3）を累計したスコア。
※※1週間の膨疹スコア（1日0~3）を累計したスコア。
※※※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［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（73例） | -8.80（70例） | -6.51（74例） | -3.70［-5.31、-2.10］p<0.001[a)] | -2.29［-3.92、-0.65］p=0.006[a)] |
| 週間膨疹スコア | -12.17（73例） | -10.04（70例） | -7.41（74例） | -4.76［-6.84、-2.67］[b)] | -2.63［-4.75、-0.50］[b)] |
| UAS7=0達成割合 | 35.6%（26/73例） | 18.6%（13/70例） | 4.1%（3/74例） | | |
| 日本人部分集団 | | | | | |
| 週間そう痒スコア | -9.54（35例） | -7.29（34例） | -5.17（36例） | -4.37［-6.77、-1.97］[c)] | -2.12［-4.54、0.30］[c)] |
| 週間膨疹スコア | -12.06（35例） | -8.36（34例） | -5.77（36例） | -6.29［-9.41、-3.17］[c)] | -2.59［-5.74、0.55］[c)] |
| UAS7=0達成割合 | 31.4%（11/35例） | 11.8%（4/34例） | 2.8%（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。

副作用発現頻度は、300 mg群で9.6%（7/73例）、150mg群で8.5%（6/71例）であった。主な副作用は、頭痛300mg群2.7%（2/73例）、150mg群1.4%（1/71例）、鼻咽頭炎300mg群1.4%（1/73例）、150mg群1.4%（1/71例）であった[9]。

## 18. 薬効薬理

### 18.1作用機序

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。

### 18.2IgEに対する阻害作用

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[3,10,11]。

### 18.3ヒスタミン遊離に対する効果

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[11]。

**18.4気道収縮に対する効果**

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[12, 13]。

**18.5気道過敏性に対する効果**

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[14]。

## 19.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に由来する軽鎖（$C_{1048}H_{1609}N_{278}O_{350}S_6$；分子量：23,895.03）と重鎖（$C_{2204}H_{3389}N_{588}O_{673}S_{15}$；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

## 21.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。

## 22.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］

## 23.主要文献


1) 社内資料：薬物動態試験　〔20090677〕
2) 社内資料：母集団薬物動態／薬力学解析（2013年8月20日承認、CTD2.7.2.3）　〔20133898〕
3) Ohta, K. et al.: Respirology 2009;14(8):1156-1165　〔20100362〕
4) Humbert, M. et al.: Allergy 2005;60(3):309-316　〔20083599〕
5) 社内資料：喘息患者を対象とした国内小児臨床試験（B1301試験）（2013年8月20日承認、CTD2.7.6-4.2.1）　［20133996］
6) Lanier, B. et al.: J Allergy Clin. Immunol. 2009;124(6):1210-1216　［20132382］
7) 社内資料：喘息患者を対象とした海外小児臨床試験（IA05試験）（2013年8月20日承認、CTD2.7.6-4.1.1）　［20133997］
8) 社内資料：スギ花粉症患者を対象とした国内臨床試験（F1301試験）（2019年XX月XX日承認、CTD2.7.6-4.1.1）
9) 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（E2306試験）（2017年3月24日承認、CTD2.7.6-4.1.1）　［20170085］
10) 社内資料：薬理試験（阻害様式）　［20090915］
11) 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）　［20090916］
12) Fahy, J. V. et al.: Am. J. Respir. Crit. Care Med. 1997;155(6):1828-1834　［20083589］
13) Zielen, S. et al.: Int Arch Allergy Immunol 2013;160(1):102-110　［20132833］
14) Boulet, L. P. et al.: Am. J. Respir. Crit. Care Med. 1997;155(6):1835-1840　［20083590］


## 24.文献請求先及び問い合わせ先


ノバルティスファーマ株式会社　ノバルティスダイレクト
〒105-6333　東京都港区虎ノ門1-23-1

NOVARTIS DIRECT
0120-003-293
受付時間：月～金 9：00～17：30
（祝祭日及び当社休日を除く）
www.novartis.co.jp


## 26.製造販売業者等

**26.1製造販売**


ノバルティスファーマ株式会社
東京都港区虎ノ門1-23-1

20xx年xx月改訂（第1版）

貯法：2～8°Cに保存［20.参照］

有効期間：18ヵ月

| 日本標準商品分類番号 |
|---|
| 87229、87449 |

| | 75mg | 150mg |
|---|---|---|
| 承認番号 | 23100AMX 00313000 | 22300AMX 00312000 |
| 販売開始 | 2019年6月 | 2019年6月 |

**気管支喘息治療剤**
**季節性アレルギー性鼻炎治療剤**
**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）**
**オマリズマブ（遺伝子組換え）注射剤**
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 75mg シリンジ
# ゾレア®皮下注 150mg シリンジ
# Xolair® for s.c.injection syringe

NOVARTIS

**2.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

## 3.組成・性状
### 3.1組成

| 販売名 | ゾレア皮下注用75mg | ゾレア皮下注用150mg |
|---|---|---|
| 有効成分 | オマリズマブ（遺伝子組換え）<br>75.0mg | オマリズマブ（遺伝子組換え）<br>150.0mg |
| 添加剤 | （1シリンジ0.5mL中）<br>L-アルギニン塩酸塩 21.05mg<br>L-ヒスチジン塩酸塩水和物 1.17mg<br>L-ヒスチジン 0.68mg<br>ポリソルベート20 0.20mg | （1シリンジ1.0mL中）<br>L-アルギニン塩酸塩 42.10mg<br>L-ヒスチジン塩酸塩水和物 2.34mg<br>L-ヒスチジン 1.37mg<br>ポリソルベート20 0.40mg |

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。

### 3.2製剤の性状

| 販売名 | ゾレア皮下注75mgシリンジ | ゾレア皮下注150mgシリンジ |
|---|---|---|
| 性状 | 無色～微褐黄色で、澄明又はわずかに混濁した液 | |
| pH | 5.8～6.2 | |
| 浸透圧 | 390～470mmol/kg | |

## 4.効能又は効果
**○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）**
**○季節性アレルギー性鼻炎（既存治療で効果不十分な重症又は最重症患者に限る）**
**○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）**

## 5.効能又は効果に関連する注意
**＜気管支喘息＞**
5.1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（$FEV_{1.0}$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

**＜季節性アレルギー性鼻炎＞**
5.2最新のガイドライン等を参考に、以下のいずれにも該当する患者に、ヒスタミン$H_1$受容体拮抗薬に追加して投与すること。［17.1.5参照］
・原因となる花粉抗原に対して血清特異的IgE抗体検査等で陽性を示す
・過去の治療において、花粉抗原の除去と回避を行ったうえで、鼻噴霧用ステロイド薬とケミカルメディエーター受容体拮抗薬を併用しても、重症又は最重症のアレルギー性鼻炎症状が認められた
・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

**＜特発性の慢性蕁麻疹＞**
5.3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$H_1$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。

## 6.用法及び用量
**＜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。

**＜季節性アレルギー性鼻炎＞**
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） | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ≥20～25 | >25～30 | >30～40 | >40～50 | >50～60 | >60～70 | >70～80 | >80～90 | >90～125 | >125～150 |
| ≥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 | 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 | | | | | | | | | | 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 | 投与不可 | | | | |
| >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0.008mg/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。

**＜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。

**7. 用法及び用量に関連する注意**

**＜気管支喘息、季節性アレルギー性鼻炎＞**

7.1 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。

7.2 本剤投与中に大幅に体重が~~増加~~変化した場合には、本剤の臨床推奨用量が投与されない可能性があるので、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。

7.3 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るので、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。［12.参照］

7.4 本剤投与中に喘息又は季節性アレルギー性鼻炎の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。

**＜気管支喘息＞**

7.5 用法及び用量どおり、16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。

**＜季節性アレルギー性鼻炎＞**

7.6 本剤投与が必要な季節性アレルギー性鼻炎に係る原因花粉抗原の飛散時期にのみ投与すること。なお、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。［15.1.5、17.1.5参照］また、症状発現初期に投与を開始することが望ましい。［18.2参照］

**＜特発性の慢性蕁麻疹＞**

7.7 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。特に、用法及び用量どおり、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。［15.1.6、17.1.6参照］

**8. 重要な基本的注意**

**＜効能共通＞**

8.1 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。

8.2 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。［11.1.1、15.1.1参照］

8.3 本剤投与中に、好酸球性多発血管炎性肉芽腫症（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。

8.4 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。

8.5 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。

8.6 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。

8.7本剤の投与によって合併する他のアレルギー性疾患の症状が変化する可能性があり、当該アレルギー性疾患に対する適切な治療を怠った場合、症状が急激に悪化し、喘息等では死亡に至るおそれもある。本剤投与中止・終了後の疾患管理も含めて、本剤投与中から、合併するアレルギー性疾患を担当する医師と適切に連携すること。患者に対して、医師の指示なく、それらの疾患に対する治療内容を変更しないよう指導すること。

**＜気管支喘息＞**

8.8本剤は気管支拡張薬、ステロイド薬、~~抗ヒスタミン薬~~ヒスタミン$H_1$受容体拮抗薬等と異なり、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。

8.9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。

8.10長期ステロイド療法を受けている患者で、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。

## 9.特定の背景を有する患者に関する注意

### 9.1合併症・既往歴等のある患者

#### 9.1.1ラテックス過敏症の既往歴又は可能性のある患者

アレルギー反応を起こすことがあるので注意すること。注射針部分のカバーは、乾燥天然ゴム（ラテックス由来）を含む。

### 9.5妊婦

妊婦又は妊娠している可能性のある女性には、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。

### 9.6授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。動物実験（サル）で乳汁中への移行が報告されている。

### 9.7小児等

**＜気管支喘息＞**

9.7.1低出生体重児、新生児、乳児又は6歳未満の幼児を対象とした臨床試験は実施していない。

9.7.2 6歳以上の小児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。

**＜季節性アレルギー性鼻炎、特発性の慢性蕁麻疹＞**

9.7.3低出生体重児、新生児、乳児、幼児又は12歳未満の小児を対象とした臨床試験は実施していない。

### 9.8高齢者

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。

## 11.副作用

次の副作用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するなど適切な処置を行うこと。

### 11.1重大な副作用

#### 11.1.1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・喉頭浮腫等があらわれることがある。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。[8.2、15.1.1参照]

### 11.2 その他の副作用

| | 5%以上 | 1%～5%未満 | 1%未満 | 頻度不明 |
|---|---|---|---|---|
| 感染症及び寄生虫症 | — | — | 鼻咽頭炎 | 上気道感染、咽頭炎、副鼻腔炎、寄生虫感染、尿路感染 |
| 血　液 | — | — | 血小板数減少 | 出血 |
| 神経系障害 | — | 頭痛 | 傾眠、めまい | 錯感覚、失神 |
| 血管障害 | — | — | 潮紅 | 起立性低血圧 |
| 呼吸器、胸郭及び縦隔障害 | — | — | — | 咳嗽、アレルギー性気管支痙攣、喉頭浮腫 |
| 胃腸障害 | — | — | 消化不良、悪心 | 下痢、上腹部痛 |
| 過敏症 | — | 蕁麻疹 | そう痒症、発疹 | 血管浮腫、血清病[注] |
| 皮　膚 | — | — | — | 光線過敏、脱毛 |
| 筋骨格系 | — | — | 四肢痛、筋骨格痛 | 関節痛、筋痛、関節腫脹 |
| 全身障害 | — | ~~けん怠感~~ — | 熱感、疲労、腕の腫脹、発熱、けん怠感 | 体重増加、インフルエンザ様疾患 |
| 注射部位 | 紅斑、腫脹~~、そう痒感、疼痛~~ | そう痒感、疼痛、出血、熱感、硬結 | 発疹、腫瘤、浮腫、蕁麻疹、しびれ感、不快感 | — |

注）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。

## 12.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、気管支喘息及び季節性アレルギー性鼻炎の用法・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。［7.3参照］

## 14.適用上の注意

### 14.1薬剤投与前の注意

14.1.1投与量が150mgを超える場合は投与液量一覧表を参考に、複数のシリンジを使用する。

14.1.2投与する約20分前に冷蔵庫から取り出し、外箱に入れたまま室温に戻すこと。

14.1.3針ガードで針が覆われてしまうのを防ぐため、使用前に針ガード作動クリップに触れないこと。

**投与液量一覧表**

| オマリズマブ（遺伝子組換 | 必要シリンジ数の例（組み合わせはこの限りではない） | 総投与液量 |
|---|---|---|

| え）投与量 | 75mgシリンジ | 150mgシリンジ | |
|---|---|---|---|
| 75mg | 1本 | ― | 0.5mL |
| 150mg | ― | 1本 | 1.0mL |
| 225mg | 1本 | 1本 | 1.5mL |
| 300mg | ― | 2本 | 2.0mL |
| 375mg | 1本 | 2本 | 2.5mL |
| 450mg | ― | 3本 | 3.0mL |
| 525mg | 1本 | 3本 | 3.5mL |
| 600mg | ― | 4本 | 4.0mL |

14.2薬剤投与時の注意

14.2.1外観に異常を認めた場合には使用しないこと。

14.2.2投与直前に開封すること。

14.2.31回につき1.0mL（150mg）を超えて投与する場合には、1箇所あたり1.0mLを超えないように部位を分けて投与すること。

14.2.41回使用の製剤であるため、使用後は再使用せず廃棄すること。

15.その他の注意

15.1臨床使用に基づく情報

15.1.1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。［8.2、11.1.1参照］

15.1.2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。

15.1.3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。

15.1.4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。

15.1.5スギ花粉症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歳以上の小児を対象として12週間の期間で実施されており、こ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。［7.6、17.1.5参照］

15.1.6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。［7.7、17.1.6参照］

15.1.7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。

15.2非臨床試験に基づく情報

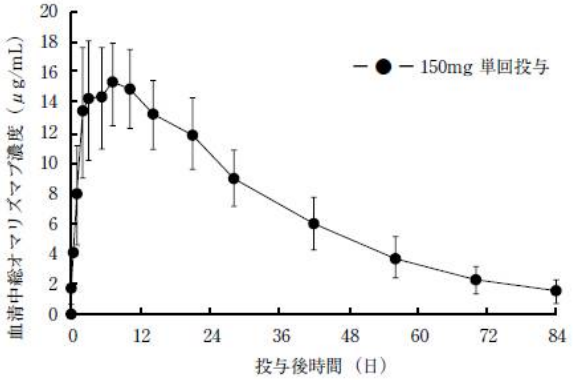
15.2.1動物を用いた反復皮下投与毒性試験において、カニクイザルでは15mg/kg/週以上（幼若動物）及び30mg/kg/週以上（成熟動物）の群で、チンパンジーでは250mg/kg/週の群で血小板数の減少が報告されている。

16.薬物動態

16.1血中濃度

16.1.1単回投与試験の成績

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、オマリズマブ（遺伝子組換え）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[1]。




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） | $T_{max}$（日） | $C_{max}$（μg/mL） | $T_{1/2}$（日） | $AUC_{0\text{-}inf}$（日·μg/mL） | $V_z/F$（L） | CL/F（mL/日） |
|---|---|---|---|---|---|---|

| 投与量（mg） | $T_{max}$（日） | $C_{max}$（μg/mL） | $T_{1/2}$（日） | $AUC_{0\text{-}inf}$（日·μg/mL） | $V_z/F$（L） | CL/F（mL/日） |
|---|---|---|---|---|---|---|
| 150 | 7 [2～14] | 16.7 ± 2.7 | 21.0 ± 3.5 | 642 ± 134 | 7.25 ± 1.33 | 242 ± 45.4 |

$T_{max}$は中央値[範囲]、その他は平均値±標準偏差

16.1.2母集団解析の成績

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オマリズマブ（遺伝子組換え）（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[2]。

## 17. 臨床成績

### 17.1有効性及び安全性に関する試験

＜気管支喘息＞

17.1.1国内第III相試験（成人）

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乗せ投与した。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、% $FEV_{1.0}$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ほぼ同様であった[3]。

副作用発現頻度は本剤群で48.3%（73/151例）であった。主な副作用は、注射部位紅斑22.5%（34/151例）、注射部位そう痒感11.3%（17/151例）であった。

17.1.2外国第III相試験（成人）

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$\beta_2$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、本剤を上乗せ投与した結果、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）[4]。

副作用発現頻度は本剤群で11.8%（29/245例）であった。主な副作用は、悪心、注射部位紅斑、頭痛及びそう痒症各1.2%（3/245例）であった。

17.1.3国内第III相試験（小児）

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週間上乗せ投与した。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。

副作用発現頻度は26.3%（10/38例）であった。主な副作用は、頭痛10.5%（4/38例）、注射部位疼痛7.9%（3/38例）、注射部位紅斑、注射部位腫脹及び蕁麻疹が各5.3%（2/38例）であった[5]（小児承認時までの集計）。

17.1.4外国第III相試験（小児）

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週間上乗せ投与した。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。

副作用発現頻度は、本剤群で6.9%（29/421例）であった。主な副作用は、頭痛1.7%（7/421例）、紅斑1.4%（6/421例）であった[6,7]。

＜季節性アレルギー性鼻炎＞

17.1.5国内第III相試験

既存治療で鼻症状が効果不十分な12歳以上のスギ花粉症患者（前スギ花粉シーズンに鼻噴霧用ステロイドに加え、経口アレルギー性鼻炎治療薬※1剤以上を投与してもくしゃみ、鼻汁及び鼻閉のすべての症状が発現し、そのうち1つ以上の鼻症状スコア※※が3点以上の重症又は最重症の患者）を対象としたプラセボ対照二重盲検比較試験において、161例に本剤をフェキソフェナジン塩酸塩に上乗せ投与した。本剤投与期間は12週間であり、フェキソフェナジン塩酸塩は12週間を通して投与し、このうち4週間では鼻噴霧用フルチカゾンプロピオン酸エステルも投与した。症状ピーク期※※※のNasal Symptom Score※※※※（平均値±標準偏差）は、本剤群が3.65±1.56、プラセボ群が4.70±2.18であり、プラセボ群に比べて本剤群で低かった。投与群間差（本剤群－ プラセボ群、最小二乗平均値［95%CI］）は−1.03［−1.44、−0.62］であり、投与群間に有意な差が認められた（$p < 0.001$）。［7.6、15.1.5参照］

※第2世代ヒスタミン$H_1$受容体拮抗薬、ロイコトリエン受容体拮抗薬及びプロスタグランジン$D_2$・トロンボキサン$A_2$受容体拮抗薬

※※くしゃみ（0～4点）、鼻汁（0～4点）、及び鼻閉（0～4点）

※※※鼻噴霧用ステロイド併用期間の70%以上を含む、又は症状ピーク期の70%以上が鼻噴霧用ステロイド併用期間を含む、のいずれかを満たす1日のNasal symptom scoreの平均値の累積値が最大となる3週間以上の最短期間（2018年2月23日～3月24日）。

※※※※鼻症状スコアの合計（0～12点）

副作用発現頻度は本剤群で1.2%（2/161例）であった。主な副作用は、AST増加2例（1.2%）であった[8]。

＜特発性の慢性蕁麻疹＞

17.1.6国際共同第III相試験

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H1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H1受容体拮抗薬に上乗せ投与した。

プラセボ又は本剤150mg[注)]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※のベースラインからの変化量、週間膨疹スコア※※のベースラインからの変化量及びUAS7※※※が0（以下、UAS7=0）となった患者の割合を次表に示す。［7.7、15.1.6参照］

（注）本剤の承認された用法及び用量は1回300mgである。）

※1週間のそう痒スコア（1日0~3）を累計したスコア。

※※1週間の膨疹スコア（1日0~3）を累計したスコア。

※※※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［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（73例） | -8.80（70例） | -6.51（74例） | -3.70［-5.31、-2.10］p<0.001[a)] | -2.29［-3.92、-0.65］p=0.006[a)] |
| 週間膨疹スコア | -12.17（73例） | -10.04（70例） | -7.41（74例） | -4.76［-6.84、-2.67］[b)] | -2.63［-4.75、-0.50］[b)] |
| UAS7=0達成割合 | 35.6%（26/73例） | 18.6%（13/70例） | 4.1%（3/74例） | | |
| 日本人部分集団 | | | | | |
| 週間そう痒スコア | -9.54（35例） | -7.29（34例） | -5.17（36例） | -4.37［-6.77、-1.97］[c)] | -2.12［-4.54、0.30］[c)] |
| 週間膨疹スコア | -12.06（35例） | -8.36（34例） | -5.77（36例） | -6.29［-9.41、-3.17］[c)] | -2.59［-5.74、0.55］[c)] |
| UAS7=0達成割合 | 31.4%（11/35例） | 11.8%（4/34例） | 2.8%（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。

副作用発現頻度は、300 mg群で9.6%（7/73例）、150mg群で8.5%（6/71例）であった。主な副作用は、頭痛300mg群2.7%（2/73例）、150mg群1.4%（1/71例）、鼻咽頭炎300mg群1.4%（1/73例）、150mg群1.4%（1/71例）であった[9]。

## 18. 薬効薬理

### 18.1作用機序

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。

### 18.2IgEに対する阻害作用

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[3, 10, 11]。

### 18.3ヒスタミン遊離に対する効果

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[11]。

### 18.4気道収縮に対する効果

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[12, 13]。

### 18.5気道過敏性に対する効果

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[14]。

## 19. 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に由来する軽鎖（$C_{1048}H_{1609}N_{278}O_{350}S_6$；分子量：23,895.03）と重鎖（$C_{2204}H_{3389}N_{588}O_{673}S_{15}$；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

## 20. 取扱い上の注意

外箱に入れたまま（遮光）の状態で、凍結を避けて冷蔵庫（2-8℃）で保管すること。

## 21. 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。

## 22. 包　　装

＜ゾレア皮下注75mgシリンジ＞　　［1シリンジ］
＜ゾレア皮下注150mgシリンジ＞　　［1シリンジ］

## 23. 主要文献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## 24. 文献請求先及び問い合わせ先

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## 26. 製造販売業者等

### 26.1製造販売（輸入）

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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

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本書では，花粉症を追加の効能・効果として承認申請するための設定根拠を記載する。

# 1 効能・効果及びその設定根拠

## 1.1 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）
○花粉症（既存治療で効果不十分な重症又は最重症患者に限る）
○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・効果の設定根拠

オマリズマブは，血清中の遊離 IgE に結合し，肥満細胞や好塩基球表面に発現している FcεRI と IgE との結合を競合的に阻害し，これら炎症細胞での抗原抗体反応を抑制することで，IgE を介するアレルギー疾患に対して薬効を示す。また，オマリズマブの結合部位である Cε3 は IgE の定常領域にあり，オマリズマブは IgE の抗原特異性にかかわらず結合することができるため，花粉症に対しても効果を発揮することが期待される。加えて，オマリズマブは既存治療とは異なり，アレルギーカスケードの初期反応を阻止する作用機序を有することから，既存治療で効果不十分な重症又は最重症花粉症患者の治療選択肢になり得ると考えた。

既存治療でコントロール不十分な重症又は最重症のスギ花粉症患者を対象に実施した国内第 III 相試験（F1301 試験）では，オマリズマブの有効性及び安全性を評価した。その結果，オマリズマブ群のプラセボ群に対する優越性が検証された。また，オマリズマブの忍容性は良好で，既存の特定されているオマリズマブのリスク以外に，新たに特定されたリスクはなかった。

以上より，既存治療で効果不十分な重症又は最重症の花粉症を効能又は効果として追加申請することとした。

なお，審査中の医薬品医療機器総合機構との協議内容を踏まえ，効能又は効果（案）を以下の通り変更した。

○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）
○季節性アレルギー性鼻炎（既存治療で効果不十分な重症又は最重症患者に限る）
○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）

以上

## 1.3 効能・効果に関連する注意

＜気管支喘息＞

5.1 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（$FEV_{1.0}$ 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

＜花粉症＞
5.2 過去に他の薬物治療を行っても効果が不十分であった重症又は最重症の花粉症患者で、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投与すること。

＜特発性の慢性蕁麻疹＞
5.3 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 $H_1$ 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・効果に関連する注意の設定根拠

オマリズマブは，既に FcεRI に結合した IgE を阻害することは出来ないため即効性は期待できず，効果発現に要する期間を考慮し，F1301 試験においては，同シーズンではなく過去に他の薬物治療で効果不十分であったスギ花粉症患者を組み入れた。その結果，1.2 項のとおり，オマリズマブの有効性及び安全性が示された。

以上に基づき，過去に他の薬物治療を行っても効果が不十分であった重症又は最重症の花粉症患者に投与することを効能又は効果に関連する使用上の注意に記載した。

また，2 章に示すとおり，既承認の気管支喘息と同じ投与量換算表を用いることから，投与量換算表で定義される基準を満たす場合に本剤を投与することを明記した。

なお，審査中の医薬品医療機器総合機構との協議内容を踏まえ，効能又は効果に関連する注意（案）を以下の通り変更した。

＜気管支喘息＞

5.1 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（$FEV_{1.0}$ 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

＜季節性アレルギー性鼻炎＞

5.2 最新のガイドライン等を参考に、以下のいずれにも該当する患者に、ヒスタミン $H_1$ 受容体拮抗薬に追加して投与すること。［17.1.5 参照］

・原因となる花粉抗原に対して血清特異的 IgE 抗体検査等で陽性を示す

・過去の治療において、花粉抗原の除去と回避を行ったうえで、鼻噴霧用ステロイド薬とケミカルメディエーター受容体拮抗薬を併用しても、重症又は最重症のアレルギー性鼻炎症状が認められた

・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

＜特発性の慢性蕁麻疹＞

5.3 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 $H_1$ 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。

以上

# 2 用法・用量及びその設定根拠

## 2.1 用法・用量

| ＜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。

＜花粉症＞

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 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） | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ≥20～25 | >25～30 | >30～40 | >40～50 | >50～60 | >60～70 | >70～80 | >80～90 | >90～125 | >125～150 |
| ≥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 | 450mg | 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 | 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 | | | | | | | | | | 375 mg |
| >300～400 | | | | | | | | | 450 mg | 525 mg |
| >400～500 | | | | | | | 375 mg | 375 mg | 525 mg | 600 mg |
| >500～600 | | | | | | 375 mg | 450mg | 450mg | 600 mg | |
| >600～700 | | 225 mg | | | 375 mg | 450mg | 450mg | 525mg | | |
| >700～800 | 225 mg | 225 mg | 300 mg | 375 mg | 450mg | 450mg | 525mg | 600mg | | |
| >800～900 | 225 mg | 225 mg | 300 mg | 375 mg | 450mg | 525mg | 600mg | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| >900～1,000 | 225 mg | 300 mg | 375 mg | 450mg | 525mg | 600mg | 投与不可 |
| >1,000～1,100 | 225 mg | 300 mg | 375 mg | 450mg | 600mg | 投与不可 | |
| >1,100～1,200 | 300 mg | 300 mg | 450mg | 525mg | 600mg | 投与不可 | |
| >1,200～1,300 | 300 mg | 375 mg | 450mg | 525mg | 投与不可 | 投与不可 | |
| >1,300～1,500 | 300 mg | 375 mg | 525mg | 600mg | 投与不可 | 投与不可 | |

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。

＜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。

## 2.2 用法・用量の設定根拠

花粉症の用法及び用量は，以下の理由から，既承認の気管支喘息と投与対象年齢を除き同一とした。

- アレルギー性鼻炎（花粉症を含む）及びアレルギー性気管支喘息はいずれも I 型アレルギー疾患であるため，オマリズマブの作用機序は同様であると考えられる。
- 投与量換算表は，アレルギー性気管支喘息及びアレルギー性鼻炎を含むアレルギー疾患の集団を対象とした臨床試験の結果に基づき作成されたものである。
- アレルギー性気管支喘息及びアレルギー性鼻炎の集団間で，オマリズマブの PK 及び PD に臨床的に重要な差異は認められなかった（Hayashi et al. 2007）。
- F1301 試験は気管支喘息と同一の投与量換算表を用いて実施され，重症のスギ花粉症患者で有効性及び安全性が示された。

また，F1301 試験は 12 歳以上のスギ花粉症患者を対象に実施された。12 歳以上 15 歳未満の被験者数が少ないため評価は困難であるが，12 歳以上 15 歳未満の部分集団の有効性，安全性の結果は全体集団での結果と同様であったことから（2.7.3, 2.7.4），成人及び 12 歳以上の小児を対象集団とした。

なお，審査中の医薬品医療機器総合機構との協議内容を踏まえ，用法及び用量（案）を以下の通り変更した。

＜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。

＜季節性アレルギー性鼻炎＞

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 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） | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ≥20～25 | >25～30 | >30～40 | >40～50 | >50～60 | >60～70 | >70～80 | >80～90 | >90～125 | >125～150 |
| ≥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 | 450mg | 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 | 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 | | | | | | | | | | 375 mg |
| >300～400 | | | | | | | | | 450 mg | 525 mg |
| >400～500 | | | | | | | 375 mg | 375 mg | 525 mg | 600 mg |
| >500～600 | | | | | | 375 mg | 450mg | 450mg | 600 mg | |
| >600～700 | | 225 mg | | | 375 mg | 450mg | 450mg | 525mg | | |
| >700～800 | 225 mg | 225 mg | 300 mg | 375 mg | 450mg | 450mg | 525mg | 600mg | | |
| >800～900 | 225 mg | 225 mg | 300 mg | 375 mg | 450mg | 525mg | 600mg | | | |
| >900～1,000 | 225 mg | 300 mg | 375 mg | 450mg | 525mg | 600mg | | | | |
| >1,000～1,100 | 225 mg | 300 mg | 375 mg | 450mg | 600mg | 投与不可 | | | | |
| >1,100～1,200 | 300 mg | 300 mg | 450mg | 525mg | 600mg | | | | | |
| >1,200～1,300 | 300 mg | 375 mg | 450mg | 525mg | | | | | | |
| >1,300～1,500 | 300 mg | 375 mg | 525mg | 600mg | | | | | | |

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。

＜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。

以上

## 2.3 用法・用量に関連する注意

＜気管支喘息、花粉症＞

7.1 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。

7.2 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ので、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。

7.3 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るので、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。［12. 参照］

7.4 本剤投与中に喘息又は花粉症の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。

＜気管支喘息＞

7.5 用法及び用量どおり、16 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。

＜花粉症＞

7.6 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。［15.1.5、17.1.5 参照］

7.7 花粉症[注)] の好発季節に、症状発現後速やかに投与を開始することが望ましい。なお、好発季節終了後は漫然と投与を続けないよう注意すること。

注）過去に他の薬物治療を行っても効果が不十分であった重症又は最重症の花粉症に限る

＜特発性の慢性蕁麻疹＞

7.8 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。特に、用法及び用量どおり、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。［15.1.6、17.1.6 参照］

## 2.4 用法・用量に関連する注意の設定根拠

花粉症の用法及び用量に関連する使用上の注意は，同じ投与量換算表を用いる既承認の気管支喘息と同一とした。ただし，花粉症については，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旨，追加で設定した。

本剤の予定される効能・効果である花粉症は季節性のアレルギー疾患であるため，花粉症の好発季節に，花粉症の症状が発現した後，速やかに本剤の投与を開始することが望ましいことから 7.7 を設定した。なお，効能・効果に従った花粉症であることを説明するために「過去に他の薬物治療を行っても効果が不十分であった重症又は最重症の花粉症に限る」と注釈記載した。また，好発季節終了後は漫然と投与することのないようにするため注意喚起した。

なお，審査中の医薬品医療機器総合機構との協議内容を踏まえ，用法及び用量に関連する注意（案）を以下の通り変更した。

＜気管支喘息、季節性アレルギー性鼻炎＞

7.1 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。

7.2 本剤投与中に大幅に体重が~~増加~~変化した場合には、本剤の臨床推奨用量が投与されない可能性があるので、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。

7.3 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るので、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。［12. 参照］

7.4 本剤投与中に喘息又は季節性アレルギー性鼻炎の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。

＜気管支喘息＞

7.5 用法及び用量どおり、16 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。

＜季節性アレルギー性鼻炎＞

7.6 本剤投与が必要な季節性アレルギー性鼻炎に係る原因花粉抗原の飛散時期にのみ投与すること。なお、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。［15.1.5、17.1.5 参照］また、症状発現初期に投与を開始することが望ましい。［18.2 参照］

＜特発性の慢性蕁麻疹＞

7.7 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。特に、用法及び用量どおり、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。［15.1.6、17.1.6 参照］

以上

### 1.8.3 使用上の注意（案）及びその設定根拠

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# 1 「2. 禁忌（次の患者には投与しないこと）」欄

## 1.1 「2. 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 「2. 禁忌（次の患者には投与しないこと）」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 「8. 重要な基本的注意」欄

## 2.1 「8. 重要な基本的注意」

＜効能共通＞

8.1 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。

8.2 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。［11.1.1，15.1.1 参照］

8.3 本剤投与中に，好酸球性多発血管炎性肉芽腫症（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。

8.4 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。

8.5 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。

8.6 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。

8.7 本剤の投与によって合併する他のアレルギー性疾患の症状が変化する可能性があり，当該アレルギー性疾患に対する適切な治療を怠った場合，症状が急激に悪化し，喘息等では死亡に至るおそれもある。本剤投与中止・終了後の疾患管理も含めて，本剤投与中から，合併するアレルギー性疾患を担当する医師と適切に連携すること。患者に対して，医師の指示なく，それらの疾患に対する治療内容を変更しないよう指導すること。

＜気管支喘息＞

8.8 本剤は気管支拡張薬，ステロイド薬，ヒスタミン $H_1$ 受容体拮抗薬等と異なり，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。

8.9　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。
8.10　長期ステロイド療法を受けている患者で，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。

（下線部：一変申請に伴う改訂）

## 2.2　「8. 重要な基本的注意」の設定根拠

本剤の投与により合併する他のアレルギー性疾患の症状が変化する可能性があるため，当該アレルギー性疾患に対する治療が適切に実施されるよう 8.7 を設定した。

その他は，現行添付文書に基づき設定した。

# 3　「9. 特定の背景を有する患者に関する注意」欄

## 3.1　「9.1 合併症・既往歴等のある患者」欄

### 3.1.1　「9.1.1 ラテックス過敏症の既往歴又は可能性のある患者」

（ゾレア皮下注シリンジ）

アレルギー反応を起こすことがあるので注意すること。注射針部分のカバーは，乾燥天然ゴム（ラテックス由来）を含む。

### 3.1.2　「9.1.1 ラテックス過敏症の既往歴又は可能性のある患者」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。

## 3.2　「9.5 妊婦」欄

### 3.2.1　「9.5 妊婦」

妊婦又は妊娠している可能性のある女性には，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。

### 3.2.2　「9.5 妊婦」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。

## 3.3　「9.6 授乳婦」欄

### 3.3.1　「9.6 授乳婦」

治療上の有益性及び母乳栄養の有益性を考慮し，授乳の継続又は中止を検討すること。動物実験（サル）で乳汁中への移行が報告されている。

### 3.3.2 「9.6 授乳婦」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。

## 3.4 「9.7 小児等」欄

### 3.4.1 「9.7 小児等」

〈気管支喘息〉

9.7.1 低出生体重児，新生児，乳児又は 6 歳未満の幼児を対象とした臨床試験は実施していない。

9.7.2 6 歳以上の小児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。

〈季節性アレルギー性鼻炎，特発性の慢性蕁麻疹〉

9.7.3 低出生体重児，新生児，乳児，幼児又は 12 歳未満の小児を対象とした臨床試験は実施していない。

（下線部：一変申請に伴う改訂）

### 3.4.2 「9.7 小児等」の設定根拠

スギ花粉症を対象とした臨床試験において，12 歳未満の患者へは投与経験がないことから，9.7.3 に季節性アレルギー性鼻炎を追記した。

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。

## 3.5 「9.8 高齢者」欄

### 3.5.1 「9.8 高齢者」

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。

### 3.5.2 「9.8 高齢者」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。

# 4 「11. 副作用」欄

## 4.1 「11. 副作用」欄

### 4.1.1 「11. 副作用」

次の副作用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するなど適切な処置を行うこと。

### 4.1.2 「11．副作用」の設定根拠

添付文書新記載要領のテンプレートにしたがい，注意喚起した。

### 4.1.3 「11.1 重大な副作用」

11.1.1 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・喉頭浮腫等があらわれることがある。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。［8.2，15.1.1 参照］

### 4.1.4 「11.1 重大な副作用」の設定根拠

「重大な副作用」及び「その他の副作用」の頻度は，特発性の慢性蕁麻疹承認時までの集計である B1301，B1301E1，A1303，A1304，A1305，A1306（A1303 extension），A1307，及び E2306 試験で本剤を投与した日本人患者に，F1301 試験で本剤を投与した日本人患者を含め再集計した結果に基づき記載した。これらの臨床試験（E2306 試験では日本人患者）で認められていない副作用については頻度不明とした。

## 4.2 「11.2 その他の副作用」欄

### 4.2.1 「11.2 その他の副作用」

| | 5%以上 | 1%～5%未満 | 1%未満 | 頻度不明 |
|---|---|---|---|---|
| **感染症及び寄生虫症** | — | — | 鼻咽頭炎 | 上気道感染，咽頭炎，副鼻腔炎，寄生虫感染，尿路感染 |
| **血液** | — | — | 血小板数減少 | 出血 |
| **神経系障害** | — | 頭痛 | 傾眠，めまい | 錯感覚，失神 |
| **血管障害** | — | — | 潮紅 | 起立性低血圧 |
| **呼吸器，胸郭及び縦隔障害** | — | — | — | 咳嗽，アレルギー性気管支痙攣，喉頭浮腫 |
| **胃腸障害** | — | — | 消化不良，悪心 | 下痢，上腹部痛 |
| **過敏症** | — | 蕁麻疹 | そう痒症，発疹 | 血管浮腫，血清病[注)] |
| **皮膚** | — | — | — | 光線過敏，脱毛 |
| **筋骨格系** | — | — | 四肢痛，筋骨格痛 | 関節痛，筋痛，関節腫脹 |

| | 5%以上 | 1%～5%未満 | 1%未満 | 頻度不明 |
|---|---|---|---|---|
| **全身障害** | — | ~~けん怠感~~<br>— | 熱感，疲労，腕の腫脹，発熱，けん怠感 | 体重増加，インフルエンザ様疾患 |
| **注射部位** | 紅斑，腫脹~~，そう痒感，疼痛~~ | そう痒感，疼痛，出血，熱感，硬結 | 発疹，腫瘤，浮腫，蕁麻疹，しびれ感，不快感 | — |

注）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：本申請に伴う追加部分，取り消し線：本申請に伴う削除部分）

### 4.2.2 「11.2 その他の副作用」の設定根拠

4.1.4 項参照。

## 5 「12. 臨床検査結果に及ぼす影響」欄

### 5.1 「12. 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，気管支喘息及び季節性アレルギー性鼻炎の用法・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。［7.3 参照］

（下線部：一変申請に伴う改訂）

### 5.2 「12. 臨床検査結果に及ぼす影響」の設定根拠

既承認の気管支喘息と同じ投与量換算表を用いることから，季節性アレルギー性鼻炎でも同一の注意喚起を設定した。

## 6 「14. 適用上の注意」欄

### 6.1 「14. 適用上の注意」

**（ゾレア皮下注用）**

14.1 薬剤調製時の注意

14.1.1 調製前の準備

投与量が 150mg を超える場合は投与液量一覧表を参考に，複数のバイアルを使用する。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。

14.1.2 調製方法：

本剤の溶解には日局注射用水以外は使用しないこと。

(1)溶解時には以下の点に留意すること。

- 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。
- 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。
- 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約 5 分毎に 5～10 秒間バイアルを回す操作を繰り返す。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。

(2)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。

14.2 薬剤投与時の注意

14.2.1 外観に異常を認めた場合には使用しないこと。

14.2.2 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。

14.2.3 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。

14.2.4 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（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 |

**（ゾレア皮下注シリンジ）**

14.1 薬剤投与前の注意

14.1.1 投与量が 150mg を超える場合は投与液量一覧表を参考に，複数のシリンジを使用する。

14.1.2 投与する約 20 分前に冷蔵庫から取り出し，外箱に入れたまま室温に戻すこと。

14.1.3 針ガードで針が覆われてしまうのを防ぐため，使用前に針ガード作動クリップに触れないこと。

投与液量一覧表

| オマリズマブ（遺伝子組換え）投与量 | 必要シリンジ数の例（組み合わせはこの限りではない） | | 総投与液量 |
|---|---|---|---|
| | 75mg シリンジ | 150mg シリンジ | |
| 75mg | 1 本 | — | 0.5mL |
| 150mg | — | 1 本 | 1.0mL |
| 225mg | 1 本 | 1 本 | 1.5mL |
| 300mg | — | 2 本 | 2.0mL |
| 375mg | 1 本 | 2 本 | 2.5mL |
| 450mg | — | 3 本 | 3.0mL |
| 525mg | 1 本 | 3 本 | 3.5mL |
| 600mg | — | 4 本 | 4.0mL |

14.2 薬剤投与時の注意

14.2.1 外観に異常を認めた場合には使用しないこと。

14.2.2 投与直前に開封すること。

14.2.3 1 回につき 1.0mL（150mg）を超えて投与する場合には，1 箇所あたり 1.0mL を超えないように部位を分けて投与すること。

14.2.4 1 回使用の製剤であるため，使用後は再使用せず廃棄すること。

## 6.2 「14. 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。

# 7 「15. その他の注意」欄

## 7.1 「15.1 臨床使用に基づく情報」欄

### 7.1.1 「15.1 臨床使用に基づく情報」

15.1.1 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。［8.2，11.1.1参照］

15.1.2 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。

15.1.3 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。

15.1.4 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。

15.1.5 スギ花粉症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歳以上の小児を対象として 12 週間の期間で実施されており，こ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。［7.6，17.1.5参照］

15.1.6 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。［7.7，17.1.6 参照］

15.1.7 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）

### 7.1.2 「15.1 臨床使用に基づく情報」の設定根拠

日本人スギ花粉症患者を対象とした臨床試験においては 12 週間を超える投与経験はないことから 15.1.5 を設定した。

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。

## 7.2 「15.2 非臨床試験に基づく情報」欄

### 7.2.1 「15.2 非臨床試験に基づく情報」

15.2.1 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。

### 7.2.2 「15.2 非臨床試験に基づく情報」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。

## 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

## ＜現行＞

| | |
|---|---|
| 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 | 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）<br>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） |
| 用法・用量 | 1. 気管支喘息<br>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。<br><br>投与量換算表（1 回投与量）<br>4 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 | 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 | 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 | | | | | | | | | | 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 | 投与不可 |
| >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。

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 300 mg を 4 週間毎に皮下に注射する。

**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）

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］

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］

ゾレア皮下注 150 mg シリンジ［1 シリンジ中オマリズマブ（遺伝子組換え）150.0 mg 含有］

ゾレア皮下注 75 mg シリンジ［1 シリンジ中オマリズマブ（遺伝子組換え）75.0 mg 含有］

**毒性**

単回投与毒性試験

| 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 |

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

反復投与毒性試験

| 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 ヵ月間，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：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／精嚢周囲 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | 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 | 気管支喘息<br>副作用発現率（成人）<br>47.2%（134 例／284 例）<br>副作用の種類　例数<br>注射部位紅斑　53 例（18.7%）<br>注射部位そう痒感　26 例（9.2%）<br>注射部位腫脹　24 例（8.5%）<br>注射部位疼痛　20 例（7.0%）<br>注射部位熱感　14 例（4.9%）<br>注射部位硬結　13 例（4.6%）<br>注射部位出血　12 例（4.2%）<br>蕁麻疹　5 例（1.8%）<br>けん怠感　5 例（1.8%）等<br><br>副作用発現率（小児）<br>26.3%（10 例／38 例）<br>副作用の種類　例数<br>頭痛　4 例（10.5%）<br>注射部位疼痛　3 例（7.9%）<br>注射部位紅斑　2 例（5.3%）<br>注射部位膨張　2 例（5.3%）<br>蕁麻疹　2 例（5.3%）等<br><br>特発性の慢性蕁麻疹<br>副作用発現率<br>9.0%（13 例／144 例）<br>副作用の種類　例数<br>頭痛　3 例（2.1%）<br>鼻咽頭炎　2 例（1.4%）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・訂正線部）**

| | |
|---|---|
| 化学名・別名 | |
| 構造式 | |
| 効能・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）<br>2. 季節性アレルギー性鼻炎（既存治療で効果不十分な重症又は最重症患者に限る）<br>3. 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） |
| 用法・用量 | 1. 気管支喘息<br>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。<br><br>2. 季節性アレルギー性鼻炎<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 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。<br><br>投与量換算表（1 回投与量）<br>4 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 | 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 | 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 | | | | | | | | | | 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 | 投与不可 | | |
| >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。

3. 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 300 mg を 4 週間毎に皮下に注射する。

| | |
|---|---|
| 劇薬等の指定 | |
| 市販名及び有効成分・分量 | |
| 毒性 | |
| 副作用 | 気管支喘息<br>副作用発現率（成人）<br>47.2%（134 例／284 例）<br>副作用の種類　例数<br>注射部位紅斑　53 例（18.7%）<br>注射部位そう痒感　26 例（9.2%）<br>注射部位腫脹　24 例（8.5%）<br>注射部位疼痛　20 例（7.0%）<br>注射部位熱感　14 例（4.9%）<br>注射部位硬結　13 例（4.6%）<br>注射部位出血　12 例（4.2%）<br>蕁麻疹　5 例（1.8%）<br>けん怠感　5 例（1.8%）等<br><br>副作用発現率（小児）<br>26.3%（10 例／38 例）<br>副作用の種類　例数<br>頭痛　4 例（10.5%）<br>注射部位疼痛　3 例（7.9%）<br>注射部位紅斑　2 例（5.3%）<br>注射部位膨張　2 例（5.3%）<br>蕁麻疹　2 例（5.3%）等<br><br>季節性アレルギー性鼻炎<br>1.2%（2 例／161 例）<br>副作用の種類　例数 |

| | |
|---|---|
| | AST　2 例（1.2%）<br><br>特発性の慢性蕁麻疹<br>副作用発現率<br>9.0%（13 例／144 例）<br>副作用の種類　例数<br>頭痛　3 例（2.1%）<br>鼻咽頭炎　2 例（1.4%）等 |
| 会　社 | |

## 1.12 添付資料一覧

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| 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（国内／海外） | 掲載誌 | 評価／参考 |
|---|---|---|---|---|---|---|---|
| **4.2 試験報告書** | | | | | | | |
| | 該当資料なし | | | | | | |

| 添付資料番号 | 著者・表 題・掲載誌 | 報種類（国内／海外） |
|---|---|---|
| **4.3 参考文献 （評価／参考の別：参考資料）** | | |
| 4.3-1 | Liu J, Lester P, Builder S, et al. (1995) Characterization of complex formation by humanized anti-IgE monoclonal antibody and monoclonal human IgE. Biochemistry; 34(33):10474-82. | 海外 |
| 4.3-2 | Mandhane SN, Shah JH, Thennati R (2011) Allergic rhinitis: an update on disease, present treatments and future prospects. Int Immunopharmacol; 11(11):1646-62. | 海外 |

# 第 5 部

| 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（国内／海外） | 掲載誌 | 評価／参考 |
|---|---|---|---|---|---|---|---|
| **5.2 全臨床試験一覧表** | | | | | | | |
| 5.2 | 全臨床試験一覧表 | ノバルティス | ― | ― | 国内 | 社内報告書 | 評価 |
| **5.3 臨床試験報告書** | | | | | | | |
| **5.3.1 生物薬剤学試験報告書** | | | | | | | |
| **5.3.1.1 バイオアベイラビリティ（BA）試験報告書** | | | | | | | |
| | 該当資料なし | | | | | | |
| **5.3.1.2 比較 BA 試験及び生物学的同等性（BE）試験報告書** | | | | | | | |
| | 該当資料なし | | | | | | |
| **5.3.1.3 *In Vitro-In Vivo* の関連を検討した試験報告書** | | | | | | | |
| | 該当資料なし | | | | | | |
| **5.3.1.4 生物学的及び理化学的分析法検討報告書** | | | | | | | |
| 5.3.1.4-1 | Quantitative detection of total Omalizumab (Xolair®) in human serum by ELISA<br>Long term stability and selectivity assessment | SYNLAB Analytics & Services Switzerland AG | 2018 年 7 月 20 日 | スイス | 海外 | 社内報告書 | 評価 |
| 5.3.1.4-2 | Quantitative detection of free IgE in human serum by fluorimetric ELISA<br>Long term stability and freeze-thaw stability assessment<br>Amendment no. 01 | SYNLAB Analytics & Services Switzerland AG | 2018 年 10 月 5 日 | スイス | 海外 | 社内報告書 | 評価 |
| 5.3.1.4-3 | Quantitative determination of Total IgE in human serum on the Phadia ImmunoCAP platform<br>Method implementation and cross-validation | SYNLAB Analytics & Services Switzerland AG | 2018 年 7 月 20 日 | スイス | 海外 | 社内報告書 | 評価 |

| 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（国内／海外） | 掲載誌 | 評価／参考 |
|---|---|---|---|---|---|---|---|
| 5.3.1.4-4 | Determination of anti-Omalizumab antibodies in human serum by ELISA<br>Additional Validation Experiments: implementation of new batches of critical reagents in the ELISA methods for detection of anti-rhuMAb-E25-Fab and anti-rhuMAb-E25-Fc antibodies and implementation of a combined assay (screening-titer-confirmatory) layout | SYNLAB Analytics & Services Switzerland AG | 2018 年 7 月 20 日 | スイス | 海外 | 社内報告書 | 評価 |
| **5.3.2 ヒト生体試料を用いた薬物動態関連の試験報告書** | | | | | | | |
| | 該当資料なし | | | | | | |
| **5.3.3 臨床薬物動態（PK）試験報告書** | | | | | | | |
| | 該当資料なし | | | | | | |
| **5.3.4 臨床薬力学（PD）試験報告書** | | | | | | | |
| | 該当資料なし | | | | | | |
| **5.3.5 有効性及び安全性試験報告書** | | | | | | | |
| **5.3.5.1 申請する適応症に関する比較対照試験報告書** | | | | | | | |
| 5.3.5.1-1 | A 12 week, multi-center, randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy and safety of omalizumab in adult and adolescent patients with inadequately controlled severe Japanese cedar pollinosis despite the current recommended therapies | ノバルティス | 2017 年 12 月 15 日（最初の被験者の同意取得日）～ 2018 年 5 月 12 日（最後の被験者の治験薬投与期終了日） | 日本，計 21 施設 | 国内 | 社内資料 | 評価 |
| | Addendum 1 to Clinical Study Report CIGE025F1301 (Pharmacokinetics, pharmacodynamics, and immunogenicity results for the post-treatment follow-up epoch) | ノバルティス | 2017 年 12 月 15 日（最初の被験者の同意取得日）～ 2018 年 10 月 20 日（最後の被験者の最終来院日） | 日本，計 21 施設 | 国内 | 社内資料 | 評価 |

| 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（国内／海外） | 掲載誌 | 評価／参考 |
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| 5.3.5.1-2 | 季節性アレルギー性鼻炎に対する IGE025 のプラセボを対照とした比較試験 | ノバルティス | 2001 年 10 月 20 日（最初の患者の同意取得日）～2002 年 6 月 19 日（最後の患者の検査・観察終了日） | 日本，計 2 施設 | 国内 | 社内資料 | 参考 |
| 5.3.5.1-3 | 季節性アレルギー性鼻炎に対する IGE025 のトシル酸スプラタストを対照とした比較試験 | ノバルティス | 2002 年 11 月 27 日（最初の被験者の同意取得日）～2003 年 8 月 9 日（最後の被験者の検査・観察終了日） | 日本，計 2 施設 | 国内 | 社内資料 | 参考 |
| | Errata list | － | － | － | 国内 | 社内資料 | 参考 |
| **5.3.5.2 非対照試験報告書** | | | | | | | |
| 5.3.5.2-1 | 季節性アレルギー性鼻炎に対する IGE025 のオープン試験（再投与試験） | ノバルティス | 2002 年 11 月 30 日（最初の被験者の同意取得日）～2003 年 6 月 22 日（最後の被験者の検査・観察終了日） | 日本，計 2 施設 | 国内 | 社内資料 | 参考 |
| **5.3.5.3 複数の試験成績を併せて解析した報告書** | | | | | | | |
| 5.3.5.3-1 | SCS Appendix 1 (Integrated Summary of Safety,date analyses) | ノバルティス | － | － | 国内 | 社内資料 | 参考 |
| **5.3.5.4 その他の臨床試験報告書** | | | | | | | |
| | 該当資料なし | | | | | | |

| 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（国内／海外） | 掲載誌 | 評価／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 01Jan2017to31Dec2017 (PSUR01Jan2017to31Dec2017) | ノバルティス | Period covered: 2017 年 1 月 1 日～ 2017 年 12 月 31 日 | ― | 海外 | 社内報告書 | 参考 |
| | Addendum Statement | ノバルティス | Period covered: 2018 年 1 月 1 日～ 2018 年 6 月 30 日 | ― | 海外 | 社内報告書 | 参考 |
| **5.3.7 患者データ一覧表及び症例記録** | | | | | | | |
| 5.3.7-1 | 症例一覧表 | ノバルティス | ― | ― | 国内 | 社内報告書 | 評価 |
| 5.3.7-2 | 副作用一覧表 | | | | | | |
| 5.3.7-3 | 重篤な有害事象一覧表 | | | | | | |
| 5.3.7-4 | 臨床検査値の異常変動一覧表 | | | | | | |

| 添付資料番号 | 著者・表 題・掲載誌 | 報種類（国内／海外） |
|---|---|---|
| **5.4 参考文献　（評価／参考の別：参考資料）** | | |
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| 5.4-4 | Hayashi N, Tsukamoto Y, Sallas WM, et al. (2007) A mechanism-based binding model for the population pharmacokinetics and pharmacodynamics of omalizumab. Br J Clin Pharmacol; 63(5):548-61. | 海外 |
| 5.4-5 | Higaki T, Okano M, Kariya S, et al. (2013) Determining minimal clinically important differences in Japanese cedar/cypress pollinosis patients. Allergol Int; 62(4):487-93. | 海外 |
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| 5.4-7 | Nagakura T, Ogino S, Okubo K, et al. (2008) Omalizumab is more effective than suplatast tosilate in the treatment of Japanese cedar pollen-induced seasonal allergic rhinitis. Clin Exp Allergy; 38(2):329-37. | 海外 |
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| 添付資料番号 | 著者・表 題・掲載誌 | 報種類（国内／海外） |
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