ゾレア皮下注用

に関する資料

ノバルティス ファーマ株式会社

1.4 特許状況

1 特許状況

[redacted]

[redacted]

2 商標

[redacted]

[redacted]

1.5 起原又は発見の経緯及び開発の経緯

目　次

略号一覧

略号	省略していない表現（英）	省略していない表現（日）
CPMP	Committee for Proprietary Medicinal Products	欧州医薬品委員会
FcεRI	Fc epsilon receptor I	高親和性 IgE 受容体
$FEV_{1.0}$/ FEV_1	forced expiratory volume in one second	努力性肺活量の 1 秒量
GINA	global initiative for asthma	喘息管理の国際指針
IgE	immunoglobulin E	免疫グロブリン E
IgG_1	immunoglobulin G_1	免疫グロブリン G_1
IL-4	interleukin-4	インターロイキン-4
IL-5	interleukin-5	インターロイキン-5
IL-13	interleukin-13	インターロイキン-13
JGL	asthma prevention and management guideline, Japan	喘息予防・管理ガイドライン
PEF	peak expiratory flow	最大呼気流量，ピークフロー
QOL	quality of life	生活の質
Th2	type2 helper t cell	2 型ヘルパーT 細胞

1 起原又は発見の経緯

ゾレア皮下注用（以下，本剤と記載）は，ヒト化マウス抗ヒト IgE モノクローナル抗体であるオマリズマブ（遺伝子組換え）（以下，オマリズマブと記載）を 1 バイアル中 202.5 mg 含む皮下注射用製剤である。

免疫グロブリン E（IgE）がアレルギー性疾患の主要な因子であることが知られ，モノクローナル抗体作製技術が 1970 年代に確立した後，IgE の高親和性受容体である FcεRI に結合する IgE 上のエピトープに対するモノクローナル抗体が開発された[Baniyash, et al 1984][Baniyash, et al 1988]。Genentech, Inc.（Novartis Pharma AG の共同開発会社）は，ヒトのアレルギー性疾患の治療薬を開発する目的で，細胞膜上に結合した IgE を架橋せず，それ自身がアナフィラキシーを惹起しない非アナフィラキシー性のマウス抗ヒト IgE モノクローナル抗体の作製に着手した。当初開発されたマウス抗ヒト IgE モノクローナル抗体 MaE11 には，抗体産生によるアレルギー反応発現の問題があり，この問題を回避するため，ヒトに対して免疫原性を有しないヒト型の抗 IgE 抗体が作製され[Vaswani, et al 1998]，その中から高力価の非アナフィラキシー性抗体としてオマリズマブを選択した。

オマリズマブは，チャイニーズハムスター卵巣由来細胞で産生される，マウス抗ヒト 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マウス抗ヒト 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）である[Boulet, et al 1997][Fahy, et al 1997][Milgrom, et al 1999]。

オマリズマブの作用機序は，血中遊離 IgE の Cε3 部位（FcεRI への結合部位）に結合することにより，IgE の肥満細胞，好塩基球といった炎症細胞への結合を阻害することであり，その結果として，炎症細胞の活性化を抑制し，ヒスタミン，ロイコトリエン等の炎症性メディエーターの放出を抑制する。さらに，Th2 サイトカインの放出抑制，好酸球数の抑制，及び FcεRI の発現抑制作用も有する。これらの作用機序及び薬理作用より，本剤の I 型アレルギー疾患への有効性を期待し，アレルギー性喘息及び鼻炎を対象として，米国においては Genentech, Inc.が，欧州においては Novartis Pharma AG が，本邦においてはノバルティス ファーマ株式会社が開発を開始した。

2 気管支喘息について

2.1 気管支喘息の病態と疫学

気管支喘息は気道の慢性炎症性疾患であり，気道狭窄と気道過敏性の亢進，そして臨床的には繰り返し起こる咳，喘鳴，呼吸困難で特徴づけられ，その病型は，環境に存在するアレルゲンに対する特異的 IgE の産生を証明できるアレルギー性と証明できない非アレルギー性に分類される。

アレルギー性の気管支喘息患者では，体内で産生された抗原特異的 IgE が肥満細胞，好塩基球細胞上の高親和性 IgE 受容体（FcεRI）に結合し，抗原の再侵入により細胞上に結合している IgE

が架橋され，ヒスタミン，ロイコトリエン等の炎症性メディエーターの脱顆粒反応が起き，気道炎症及び喘息症状が惹起される。また，吸入した抗原が気道の抗原提示細胞上に提示されると，T 細胞が活性化されて，Th2 サイトカイン（IL-4，IL-5，IL-13）を産生する。これらサイトカインは，好酸球の分化・増殖，IgE の産生，接着因子の発現を増強し，気道炎症の増悪をもたらす。血清中総 IgE 値と気道過敏性には関連が認められているとの報告[Sears, et al 1991]や，喘息死患者では気道組織の粘膜固有層に浸潤している細胞に FcεRI の発現が増えているとの報告[Fregonese, et al 2004]があり，これらの報告は，気道過敏性亢進－喘息発作－喘息死という経過をたどる喘息の病態に，IgE が深く関与することを示唆するものである。

国内で医療機関を受診した気管支喘息患者数は 2002 年の厚生労働省の調査で 107 万人と推計されているが[厚生労働省 2002]，実際の患者数はその 3～4 倍は存在すると見積もられている[足立，他 2005]。成人の気管支喘息の有症率は近年急速に増加しており，1960 年代に 1%弱であったものが，現在 3%程度まで増加したとの報告がある[牧野，他 2003]。成人喘息の年齢分布は，60 歳代を中心に 50～70 歳代に多くみられる傾向があり[秋山，他 1998]，発症年齢については 20～30 歳代にやや発症頻度が高いものの，各年齢にわたってほぼ等しい頻度である[牧野，他 2003]。喘息は致死性の疾患であり，喘息による死亡者数は 2004 年で 3283 名[厚生労働省 2004]，2007 年で 2533 名 [厚生労働省 2007]と報告されている。

2.2 気管支喘息の治療

気管支喘息の管理・治療指針については，国内では 1998 年に喘息予防・管理ガイドライン「JGL1998」が発表された後，2003 年に「JGL2003」[牧野，他 2003]が発表され，2006 年の「JGL2006」[大田，他 2006]が最新のガイドラインである。欧米では，喘息管理の国際指針（Global Initiative for Asthma，GINA）[O'Byrne, et al 2005]が広く認知され，参照されている。

気管支喘息は病因の不明な体質的な疾患であり，病因の除去によって疾患の治癒を目指すことは困難な現状である。現在，到達しうると考えられる管理・治療は，気道炎症の原因の回避・除去，気流制限を惹起する因子の回避・除去，そして薬物療法による炎症の抑制と気道拡張による気道過敏性と気流制限の軽減・寛解である。JGL2003 では，喘息治療の目標として「健常人と変わらない日常生活が送れること」，「正常に近い肺機能を維持すること」，「夜間や早朝の咳や呼吸困難がなく十分な睡眠が可能なこと」，「喘息発作が起こらないこと」，「喘息死の回避」及び「治療薬による副作用がないこと」を規定している。これらの治療目標に向けて種々の喘息治療薬が推奨されているが，それらは長期管理薬及び発作治療薬に大別され，喘息の重症度に応じて 4 段階に分けた段階的薬物投与プランが採用されている。長期管理薬は，喘息発作の発現を抑制し，喘息をコントロールするための薬剤であり，発作治療薬は，長期管理薬の使用にもかかわらず喘息をコントロールしきれず，喘息発作を発現した場合に使用する薬剤である。重症度は，治療開始時の症状及び呼吸機能，過去の治療内容から総合的に決定され，その後 3 ヵ月程度，症

状の管理状況を観察したうえで治療をステップアップ又はステップダウンすることとしている[2.5.1.1.3]。

また，GINA においても，喘息の重症度に応じた段階的薬物投与プランが採用されており，重症度の判定，長時間作用型吸入 β_2 刺激薬の位置付け等に相違はあるものの，日本と欧米における気管支喘息に対する治療指針は概ね同様である。本剤は，GINA2006 において，最大の治療内容を推奨する治療ステップ 5 の長期管理薬として採用されている。

2.3 現在の気管支喘息治療における問題点

喘息治療ガイドラインにおいて第一選択薬として吸入ステロイド薬が推奨され，その普及とともに急性増悪による喘息死，ならびに入院や救急外来受診数が減少してきてはいるものの，国内での喘息死亡数（10 万人対）は 2004 年で 2.6 人であり[厚生労働省 2004]，欧米に比べても高い水準である[足立，他 2005]。1998～2003 年の 6 年間を調査対象とした喘息死特別委員会の報告[中澤，他 2004]によると，死亡前の喘息の重症度は，重症 53%，中等症 37%と中等症以上が全体の 9 割を占め，また，喘息により死亡した患者のうち，26%は過去に致死的な喘息発作を経験し，51%は重度の喘息発作による入院を経験したとされる。Tough らは，過去の気管挿管を要する発作の経験や入院の経験が，喘息死や near-death 発作の危険因子であることを報告しており[Tough, et al 1998][Tumer, et al 1998]，国内においても，重症度が高いことや過去に重度の喘息発作を経験していることは喘息死の危険因子であると認識されている。

気管支喘息患者 803 名（成人 401 名，小児 402 名）を対象とした実態電話調査[足立，他 2002]において，調査対象患者の 40%が JGL1998 改訂版でのステップ 4（重症持続型）又はステップ 3（中等症持続型）に該当した。症状コントロール状況については，成人喘息患者の 52%に日中の喘息症状が認められ，最近 1 年間の予定外の受診（入院，緊急治療を含む）の経験は 41%に，喘息による欠勤・欠席の経験は 30%に認められた。また，70%が日常生活における活動の際に何らかの制約を感じており，生活の質（QOL）が低下していた。さらに，重症持続型患者の 21%，中等症持続型患者の 11%が，自らの喘息症状の管理状況をコントロール不良と評価していた[足立，他 2002]。疾患の重症度が高くなるほど，日常社会生活活動（発作時及び非発作時の日常生活，予定・希望の実現，退職・転職，休業日数）への影響が認められ，QOL が著しく障害されている現状が明らかとなっている[秋山，他 1998]。さらに，経済的側面からみると，1 年間に入院及び救急外来受診を経験した患者ののべ人数はそれぞれ約 30 万人及び 100 万人と推計され，喘息増悪による入院及び救急外来受診が医療財政に与える負担額は 3,350 億円にのぼると算定されている[足立，他 2005]。

喘息コントロールが十分でない重症患者が依然として多く存在する背景には，喘息増悪因子を完全に回避・除去することが困難であることに加えて，現状では重症患者に対する薬物治療手段が十分でないことが挙げられる。すなわち，重症患者に対しては，吸入ステロイド薬を増量してもその有効性に限界があるほか[Harrison, et al 2004]，増量の効果が期待できるのは 6～9 ヵ月程度

であると報告されている[Bateman, et al 2004]。そこで，他の長期管理薬を含めた多剤併用による治療が施されるが，既存の長期管理薬を上乗せすることにより得られる効果はごくわずかであり[Robinson, et al 2001]，また経口ステロイド薬を追加しても完全に喘息症状をコントロールすることは困難である[森 2004]。さらに，これらの患者では治療薬による副作用が懸念され，経口ステロイド薬の長期使用では，副腎抑制，糖尿病，骨粗鬆症，クッシング症候群といった全身性副作用のほか，悪性新生物の発現リスク増大などの問題もある[Karagas, et al 2001]。ステップ 4 の治療で十分効果が得られない場合に追加使用を考慮するとされている非特異的療法（金チオリンゴ酸ナトリウム，オーラノフィン）は，気管支喘息の適応を有しておらず，再生不良性貧血や無顆粒球症などの重篤な副作用が発現する可能性もある。

これらのことから，現在の気管支喘息治療体系では，特に重症患者に対する治療が十分でないことがうかがえる。

3 開発の経緯

本剤の国内外における開発は，その作用機序よりアレルギー性喘息及びアレルギー性鼻炎への適応が考えられ，海外が先行する形で進められた。アレルギー性喘息に関する開発の経緯図を図 1.5.3-1 に示す。

臨床試験に先立ち，本薬の安全性及び有効性を動物を用いて検討する目的で，19[redacted]年より非臨床試験（薬理試験，薬物動態及び毒性試験）を Genentech, Inc.が実施した。なお，オマリズマブはヒト IgE に対する親和性とほぼ同等の親和性をカニクイザルの IgE で示すことから[2.4.3.3.2]，カニクイザルはオマリズマブの非臨床評価に適切な動物種であると考え，非臨床試験ではカニクイザルを主に使用した。

3.1 製造過程変更の経緯

本剤の開発中，原薬の製造方法の変更[2.3.S.2 (6)]及び製剤処方の変更[2.3.P.2 (2)]を行った。

本剤は，当初，[redacted]で開発が開始されたが，[redacted]製剤の必要性に伴い，凍結乾燥注射剤を開発し，処方コード G120BB の液剤（オマリズマブの濃度：[redacted]mg/mL）から処方コード G129BK の凍結乾燥注射剤（オマリズマブの濃度：[redacted]mg/mL）へ変更した。このとき，原薬の製造においても，[redacted]するため，オマリズマブ産生細胞株を[redacted]細胞株から，この細胞株と同じ親細胞（[redacted]）よりメトトレキサートの濃度を上げて培養した[redacted]細胞株へ変更した。また，製造スケールも(1)*L スケールから(2)*L スケールへ変更した。これらの剤形，処方及び原薬の製造方法変更によるオマリズマブの薬物動態及び薬力学的作用への影響を，カニクイザルでの薬物動態試験により検討した結果，変更による影響は認められなかった[2.6.4.8.1.1]。さらに，変更に伴う安全性への影響をカニクイザルでの単回投与毒性試験及びウサギでの局所刺激性試験において検討した結果，安全性プロファイルへの影響も認められなかった[2.6.6.2.3][2.6.6.7.1]。

＊：新薬承認情報提供時に置き換えた

1.5 起源又は発見の経緯及び開発の経緯

更なる[redacted]製剤の必要性により，処方コード G129BK から処方コード G136H の凍結乾燥注射剤（オマリズマブの濃度：100 mg/mL）への変更を行った。この変更によるオマリズマブの薬物動態及び薬力学的作用への影響をカニクイザルを用いた薬物動態試験において検討した結果，変更による影響は認められなかった[2.6.4.8.1.2]。

市販製剤に使用する原薬の製造方法は，19BB*年に Genentech, Inc.，[redacted]で確立された。次いで，20[redacted]年に原薬の製造場所が，Genentech, Inc.，[redacted] へ移された。CTD2.3.S.2 (6) 製造工程の開発の経緯で示すように，19BB*年に確立された製造方法とそれ以前の製造方法（19AA*年）で製造されたオマリズマブでは，その糖鎖のプロファイルに差が認められた。このため，これらの原薬から製造した製剤を用いて生物学的同等性試験を実施し，両製剤間の生物学的同等性を確認した[2.7.1.3.2.3]。

製剤は，処方コード G136H の後，処方コード G158BP，G158BZ 及び G158CF へと変更されたが，これらは，バイアル内の凍結乾燥物の充てん量が異なるのみで，再調製後の薬液中のオマリズマブの濃度（125 mg/mL）及び添加剤の濃度は同じとなるものである。

市販予定製剤は，処方コード G158CF と同じ処方の凍結乾燥注射剤で，バイアル内の減圧度を変更した処方コード GA158CF である。

＊：新薬承認情報提供時に置き換えた

図 1.5.3-1　開発の経緯図

試験項目		[redacted]
品質に関する試験	物理的化学的性質並びに規格及び試験方法	
	安定性	
薬理	効力を裏付ける試験	
吸収・分布代謝・排泄	吸収	
	分布	
毒性	単回投与	
	反復投与	
	遺伝毒性	
	生殖発生毒性	
	局所刺激性	
臨床薬理	薬物動態試験	
臨床	比較対照試験（プラセボ対照試験）	
	一般臨床試験	
	申請適応症を対象とした中止試験	
	申請する適応症以外の疾患を対象とした試験	
治験相談		

1.5 起源又は発見の経緯及び開発の経緯

試験項目		[redacted]
品質に関する試験	物理的化学的性質並びに規格及び試験方法	
	安定性	
薬理	効力を裏付ける試験	
吸収・分布代謝・排泄	吸収	
	分布	
毒性	単回投与	
	反復投与	
	遺伝毒性	
	生殖発生毒性	
	局所刺激性	
臨床薬理	薬物動態試験	
臨床	比較対照試験(プラセボ対照試験)	
	一般臨床試験	
	申請適応症を対象とした中止試験	
	申請する適応症以外の疾患を対象とした試験	
治験相談		

[redacted]

3.2 海外での開発経緯

海外では，検証試験として，中用量以上の吸入ステロイドの連日投与と吸入短時間作用型 β_2 刺激薬の必要時又は定期使用においても症状が安定しない中等症から重症持続型のアレルギー性喘息患者を対象に，2 つの無作為化二重盲検プラセボ対照並行群間比較第 III 相試験（008 及び 009 試験）を実施した。いずれの試験においても，本剤群はプラセボ群に比較して喘息増悪頻度を有意に減少させることが検証されたことから，これらを主要試験成績として 20[redacted]年[redacted]月に Genentech, Inc.が米国において，Novartis Pharma AG が欧州において，それぞれ承認申請を行った。その結果，米国では 2003 年 6 月に「吸入ステロイドの投与にもかかわらず症状が安定しない 12 歳以上の中等症から重症持続型のアレルギー性喘息患者における喘息増悪頻度の抑制」の適応で承認を取得した。一方，1997 年から 2000 年にかけて喘息の標準的治療は進歩し，2000 年当時には，前述の 008 及び 009 試験に参加した被験者と同様な重症度の患者は，吸入長時間作用型 β_2 刺激薬等の他の治療も受けられるようになっていた。このような医療環境の変化を踏まえ，欧州においては，Committee for Proprietary Medicinal Products（CPMP）との協議により，本剤によって最良のリスクベネフィットが得られる患者集団は，最も高度な治療においても十分な治療効果の得られない，喘息死リスクの高い患者集団に制限すべきであるとの結論を得た。そこで，申請を取り下げるとともに，新たな検証試験として，GINA2002 ガイドラインで定義されるステップ 4 治療，すなわち少なくとも 3 ヵ月間高用量吸入ステロイドと吸入長時間作用型 β_2 刺激薬を併用しても，2 回以上の喘息悪化もしくは重度の喘息悪化を経験した重症持続型のアレルギー性喘息患者を対象とした無作為化二重盲検プラセボ対照並行群間比較試験（2306 試験）を 20[redacted]年[redacted]月より実施した。その結果，当該患者層においても，本剤による喘息増悪頻度の抑制効果が確認されたことから，20[redacted]年[redacted]月に再度[redacted]を行い，2005 年 10 月に「高用量吸入ステロイドと吸入長時間作用型 β_2 刺激薬を併用しているにもかかわらず複数回の喘息の増悪を経験し，頻回の日中症状もしくは睡眠障害とともに呼吸機能の低下（FEV_1 が予測正常値の 80%未満）を伴う 12 歳以上の重症持続型のアレルギー性喘息患者における喘息症状の改善のための追加療法」の適応で承認を取得した。

なお，20[redacted]年[redacted]月の欧米での承認申請時には，[redacted]も含めて申請を行ったが，[redacted]こと，及び[redacted]という理由からこれらの申請は取り下げている。

また，長期投与時の悪性新生物発生リスクを検討するために，米国において，中等症持続型及び重症持続型のアレルギー性喘息患者を対象とした 5 年間の前向きコホート研究（Q2948g 試験）を 20[redacted]年[redacted]月より実施している[2.5.5.3.1]。

2008 年 8 月現在，アレルギー性喘息治療薬として，米国，欧州，オーストラリア，カナダをはじめとして世界 70 ヵ国において承認を取得している[1.6]。また，GINA2006 においては，最大の

治療内容を推奨する治療ステップ 5 の長期管理薬の一つとして採用されており，薬理学の教科書[Goodman & Gilman 2005]においても新たな喘息治療薬として紹介されている。

3.3 国内での開発経緯

本邦においては，1999 年[redacted]月から 20[redacted]年[redacted]月に，健康成人男子を対象に第 I 相試験（1101 試験）を実施し，日本人での本剤の安全性及び忍容性，薬物動態を確認した。また 1101 試験と海外探索的試験（006 試験）において，本剤の薬物動態と血清中遊離 IgE 濃度に対する薬理効果は，人種の違いによる影響を受けないことを確認し，その結果に基づき，海外臨床試験成績より設定された臨床推奨用量及び投与量換算表を国内臨床試験に適応して，以後の開発を進めることとした。

1101 試験終了後，海外臨床試験成績を日本人へ外挿する可能性について[redacted]相談を 20[redacted]年[redacted]月[redacted]日に実施した。その結果，[redacted]について十分検討するように指摘された。さらに，[redacted]すること，[redacted]すること，等についても検討すべき点として挙げられた[5.4.1]。

前述の治験相談の指摘を踏まえ，海外でのアレルギー性喘息患者を対象とした検証試験（[redacted]）とのブリッジング試験として，国内 1301 試験を実施した。対象患者は，中用量以上の吸入ステロイドの連日投与と吸入短時間作用型 β_2 刺激薬の必要時又は定期使用においても症状が安定しないアレルギー性の気管支喘息患者とし，喘息増悪頻度を主要評価項目としてプラセボを対照に比較検討した。しかし，[redacted]，治験実施計画が国内の医療実態にそぐわないものであったことから被験者の組み入れができず，予定被験者数の登録が完了する前に試験を中止した。

そこで，日本の医療実態に合わせた評価を行うことを主眼において，新たな検証試験として 2003 年 2 月から 2005 年 5 月にかけて 1304 試験を実施した。試験デザインは無作為化二重盲検プラセボ対照並行群間比較試験とし，既存治療に本剤を追加したときの有効性及び安全性を評価した。対象患者は，JGL1998 で推奨される治療においても症状が安定しない中等症から重症持続型と診断されたアレルギー性の気管支喘息患者とし，高用量吸入ステロイドに加えて 1 剤以上の長期管理薬あるいは経口ステロイドを併用していることを選択基準の一つとした。当該試験における患者層で喘息増悪頻度の抑制効果を評価するには長期の評価期間が必要であり，さらに，評価に適格な症例の組み入れも困難であると予想されたことから，喘息コントロールの状況を客観的に示し，本邦において喘息治療薬の薬効判定に標準的に用いられている朝のピークフロー（PEF）を主要評価項目とした。副次的評価項目として他の呼吸機能値（夜の PEF，等）や喘息

1.5 起源又は発見の経緯及び開発の経緯

症状点数などのスコア評価，レスキュー薬の使用回数などを設定した。さらに喘息増悪に関する項目として，喘息増悪による試験中止症例数及び中止までの期間，喘息悪化週の経験数を探索的に評価した。その結果，主要評価項目である朝の PEF はプラセボと比較して有意に改善し，その他の呼吸機能や症状の改善，喘息増悪の抑制などにおいても本剤の有効性が示された。安全性については，臨床上特に問題となるような有害事象の発現や臨床検査値の変動は認められなかった[2.5]。

また，本剤の長期投与による安全性を評価することを目的として 48 週間非盲検試験（1307 試験）を 2003 年 11 月より実施した。

なお，季節性アレルギー性鼻炎患者に関する第 III 相試験終了後，[redacted]の妥当性について，20[redacted]年[redacted]月[redacted]日に[redacted]相談を実施した。その結果，[redacted]との助言を得た。さらに，[redacted]との助言も得た[5.4.2]。

これらの助言に基づき，国内外での薬物動態及び薬理効果の関係を詳細に確認し，開発の経緯の妥当性を検証するため，日本人と外国人での国際共同試験（2206 試験）を実施すると共に，国内外臨床試験の薬物動態及び薬理効果データを用いた作用機序に基づく母集団薬物動態－薬理効果の解析を実施した。その結果，本剤の薬物動態－薬理効果は，投与前血清中 IgE 濃度と体重の影響を除き，その他の内因性民族的要因及び疾患の違いの影響を受けないことを確認し，海外臨床試験成績で設定された臨床推奨用量及び投与量換算表を国内臨床試験に適用することの妥当性を確認した[2.7.2]。さらに，欧州での承認取得適応症並びに現在の国内の医療実態を踏まえ，既存治療においても症状が安定せず追加治療手段が乏しい患者は，喘息増悪による喘息死のリスクが高いことから，本剤の治療の対象になると考え，1304 試験に組み入れた被験者のうち，JGL2003 によるステップ 4 の治療を受けているにもかかわらず治療目標を達成できていない被験者を，本剤のリスク・ベネフィットが得られる患者と考え，更なる評価を行った。その結果，より重症度の高い集団においても，本剤の有効性が示された。

これらの結果を受けて，20[redacted]年[redacted]月[redacted]日に，[redacted]について[redacted]相談を実施した。その結果，[redacted]ことが妥当と考える。また，[redacted]

[redacted]との回答を得た。さらに[redacted]との回答も得た。また，本邦での承認申請に際しては[redacted]，等の助言も得た[5.4.3]。

以上の経緯より，本邦においても海外と同様に，既存治療で効果不十分な気管支喘息に対し，本剤の有用性は証明されたと判断し，申請するに至った。48 週間長期投与時の安全性及び有効性を検討している国内 1307 試験については，24 週間の中間集計結果をもって申請し，申請後，48 週間の結果を提出した。なお，20[redacted]年[redacted]月から 20[redacted]年[redacted]月まで[redacted]と共同で国内 1304 及び 1307 試験を実施したが，試験終了後，[redacted]との共同開発契約を解消した[1.3.6][1.3.7]。また，[redacted]の開発については，海外での開発状況を踏まえ，現在新たな臨床試験は計画・実施していない。

現在まで，本邦において計 285 名の喘息患者に本剤は投与され，その有効性及び安全性が示されている。さらに，市販後計画として，市販直後調査，再審査期間中の自発報告に加え，全例を対象とした特定使用成績調査（長期）を計画している[1.11]。

4 特徴及び有用性

現在の気管支喘息治療体系における高用量吸入ステロイド及び他の複数の治療薬の併用下でも持続的な症状がある重症気管支喘息患者では，他の喘息患者と比較して，喘息増悪，入院及び死亡のリスクが高く，それらのリスクを軽減するために可能な限りの治療が試みられるものの管理は困難であり，喘息症状を抑えるには十分ではないのが現状である。本剤は，抗ヒト IgE モノクローナル抗体であり，血中遊離 IgE に特異的に結合し，これを不活化することから，喘息治療に対して既存の治療薬とは異なる機序により効果を示す。

国内臨床試験において，既存治療でも効果不十分な中等症から重症の気管支喘息患者を対象に，本剤を上乗せして投与したときの有効性及び安全性を検討した。試験全体集団のうち，高用量吸入ステロイド及び他の複数の治療薬の併用下でも持続的な症状がある重症気管支喘息患者部分集団における検討の結果，以下のベネフィットを得た。

- 本剤は，既存治療においても症状が安定せず追加治療手段が乏しい重症の気管支喘息患者の呼吸機能を改善する

投与開始時からの朝の PEF の平均変化量は，本剤群 13.92 L/min，プラセボ群 3.15 L/min と群間差は 10.77 L/min であり，朝の PEF を有意に改善した。さらに，朝の PEF について，JGL2003 に提唱されているゾーン分類で 1 段階以上の改善が認められた被験者の割合は，本剤群 15.7%，プラセボ群 4.4%であり，本剤群でゾーンが改善した被験者が多かった。

1.5 起源又は発見の経緯及び開発の経緯

- 本剤は，既存治療においても症状が安定せず追加治療手段が乏しい重症の気管支喘息患者の喘息増悪の発現を抑制する

喘息増悪による中止例数は，本剤群 5/70 名，プラセボ群 9/91 名と，本剤群で少なく，さらに大発作，中発作もしくは小発作のいずれかの喘息症状を経験した週を喘息悪化週と定義した時，喘息悪化週の頻度は本剤群で有意に少なかった。

- 本剤は，既存治療においても症状が安定せず追加治療手段が乏しい重症の気管支喘息患者の喘息症状を改善し，レスキュー薬の使用を減少させる

症状点数，日常生活点数，夜間睡眠点数の改善では，群間に統計学的な有意差は認められなかったが，いずれも本剤群で点数の減少が大きかった。症状点数が 0 である週を 1 回以上経験した被験者の割合は，本剤群 58.1%，プラセボ群 33.3%であり，本剤群で有意に多かった。さらに，「喘息症状がない（症状点数 0 点）」，「日常生活の障害がない（日常生活点数 0 点）」，「夜間症状がない（夜間睡眠点数 0 点）」，「レスキュー薬の使用がない」の基準をすべて満たし，かつ，「喘息増悪による中止」が認められない週を「Controlled Week」と定義した時，「Controlled Week」の頻度は，本剤群で有意に多かった。また，レスキュー薬の使用量は，本剤群 -1.74 puff，プラセボ群 -0.35 puff で，統計学的な有意差は認められなかったが，本剤群でより少なかった。

一方，リスクに関しては，国内臨床試験において，呼吸器系炎症疾患，感染症及び注射部位反応が比較的高頻度に認められた。呼吸器系炎症疾患は，気管支喘息患者に一般的にみられるものであり，本剤投与に起因した可能性は低いと考えられた。注射部位反応は，本剤群でやや発現率が高い傾向であったが，その重症度は低く，注射当日又は翌日に発現し，そのほとんどが無処置にて短期間で消失したことから，本剤の実用性を損なうような事象ではないと判断した。その他，本剤投与に伴うリスクとして，本剤が生物学的製剤であることに起因するアナフィラキシー反応及び抗オマリズマブ抗体産生の可能性，薬理作用に基づくと考えられる寄生虫感染症，悪性新生物の発現頻度を増大させる可能性，及び非臨床試験で認められた血小板数減少が挙げられた。しかしながら，これらの有害事象は発現頻度が低く，比較対照群との間に統計学的に差はなかった。従って，これらの情報および対処法を，医師及び患者に提供し，慎重に観察することにより本剤は安全に使用できるものと考えている。

以上，本剤は，高用量吸入ステロイドに複数の喘息治療薬を併用しても十分な喘息症状の安定が得られないアレルギー性の気管支喘息患者に対する追加療法として，良好なリスク・ベネフィットのバランスを持つ臨床的に極めて有用な薬剤である。

5　まとめ

国内で実施した臨床試験での有効性成績及び国内外臨床試験からの安全性成績を基に総合的に検討し，下記の内容で承認申請を行うこととした。

【申 請 品 目】ゾレア皮下注用

【一般的名称】オマリズマブ（遺伝子組換え）

【効能又は効果(案)】気管支喘息（既存治療によっても喘息症状をコントロールできない難治の患者に限る）

【用法及び用量(案)】通常，成人にはオマリズマブ(遺伝子組換え)として 1 回 75～375 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)							
	>30～40	>40～50	>50～60	>60～70	>70～80	>80～90	>90～125	>125～150
≥ 30～100	75 mg	150 mg	150 mg	150 mg	150 mg	150 mg	300 mg	300 mg
>100～200	150 mg	300 mg	300 mg	300 mg	300 mg	300 mg		
>200～300	225 mg	300 mg	300 mg					
>300～400	300 mg							
>400～500	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							
>500～600								
>600～700								

2 週間毎投与

投与前の血清中総 IgE 濃度（IU/mL）	体重 (kg)							
	>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							
>100～200	従い投与すること						225 mg	300 mg
>200～300				225 mg	225 mg	225 mg	300 mg	375 mg
>300～400		225 mg	225 mg	225 mg	300 mg	300 mg		
>400～500	225 mg	225 mg	300 mg	300 mg	375 mg	375 mg		
>500～600	225 mg	300 mg	300 mg	375 mg	投与不可			
>600～700	225 mg	300 mg	375 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。

なお，本剤が適正に使用されるよう下記の効能又は効果に関連する使用上の注意（案）を設定した。

【効能又は効果に関連する使用上の注意（案）】

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。

- 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

また，本剤は凍結乾燥製剤であり適切な量の注射用水により投与液を作製すること，投与量は初回投与前の血清中総 IgE 濃度及び体重を基に算出すること，並びに投与量算出にあたり簡便化を図ることを目的として，下記の用法及び用量に関連する使用上の注意（案）を設定した。

【用法及び用量に関連する使用上の注意（案）】

1. 本剤 1 バイアルあたり 1.4 mL の日局注射用水で溶解する。溶液 1.2 mL がオマリズマブ（遺伝子組換え）150 mg に相当する。
2. 投与量並びに投与間隔は，初回投与前の血清中総 IgE 濃度及び体重を基に，投与量換算表により設定し，投与量換算表に該当しない患者への投与は行わないこと。
3. 本剤投与中に体重が変化した場合には，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。ただし，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。
4. 本剤投与中に喘息症状の改善が認められた場合においても，投与量換算表により設定された投与量を変更しないこと。

6 参考文献

[Baniyash M, Eshhar Z (1984)] Inhibition of IgE binding to mast cells and basophils by monoclonal antibodies to murine IgE. Eur J Immunol; 14:799–807 [4.3-4].

[Baniyash M, Kehry M, Eshhar Z (1988)] Anti-IgE monoclonal antibodies directed at the Fcε receptor binding site. Mol Immunol; 25:705–11 [4.3-5].

[Bateman ED, Boushey HA, Bousquet J, et al (2004)] Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control Study. Am J Respir Crit Care Med; 170 (8): 836-844 [5.4-5].

[Boulet L-P, Chapman KR, Cote J, et al (1997)] Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. Am J Respir Crit Care Med; 155:1835–1840 [4.3-6].

[Fahy JV, Fleming HE, Wong HH, et al (1997)] The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. Am J Respir Crit Care Med; 155:1828–34 [4.3-12].

[Fregonese L, Patel A, Schadewijk A, et al (2004)] Expression of the high-affinity IgE receptor (FcεRI) is increased in fatal asthma. Am J Respir Crit Care Med; 169 (7); A297 [5.4-8].

[Goodman & Gilman (2005)] The Pharmacological Basis of Therapeutics, 11th Edition. Chapter 27, 2005 updated [5.4-9].

[Harrison TW, Oborne J, Newton S, et al (2004)] Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomised controlled trial. Lancet; 363 (9405): 271-275 [5.4-10].

[Karagas MR, Cushing GL, Greenberg ER, et al (2001)] Non-melanoma skin cancers and glucocorticoid therapy. Br J Cancer; 85(5): 683-686 [5.4-12].

[Milgrom H, Fick RB Jr, Su JQ, et al (1999)] Treatment of allergic asthma with monoclonal anti-IgE antibody. New Eng J Med; 341:1966–73 [4.3-31].

[O'Byrne P, Bateman ED, Busse W, et al (2005)] Global Initiative for Asthma (updated 2005) [5.4-17].

[Robinson DS, Campbell D, Barnes PJ (2001)] Addition of leukotriene antagonists to therapy in chronic persistent asthma: a randomised double-blind placebo-controlled trial. Lancet; 357 (23): 2007-2011 [5.4-20].

[Sears MR, Burrows B, Flannery EM, et al (1991)] Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. N Engl J Med; 325 (15): 1067-1071 [5.4-21].

[Tough SC, Hessel PA, Ruff M, et al (1998)] Features that distinguish those who die from asthma from community controls with asthma. J Asthma; 35 (8): 657-65 [5.4-22].

[Turner MO, Noertjojo K, Vedal S, et al (1998)] Risk factors for near-fatal asthma. A case-control study in hospitalized patients with asthma. Am J Respir Crit Care Med; 157 (6): 1804-1809 [5.4-23].

[Vaswani SK, Hamilton RG (1998)] Humanized antibodies as potential therapeutic drugs. Ann Allergy Asthma Immunol; 81:105–19 [4.3-44].

[秋山 (1998)] 国立病院治療共同研究・国立療養所中央研究 研究報告書. 我が国の気管支喘息患者の実態調査－小児喘息及び成人喘息－ [5.4-27].

[足立，森川，石原 (2002)] 日本における喘息患者実態電話調査. アレルギー; 51 (5): 411-420 [5.4-28].

[足立，福田，森川，他 (2005)] 日本における喘息死と喘息の疾病負担. アレルギー・免疫; 12 (10): 1438-1447 [5.4-29].

[大田，冨岡，西間，他 (2006)] 「喘息予防・管理ガイドライン 2006」作成委員会　喘息予防・管理ガイドライン 2006 : 1-9, 95-109. [5.4-46]

[厚生労働省(2002)] 厚生労働省大臣官房統計情報部人口動態 - 保健統計課 - 人口動態統計 2002［第 5 表-15 性・年齢別にみた死因年次推移分類別死亡数及び率（人口 10 万対）］

[厚生労働省(2004)] 厚生労働省大臣官房統計情報部人口動態 - 保健統計課 - 人口動態統計 2004［第 1 表-1 死亡数，性・年齢（5 歳階級）・死因（三桁基本分類）別］

[厚生労働省 (2007)] 厚生労働省大臣官房統計情報部人口動態 - 保健統計課 - 人口動態統計 2007［第 6 表　死亡数・死亡率（人口 10 万対），死因簡単分類別］. [5.4-48]

Available from <http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/geppo/nengai07/index.html>

[中澤，松井，赤坂，他 (2004)] 喘息死特別委員会報告. アレルギー; 53 (12): 1216-1219 [5.4-33].

[牧野，古庄，宮本，他 (2003)] 厚生省免疫・アレルギー研究班　喘息予防・管理ガイドライン 2003.（JGL1998 改訂第 2 版）: 1-26, 71-91 [5.4-34].

[森 (2004)] 難治性喘息とは. 日本胸部臨床; 63 (9): 821-831 [5.4-36].

1.6　外国における使用状況等に関する資料

目　次

1　外国における使用状況等

本剤は 20■年■月にアレルギー性喘息の治療薬として，オーストラリア，米国，欧州で承認申請した。オーストラリアでは 2002 年 6 月に，「吸入ステロイド剤による治療を受けており血清 IgE 値が上昇している成人及び青少年の，中等症のアレルギー性喘息の管理」を適応として承認され，米国では 2003 年 6 月に「吸入ステロイドの投与にもかかわらず症状が安定しない 12 歳以上の中等症から重症持続型のアレルギー性喘息患者における喘息増悪頻度の抑制」の適応で承認を取得した。欧州では，Committee for Proprietary Medicinal Products（CPMP）との協議により，20■年■月に申請を取り下げ，追加試験を実施後，20■年■月に再度承認申請を行い，2005 年 10 月に「高用量吸入ステロイドと吸入長時間作用型 β_2 刺激薬を併用しているにもかかわらず複数回の喘息の増悪を経験し，頻回の日中症状もしくは睡眠障害とともに呼吸機能の低下（FEV_1 が予測正常値の 80%未満）を伴う 12 歳以上の重症持続型のアレルギー性喘息患者における喘息症状の改善のための追加療法」の適応で承認を取得した。

2008 年 8 月現在，アレルギー性喘息治療薬として，米国，欧州，オーストラリア，カナダをはじめとして世界 70 カ国において承認されている。

主要国における状況を，表 1.6.1-1 に示す。（外国における販売名；Xolair®）

表 1.6.1-1　主要国における承認状況

国名	承認年月日	承認剤型	承認効能	用法・用量
オーストラリア	2002 年 6 月 13 日	皮下注用 150mg	Xolair は，吸入ステロイド剤による治療を受けており血清 IgE 値が上昇している成人及び青少年の，中等症のアレルギー性喘息の管理に適応される。	用量換算表に従い投与する。用量換算表：表 1.6.1-2
米国	2003 年 6 月 20 日	皮下注用 150mg	Xolair（オマリズマブ）は，中等症～重症持続性喘息を有する成人及び青少年（12 歳以上）のうち，1 種類以上の通年性吸入抗原に陽性反応又は *in vitro* 反応性を示し，かつ吸入コルチコステロイドで症状が十分にコントロールされない患者に適応される。Xolair はこれらの患者において喘息増悪の発現率を低下させることが示されている。他のアレルギー性疾患に対する安全性及び有効性は確立されていない。	用量換算表に従い投与する。用量換算表：表 1.6.1-3,1.6.1-4
カナダ	2004 年 11 月 18 日	皮下注用 150mg	Xolair（オマリズマブ）は，中等症～重症持続性喘息を有する成人及び青少年（12 歳以上）のうち，1 種類以上の通年性吸入抗原に陽性反応又は *in vitro* 反応性を示し，かつ吸入コルチコステロイドで症状が十分にコントロールされない患者に適応される。Xolair はこれらの患者においていちじるしく喘息増悪の発現率を低下させることと喘息症状のコント	用量換算表に従い投与する。用量換算表：表 1.6.1-5,1.6.1-6

1.6 外国における使用状況等に関する資料

国名	承認年月日	承認剤型	承認効能	用法・用量
			ロールを改善することが示されている。ほかのアレルギー状態に対する安全性及び有効性は確立されていない。	
EU	2005年10月25日	皮下注用 75mg, 150mg	Xolairは，1種類以上の通年性吸入抗原に対する陽性皮膚反応は，*in vitro*反応性，肺機能低下（FEV_1<80%）及び頻繁な昼間症状または夜間覚醒がみられ，かつ高用量吸入コルチコステロイドの連日投与と長時間作用型吸入β2刺激薬の併用にも関わらず重度の喘息増悪が繰り返しみられる重症持続性アレルギー性喘息の成人及び青少年（12歳以上）の喘息コントロールを改善するための追加療法として適応される。Xolairの投与は，IgE介在性喘息と考えられる患者でのみ検討すること。	用量換算表に従い投与する。用量換算表：表1.6.1-7,1.6.1-8

2006年4月27日現在

表 1.6.1-2　投与量換算表（オーストラリア）：成人及び青少年（12歳以上）のアレルギー喘息患者への皮下注射による Xolair の投与量

ベースラインの IgE 濃度 (IU/mL)	4週間隔当たりに必要な Xolair の総投与量（mg） 体重（kg）						
	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-150
>30-100	150	150	150	150	150	150	300
>100-200	150	300	300	300	300	300	450
>200-300	300	300	300	450	450	450	600
>300-400	300	450	450	450	600	600	
>400-500	450	450	600	600	750	750	
>500-600	450	600	600	750			
>600-700	450	600	750				
>700-800	600	750	注記：				
>800-900	600	750	4週間隔当たりの用量が300 mg以下の場合は，4週毎に1回投与する。				
>900-1000	750						
>1000-1100	750		4週間隔当たりの用量が300 mgを超える場合は，2分割して2週毎に等用量ずつ投与する（すなわち計600 mgは2週毎に300 mgずつ）。				
>1100-1200							
>1200-1300							

表 1.6.1-3　投与量換算表（米国）：4 週間隔投与。喘息の成人及び青少年患者（12 歳以上）に対する 4 週毎の皮下注射による Xolair の投与量（mg）

投与前の血清中 IgE 濃度（IU/mL）	体重（kg）			
	30-60	>60-70	>70-90	>90-150
≥30-100	150	150	150	300
＞100-200	300	300	300	
＞200-300	300			
＞300-400	表 1.6.1-4 参照			
＞400-500				
＞500-600				

表 1.6.1-4　投与量換算表（米国）：2 週間隔投与。喘息の成人及び青少年患者（12 歳以上）に対する 2 週毎の皮下注射による Xolair の投与量（mg）

投与前の血清中 IgE 濃度（IU/mL）	体重（kg）			
	30-60	>60-70	>70-90	>90-150
≥30-100				
＞100-200				225
＞200-300		225	225	300
＞300-400	225	225	300	
＞400-500	300	300	375	
＞500-600	300	375	投与しないこと	
＞600-700	375			

表 1.6.1-5　投与量換算表（カナダ）：4 週間隔投与。4 週毎の皮下投与による Xolair の投与量（1 回投与量 [mg]）

	体重(kg)								
ベースラインの IgE 濃度*	>20–30	>30–40	>40–50	>50–60	>60–70	>70–80	>80–90	>90–125	>125-150
≥30–100 IU/mL 又は ≥72 -240 ng/mL	150	150	150	150	150	150	150	300	300
>100–200 IU /mL 又は >240-480 ng/mL	150	150	300	300	300	300	300		
>200–300 IU/mL 又は >480-720 ng/mL	150	300	300	300					
>300–400 IU/mL 又は >720-960 ng/mL	300	300			2 週間隔投与の表を参照				
>400–500 IU/mL 又は >960-1200 ng/mL	300								
>500–600 IU/mL 又は >1200-1440 ng/mL	300								
>600–700 IU/mL 又は >1440-1680 ng/mL									

*1 IU /mL = 2.4 ng/mL = 2.4 mcg / L

表 1.6.1-6　投与量換算表（カナダ）：2 週間隔投与。2 週毎の皮下投与による Xolair の投与量（1 回投与量 [mg]）

	体重(kg)								
ベースラインの IgE 濃度*	>20–30	>30–40	>40–50	>50–60	>60–70	>70–80	>80–90	>90-125	>125–150
≥30-100 IU/mL 又は ≥72-240 ng/mL	4 週間隔投与の表を参照								
>100–200 IU/mL 又は >240-480 ng/mL								225	300
>200–300 IU/mL 又は >480-720 ng/mL					225	225	225	300	375
>300–400 IU/mL 又は >720-960 ng/mL			225	225	225	300	300		
>400–500 IU/mL 又は >960-1200 ng/mL		225	225	300	300	375	375		
>500–600 IU/mL 又は >1200-1440 ng/mL		225	300	300	375	投与しないこと			
>600–700 IU/mL 又は >1440-1680 ng/mL	225	225	300	375					

*1 IU /mL = 2.4 ng/mL = 2.4 mcg / L

表 1.6.1-7　投与量換算表（欧州）：4 週間隔投与。4 週毎の皮下投与による Xolair の投与量（1 回投与量 [mg]）

	体重（kg）									
ベースラインの IgE 濃度（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		
>200-300	150	150	225	300	300					
>300-400	225	225	300							
>400-500	225	300				2 週間隔投与				
>500-600	300	300				表 1.6.1-8 参照				
>600-700	300									

表 1.6.1-8　投与量換算表（欧州）：2 週間隔投与。2 週毎の皮下投与による Xolair の投与量（1 回投与量 [mg]）

ベースラインの 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	4 週間隔投与 表 1.6.1-7 参照									
>100-200									225	300
>200-300						225	225	225	300	375
>300-400				225	225	225	300	300		
>400-500			225	225	300	300	375	375		
>500-600			225	300	300	375	投与しないこと - 推奨用量に関するデータがない			
>600-700		225	225	300	375					

1.1　外国における他の効能についての開発状況

外国においては，現在までにアレルギー性鼻炎，アトピー性皮膚炎及び食物アレルギーについて臨床試験が実施されている。

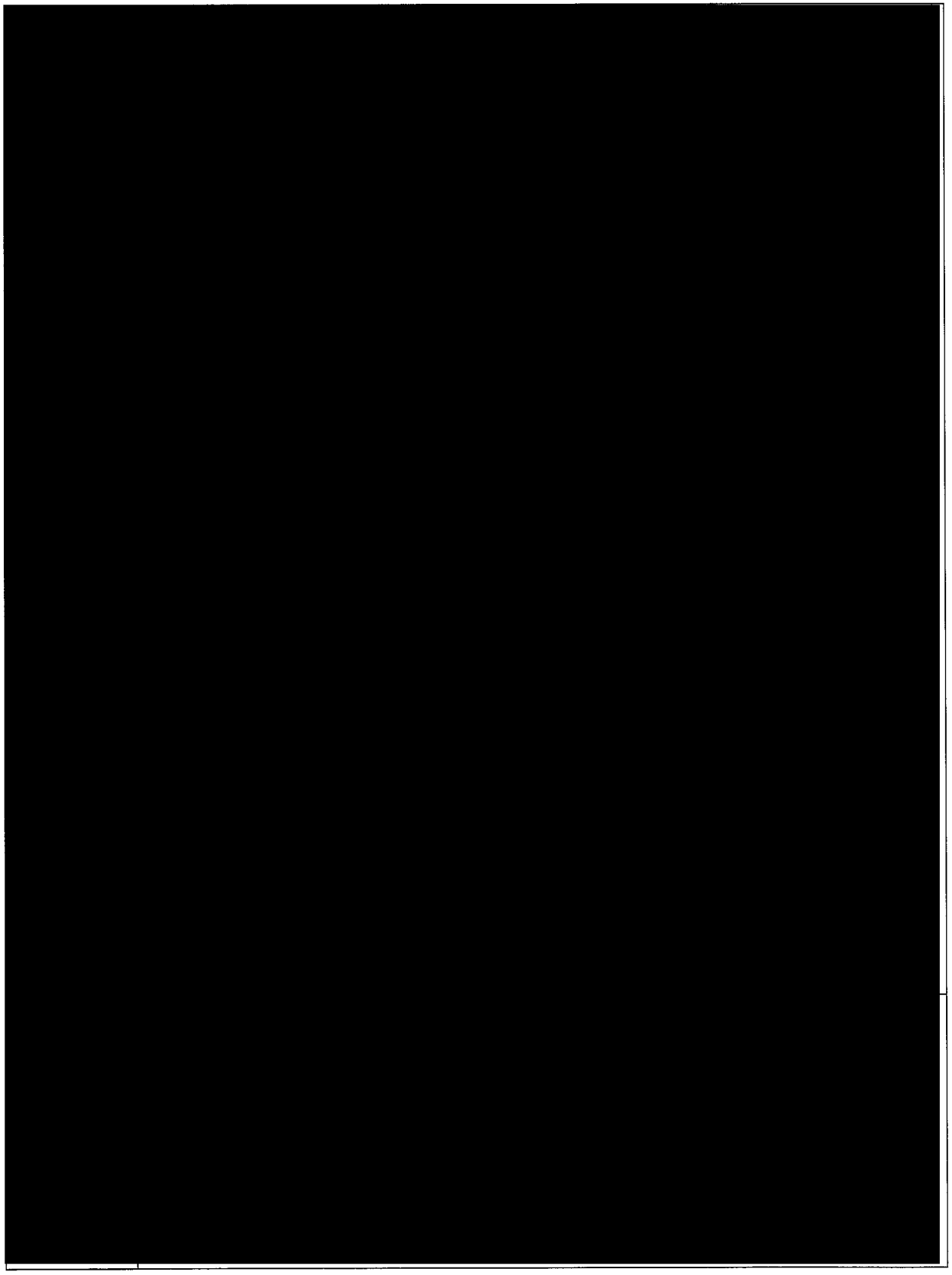
2　　外国の添付文書等の概要

スイス ノバルティス ファーマ社の企業中核データシート（CCDS / Basic Prescribing Information, 20[redacted]年[redacted]月[redacted]日）の概略を表 1.6.2-1 に，米国の添付文書（2008 年 7 月改訂）の概略を表 1.6.2-2 に，EU の製品概要（SmPC / **Summary of Product Characteristics**）（2007 年 5 月 30 日）の概略を表 1.6.2-3 に示す。

表 1.6.2-1　　CCDS の概略

販売名	Xolair® 75 mg powder and solvent for solution for injection. Xolair® 150 mg powder and solvent for solution for injection.
[redacted]	

1.6 外国における使用状況等に関する資料



1.6 外国における使用状況等に関する資料

[redacted]

1.6 外国における使用状況等に関する資料

[redacted]

1.6 外国における使用状況等に関する資料

[redacted]	[redacted]
[redacted]	[redacted]

表 1.6.2-2　　米国の添付文書の概略

<table>
<tr><td>販売名</td><td>Xolair®</td></tr>
<tr><td>剤型・含量</td><td>注射用凍結乾燥粉末製剤　150mg</td></tr>
<tr><td>効能・効果</td><td>Xolair（オマリズマブ）は，中等症～重症持続性喘息を有する成人及び青少年（12歳以上）のうち，1種類以上の通年性吸入抗原に陽性皮膚反応又は in vitro 反応性を示し，かつ吸入コルチコステロイドで症状が十分にコントロールされない患者に適応される。Xolairは，これらの患者において喘息増悪の発現率を低下させることが示されている。他のアレルギー性疾患に対する安全性及び有効性は確立されていない。</td></tr>
<tr><td>用法・用量</td><td>Xolair（オマリズマブ）150～375mgを2又は4週間毎に皮下投与する。本溶液はわずかに粘性があるため，注射するのに5～10秒を要する場合がある。投与量(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）により決定する。適切な用量の割り当てについては以下の投与量換算表（表1及び表2）を参照されたい。1回につき150mgを超えて投与する場合には，1箇所あたり150mgを超えないように注射部位を分けて投与すること。
継続療法の必要性については，患者の疾患重症度及び喘息コントロールのレベルに基づき，定期的に再評価するものとする。
表1：4週間隔投与
喘息の成人及び青少年患者（12歳以上）に対する4週毎の皮下注射によるXolairの投与量(mg)
<table>
<tr><td rowspan="2">投与前の血清中IgE濃度（IU/mL）</td><td colspan="4">体重（kg）</td></tr>
<tr><td>30－60</td><td>>60－70</td><td>>70－90</td><td>>90－150</td></tr>
<tr><td>≥30－100</td><td>150</td><td>150</td><td>150</td><td>300</td></tr>
<tr><td>>100－200</td><td>300</td><td>300</td><td>300</td><td></td></tr>
<tr><td>>200－300</td><td>300</td><td colspan="3" rowspan="4">表2参照</td></tr>
<tr><td>>300－400</td></tr>
<tr><td>>400－500</td></tr>
<tr><td>>500－600</td></tr>
</table>
表2：2週間隔投与
喘息の成人及び青少年患者（12歳以上）に対する2週毎の皮下注射によるXolairの投与量(mg)
<table>
<tr><td rowspan="2">投与前の血清中IgE濃度（IU/mL）</td><td colspan="4">体重（kg）</td></tr>
<tr><td>30－60</td><td>>60－70</td><td>>70－90</td><td>>90－150</td></tr>
<tr><td>≥30－100</td><td></td><td></td><td></td><td></td></tr>
<tr><td>>100－200</td><td></td><td></td><td></td><td>225</td></tr>
<tr><td>>200－300</td><td></td><td>225</td><td>225</td><td>300</td></tr>
<tr><td>>300－400</td><td>225</td><td>225</td><td>300</td><td></td></tr>
<tr><td>>400－500</td><td>300</td><td>300</td><td>375</td><td></td></tr>
<tr><td>>500－600</td><td>300</td><td>375</td><td colspan="2">投与しないこと</td></tr>
<tr><td>>600－700</td><td>375</td><td colspan="3"></td></tr>
</table>
用量調節
総IgE濃度は投与中に上昇し，投与中止から1年が経過しても上昇したままの場合がある。このため，Xolairの投与中に再測定したIgE濃度は用量設定の指標として使用することはできない。1年未満の投与中断後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IgE濃度に基づいて用量を設定すること。Xolairの投与中断期間が1年以上の場合は，用量設定のために血清中総IgE濃度を再測定してもよい。
体重が大きく変化した場合には，用量を調節すること （表1及び表2参照）。</td></tr>
<tr><td></td><td></td></tr>
</table>

1.6 外国における使用状況等に関する資料

使用上の注意	**警告** 気管支けいれん，低血圧，失神，蕁麻疹や咽喉もしくは舌の血管浮腫として発現するアナフィラキシーが，Xolairの投与後に生じたと報告されている。アナフィラキシーはXolairの初回投与後早期に発生しているが，定期的投与による治療開始から，1年以上経過してから生じている場合もある。Xolair投与後は，アナフィラキシーのリスクがあるため，適当な期間は厳重に患者を観察するべきであり，Xolairを投与する際，医療従事者は生命を脅かしうるアナフィラキシーを治療する態勢を整えておくべきである。さらに患者には，アナフィラキシーの徴候や症状について知らせ，もし症状が生じたら速やかに治療を受けるよう指導しておく（*「警告，使用上の注意，患者のための情報」参照*）。 **禁忌** 本剤に対する重度の過敏症の既往歴を有する患者に投与してはならない（*「警告：アナフィラキシー」参照*）。 **警告** **アナフィラキシー** 市販前臨床試験及び市販後の自発報告において，Xolair投与後にアナフィラキシーが生じたと報告されている。報告されたこれらの症例の徴候や症状には，気管支けいれん，低血圧，失神，蕁麻疹や咽喉もしくは，舌の血管浮腫が含まれている。これら事象の一部は，生命を脅かすものとなっている。市販前臨床試験において，Xolairの使用によるアナフィラキシーの頻度は0.1%と推定された。市販後の自発報告では，Xolairの使用によるアナフィラキシーの頻度が，2003年6月～2006年12月の期間の患者約57,300名という推定曝露量に基づき，少なくとも患者の0.2%と推定された。アナフィラキシーはXolair初回投与後早期に発生しているが，定期的投与を開始してから，1年以上経過してから生じている場合もある。
使用上の注意	Xolairは，生命を脅かしうるアナフィラキシーの治療に対し備えのある医療従事者が，医療の場でのみ投与すべきである。市販前臨床試験及び市販後の自発報告でみられたアナフィラキシー発現までの時間を考慮し，Xolair投与後は患者を適当な期間厳重に観察する（*「副作用」参照*）。患者には，アナフィラキシーの徴候や症状について知らせ，もし症状が生じたら速やかに治療を受けるよう指導しておく（*「使用上の注意，患者のための情報」参照*）。 重度の過敏反応が生じた患者で，Xolairを中止する（*「禁忌」参照*）。 **悪性腫瘍** 喘息及びその他のアレルギー性疾患の臨床試験ではXolair投与患者4127例中20例（0.5%）及び対照群患者2236例中5例（0.2%）に悪性新生物が観察された。Xolair投与患者に観察された悪性腫瘍の種類は多岐にわたっており，乳癌，黒色腫以外の皮膚癌，前立腺癌，黒色腫及び耳下腺癌がそれぞれ2例以上に生じたほか，その他5種類の癌が各1例に生じた。これらの患者の大部分は1年以内に観察された。Xolairに長期間曝露した場合の影響及び悪性腫瘍のリスクが高い患者（例：高齢者，現喫煙者）に使用した場合の影響は不明である（*「副作用：悪性腫瘍」参照*）。 **使用上の注意** **全般的注意** Xolairが喘息増悪を急速に緩和させることは示されていないため，急性の気管支痙攣及び喘息発作重積の治療には使用しないこと。 **患者への情報** 投与開始時および以降投与する毎に，事前に患者に添付の医薬品ガイドを渡し，読むように指導する。医薬品ガイドの全文は，本文書の終わりに記載されている。 患者には，Xolairによる生命を脅かすアナフィラキシーのリスクと，Xolair投与後4日までのアナフィラキシー報告があることを忠告する。Xolairは，医療従事者が医療の場でのみ投与すべきである。投与後は，患者を厳重に観察する。患者にはアナフィラキシーの徴候と症状について知らせておく。もしこのような徴候や症状が生じたら，速やかに治療を受けるよう指導しておく。（*「警告，アナフィラキシー」参照*）。

1.6 外国における使用状況等に関する資料

使用上の注意	Xolairの投与を受けている患者には，医師による特別な指示がない限り，他の喘息治療薬を減量したり，服用を中止しないよう伝えること。また，Xolairの投与を開始してもすぐには喘息の改善がみられない場合があることを患者に伝えること。 **コルチコステロイドの減量** Xolairの投与開始後に全身性又は吸入コルチコステロイドの投与を突然中止しないこと。コルチコステロイドの減量は，医師による直接の監視下で徐々に行うこと。 **寄生虫（蠕虫）感染** 土源性蠕虫感染（回虫，鉤虫，鞭虫，糞線虫）のリスクが高い患者を対象にしたブラジルで行われた1年間の臨床試験において，標準の検便により診断した際，感染が生じたのはオマリズマブ投与患者で53%（36/68）であったのに対し，プラセボ対照では42%（29/69）であった。感染に対するオッズ比の点推定値は1.96，95%信頼区間（0.88，4.36）となり，この試験において，感染を生じた患者では感染しなかった患者と比べ，オマリズマブ服用者が0.88～4.36倍多かったことが示唆された。便中の卵数により評価した適切な抗蠕虫感染治療への反応は，投与群間で差がなかった。土源性蠕虫感染リスクの高い患者に対し，Xolair療法中はこれらの感染についてモニタリングを行うべきである。Xolair投与中止後の，土源性蠕虫感染に対し必要なモニタリング期間を判断するのに，十分なデータは得られていない。 **臨床検査** Xolairの投与後には，Xolair：IgE複合体の形成により，血清中総IgE濃度が上昇する（*「臨床薬理」，「用法及び用量」参照*）。血清中総IgE濃度の上昇は，Xolairの投与中止後最大1年間にわたって持続する場合がある。投与中止後1年未満に得られた血清中総IgE濃度は定常状態の遊離IgE濃度を反映していない場合があるため，投与計画の再評価には使用しないこと。 **薬物相互作用** Xolairを用いた正式な薬物相互作用試験は実施されていない。Xolairとアレルゲン免疫療法の併用は評価されていない。 **がん原性，遺伝毒性，生殖機能障害** Xolairのがん原性を評価するための長期の動物実験は実施されていない。6種類の細菌株を用いたAmes試験では，最大5000μg/mL濃度のオマリズマブを使用しても，代謝活性化の有無に関わらず遺伝毒性の証拠は観察されなかった。 カニクイザルの試験で雌雄の受胎能に対するオマリズマブの影響が評価されている。最大75mg/kg/週のオマリズマブを投与しても，雄カニクイザルに生殖毒性は認められず，着床を含む雌カニクイザルの生殖能にも障害は認められなかった。成人臨床用量の範囲における総用量に基づくこれらの用量の安全係数は2～16倍であり，AUCに基づく安全係数は2～5倍である。 **妊娠（カテゴリーB）** カニクイザルを用いたオマリズマブの生殖試験が実施されている。最大75mg/kg（最高臨床用量の12倍に相当）のオマリズマブを器官形成期を通して皮下投与しても，母体毒性，胚毒性及び催奇形性は認められず，最大75mg/kgを妊娠後期，出産及び授乳期を通して投与しても胎児及び新生児の発育に対する有害な影響は認められなかった。 IgG分子は胎盤関門を通過することが知られている。妊婦を対象としたXolairの適切な比較対照試験は実施されていない。動物を用いた生殖試験の結果からヒトの反応を常に予測できるわけではないため，妊娠中は明らかに必要な場合にのみ本剤を使用すること。 **妊娠曝露登録** 受胎前8週間以内，もしくは妊娠中のあらゆる時点において，Xolair投与を1回でも受けた女性を含むXolair曝露妊婦の転帰をモニターするため，妊娠曝露登録が設定されている。医療従事者らは，患者に1-866-4XOLAIR（1-866-496-5247）に電話し，Xolair妊娠曝露登録に登録するよう勧める。医療従事者はこの番号に電話し，本登録についてさらなる情報を得ることが可能である。 **授乳婦** 75mg/kg/週を皮下投与した雌カニクイザルを用いてオマリズマブの乳汁中への排出を評価した。

1.6 外国における使用状況等に関する資料

使用上の注意	子宮内曝露後及び授乳28日後における新生児のオマリズマブの血漿中濃度は，母体血漿中濃度の11%～94%であった。オマリズマブの乳汁中濃度は母体血中濃度の1.5%であった。ヒト乳汁中のXolairの存在に関する検討は実施されていないが，IgGはヒト乳汁中に排出されるため，Xolairもヒト乳汁中に排出されると予測される。Xolairが乳児に吸収されるかどうか，あるいは吸収されたXolairが乳児に有害な影響を及ぼすかどうかは不明であるため，授乳婦にXolairを投与する場合には注意が必要である。 **小児への投与** 12歳未満の小児患者における安全性及び有効性は確立されていない。 **高齢者への投与** 臨床試験では，65歳以上の患者134例にXolairを投与した。これらの試験では年齢に関連する明らかな差は観察されなかったが，65歳以上の患者数が十分ではないため，高齢患者が若年患者と異なる反応を示すかどうかを明らかにすることはできない。 **副作用** **臨床試験における経験** Xolairの臨床試験で生じた最も重篤な副作用は，アナフィラキシーと悪性腫瘍であった（*「警告」参照*）。臨床試験において，アナフィラキシーは患者3507名中3名（0.1%）で報告された。アナフィラキシーは，2名の患者ではXolairの初回投与で生じ，1名の患者では4回目の投与で生じた。アナフィラキシー発現までの時間は，2名の患者で投与後90分，1名の患者で投与後2時間であった。 臨床試験において，Xolair投与患者に認められた悪性腫瘍発生率（0.5%）は，対照群患者（0.2%）に比べ数値的に高かった。 Xolair投与患者に最も高頻度に観察された副作用には，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%）があった。これらの事象は，Xolair投与患者と対照群患者に同様の頻度で観察された。これらの事象は，臨床的介入（例：Xolairの投与中止，又は副作用を治療するための併用薬の投与）に至った副作用としても最も高頻度に報告された。 臨床試験はさまざまな条件下で実施されるため，ある薬剤の臨床試験で観察された副作用の発生率は，他の薬剤の臨床試験で得られた値と直接比較することができない上，臨床の現場で観察される発生率を反映していないことがある。 上記のデータは，プラセボ対照喘息試験又は他の対照喘息試験で投与を6カ月以上実施した1687例及び投与を1年以上実施した555例を含む成人及び青少年患者2076例におけるXolairの投与を反映している。Xolair投与患者の平均年齢は42歳，65歳以上の患者は134例であった。また，60%が女性，85%が白人であった。患者にはXolair150～375mgを2又は4週毎に投与し，対照群に割り付けられた患者には標準治療又は標準治療とプラセボを投与した。 プラセボ対照喘息試験で認められた有害事象のうち，プラセボ投与患者よりもXolair投与患者の方が発現率が1%以上高かった有害事象を表3に示す。有害事象は，International Medical Nomenclature（IMN）辞書の基本語を用いて分類した。注射部位反応は他の有害事象の報告と別個に記録した。注射部位反応については表3の後に記載する。 表3：Xolair投与患者において発現率が1%以上高かった有害事象

1.6 外国における使用状況等に関する資料

有害事象	Xolair N=738 (%)	プラセボ N=717 (%)	有害事象	Xolair N=738 (%)	プラセボ N=717 (%)
全身障害			**神経系**		
疼痛	7	5	浮動性めまい	3	2
疲労	3	2	**皮膚及び皮膚付属器**		
筋骨格系			そう痒症	2	1
関節痛	8	6	皮膚炎	2	1
骨折	2	1	**特殊感覚**		
下肢痛	4	2	耳痛	2	1
上肢痛	2	1			

（65 歳未満の患者の）年齢，人種及び性別が有害事象発現率の群間差に影響を及ぼすとは考えられなかった。

注射部位反応

注射部位反応（重症度は問わない）の発現率は，Xolair 投与患者 45%，プラセボ投与患者 43%であった。注射部位反応には，挫傷，発赤，熱感，灼熱感，刺痛感，そう痒感，蕁麻疹形成，疼痛，硬結，腫瘤及び炎症があった。

重度の注射部位反応の発現率は，プラセボ投与患者（9%）よりも Xolair 投与患者（12%）の方が高かった。

注射部位反応の大部分は注射後 1 時間以内に生じ，持続期間は 8 日未満であった。一般に，それ以降の投与来院では発現率が低下した。

免疫原性

Xolair 投与患者約 1723 例中 1 例（＜0.1%）の割合で低力価の抗 Xolair 抗体が検出された。このデータは，ELISA アッセイの検査結果が抗 Xolair 抗体陽性と判定された患者の割合を反映しているため，アッセイの感度及び特異性に大きく依存している。さらに，このアッセイで観察された抗体陽性率は，サンプルの取り扱い，サンプルの採取時期，併用薬及び基礎疾患を含むいくつかの要因の影響を受けている可能性がある。このため，抗 Xolair 抗体の出現率を他の製品に対する抗体発現率と比較すると，誤解を招くおそれがある。

Xolair 投与患者に蕁麻疹，皮膚炎及びそう痒症を含むアレルギー症状が観察された。また，アレルギーの原因が他に見当たらない 3 例において，Xolair の投与後 2 時間以内にアナフィラキシーが認められた（*「警告：アナフィラキシー」参照*）。

市販後の自発報告

アナフィラキシー：自発報告と 2003 年 6 月～2006 年 12 月の期間の患者約 57,300 名という推定曝露量に基づき，Xolair 使用によるアナフィラキシーの頻度は患者の少なくとも 0.2%になると推定された。アナフィラキシーの診断基準は，皮膚や粘膜組織の症状があり，かつ，気道症状か血圧低下（随伴症状の有無を問わず）のいずれか，もしくは両者が生じ，他に特定可能な原因がなく，Xolair 投与と時間的に関連する場合とした。これらの報告された症例の徴候や症状には，気管支けいれん，低血圧，失神，蕁麻疹，咽喉や舌の血管浮腫，呼吸困難，咳嗽，胸苦しさ，皮膚血管浮腫等があった。肺症状は 89%の症例で報告された。低血圧や失神は 14%の症例で報告された。報告された症例のうち 15%が入院となった。24%の症例において，Xolair の関連しないアナフィラキシーの既往が報告された。

Xolair によるアナフィラキシーと報告された症例のうち，39%が初回投与，19%が 2 回目の投与，10%が 3 回目の投与で，残りがその後の投与で生じていた。1 症例では 39 回の投与後に生じていた（19 ヶ月継続療法した後，3 ヶ月の間隔を置いて投与を再開した際，アナフィラキシーが生じた）。これらの症例におけるアナフィラキシー発現までの時間は，35%で 30 分以内，16%で 30 分超～60 分以内，2%で 60 分超～90 分以内，6%で 90 分超～120 分以内，5%で 2 時間超～6 時間以内，14%で 6 時間超～12 時間以内，8%で 12 時間超～24 時間以内，5%で 24 時

1.6 外国における使用状況等に関する資料

	間超～4日以内であった。9%の症例において，発現までの時間が不明であった。 アナフィラキシーを生じた23名の患者にXolairによる再誘発が行われ，18名の患者にアナフィラキシーと同様の症状が再発した。さらに，先に蕁麻疹のみが生じた患者4名において，Xolairによる再誘発でアナフィラキシーが生じた。 好酸球増多症：市販後のゾレアの使用経験において好酸球増多症が報告された。*（「使用上の注意：好酸球増多症」参照）* 血液：Xolairの承認後の使用において，重度の血小板減少が報告されている。 皮膚：Xolairの承認後の使用において，脱毛が報告されている。 **過量投与** Xolairの最大耐容量は明らかにされていない。最大4000mgを患者に単回静脈内投与しているが，用量を制限する毒性は認められていない。また，患者への最高累積投与量は20週間かけて投与された44,000mgであるが，毒性は認められなかった。
改訂年月日	2008年7月

表 1.6.2-3　　EU の SmPC の概略

<table>
<tr><td>販売名</td><td>Xolair®</td></tr>
<tr><td>剤型・含量</td><td>注射用粉末製剤及び溶媒 75mg，150mg</td></tr>
<tr><td>効能・効果</td><td>Xolair は，1 種類以上の通年性吸入抗原に対する陽性皮膚反応又は in vitro 反応性，肺機能低下（FEV_1＜80%）及び頻繁な昼間症状又は夜間覚醒がみられ，かつ高用量吸入コルチコステロイドの連日投与と長時間作用型吸入 β 2 刺激薬の併用にも関わらず重度の喘息増悪が繰り返しみられる重症持続性アレルギー性喘息の成人及び青少年患者（12 歳以上）の喘息コントロールを改善するための追加療法として適応される。Xolair の投与は，IgE 介在性喘息と考えられる患者でのみ検討すること（用法・用量参照）。</td></tr>
<tr><td>用法・用量</td><td><u>青少年及び成人（12 歳以上）への投与</u>
Xolair の投与は，重症持続性喘息の診断及び治療経験が豊富な医師が開始すること。
Xolair の適切な用量及び投与頻度は，投与開始前に測定したベースラインの IgE 濃度（IU/ml）及び体重（kg）により決定する。用量を割り当てるため，投与開始前に市販の血清中総 IgE アッセイを用いて患者の IgE 濃度を測定する。各投与では，これらの測定値に基づいて Xolair 75～375mg を 1～3 回に分けて注射する。
IgE 濃度が 76IU/ml 未満の患者は，76IU/ml 以上の患者よりも有益な効果が得られる確率が低かった。処方医師は，IgE 濃度が 76IU/ml 未満の患者への投与を開始する前に通年性アレルゲンに対する明確な in vitro 反応性（RAST）がみられることを確認すること。
投与容量換算表については表 1，投与量換算表については表 2 及び 3 を参照されたい。
ベースラインの IgE 濃度又は体重（kg）が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。
最高推奨用量は，オマリズマブ 375mg の 2 週毎の投与である。
本剤の投与は皮下投与のみとし，静脈内及び筋肉内への投与は行わないこと。
本剤は腕の三角筋部に皮下投与する。三角筋部への投与を行うことができない理由がある場合は，大腿部に投与してもよい。
Xolair の自己投与経験はわずかである。このため，本剤は医療従事者による投与を意図している。
表 1：用量から各投与のバイアル数，注射回数及び総投与容量への換算
<table>
<tr><th rowspan="2">用量（mg）</th><th colspan="2">バイアル数</th><th rowspan="2">注射回数</th><th rowspan="2">総投与容量（ml）</th></tr>
<tr><th>75 mg[a]</th><th>150 mg[b]</th></tr>
<tr><td>75</td><td>1[c]</td><td>0</td><td>1</td><td>0.6</td></tr>
<tr><td>150</td><td>0</td><td>1</td><td>1</td><td>1.2</td></tr>
<tr><td>225</td><td>1[c]</td><td>1</td><td>2</td><td>1.8</td></tr>
<tr><td>300</td><td>0</td><td>2</td><td>2</td><td>2.4</td></tr>
<tr><td>375</td><td>1[c]</td><td>2</td><td>3</td><td>3.0</td></tr>
</table>
[a] バイアル（Xolair 75mg）1 本あたりの最高投与容量は 0.6ml。
[b] バイアル（Xolair 150mg）1 本あたりの最高投与容量は 1.2ml。
[c] 又は 150mg バイアルから 0.6ml を使用。</td></tr>
</table>

1.6 外国における使用状況等に関する資料

用法・用量

表 2：4 週間隔投与。4 週毎の皮下投与による Xolair の投与量（1 回投与量 [mg]）

	体重（kg）									
ベースラインの IgE 濃度（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		
>200-300	150	150	225	300	300					
>300-400	225	225	300							
>400-500	225	300	2 週間隔投与							
>500-600	300	300	表 3 参照							
>600-700	300									

表 3：2 週間隔投与。2 週毎の皮下投与による Xolair の投与量（1 回投与量 [mg]）

	体重（kg）									
ベースラインの IgE 濃度（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	4 週間隔投与								225	300
>200-300	表 2 参照					225	225	225	300	375
>300-400				225	225	225	300	300		
>400-500			225	225	300	300	375	375		
>500-600			225	300	300	375	投与しないこと - 推奨用量に関するデータがない			
>600-700		225	225	300	375					

投与期間，モニタリング及び用量調節

Xolair の投与中止により，一般に遊離 IgE 濃度が再度上昇し，関連症状が生じる。

Xolair 療法の開始から 16 週後に，さらに投与を実施する前にかかりつけの医師が治療効果を評価する必要がある。Xolair の投与継続は，全般的な喘息コントロールに著明な改善がみられるかどうかによって決定する。

総 IgE 濃度は投与中に上昇し，投与中止から 1 年が経過しても上昇したままの場合がある。このため，Xolair の投与中に再測定した IgE 濃度は用量設定の指標として使用することはできない。1 年未満の投与中断後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 IgE 濃度に基づいて用量を設定すること。Xolair の投与中断期間が 1 年以上の場合は，用量設定のために血清中総 IgE 濃度を再測定してもよい。

体重が大きく変化した場合には，用量を調節すること（表 2 及び 3 参照）。

高齢者（65 歳以上）

65 歳以上の患者への Xolair の使用については限られたデータしかないが，高齢患者が若年成人患者と異なる用法・用量を要することを示す証拠は認められていない。

小児（12 歳未満）

12 歳未満の小児患者における安全性及び有効性は確立されていないため，これらの小児患者への Xolair の使用は勧められない。

使用上の注意

禁忌

本剤の有効成分又は添加物に対する過敏症の既往歴を有する患者

警告及び使用上の注意

全般的注意

急性の喘息増悪，急性の気管支痙攣及び喘息発作重積の治療には使用しないこと。

高 IgE 症候群及びアレルギー性気管支肺アスペルギルス症の患者を対象とした Xolair の検討やアナフィラキシー反応（食物アレルギーにより誘発されるものを含む）の予防に関する Xolair の検

1.6 外国における使用状況等に関する資料

使用上の注意	討は実施されていない。 自己免疫疾患，免疫複合体介在性疾患及び既存の腎又は肝機能障害を有する患者を対象としたXolairの検討は実施されていない。これらの患者集団へのXolairの投与は慎重に行う必要がある。 Xolairの投与開始後に全身性又は吸入コルチコステロイドの投与を突然中止してはならない。コルチコステロイドの減量は，医師による直接の監視下で徐々に行うこと。 糖尿病，グルコース-ガラクトース吸収不全症候群，フルクトース不耐症又はスクラーゼ-イソマルターゼ欠損症を有する患者には，Xolairの1回投与量75mg/150mgあたりショ糖が54mg/108mg含まれることを伝える必要がある。 アレルギー反応 長期間治療後に発症した際に投与した場合でも，オマリズマブはアナフィラキシー及びアナフィラキシーショック等の局所もしくは全身のアレルギー反応が生じる可能性がある。これら反応の多くは，Xolairの初回及びそれ以降の注射をしてから2時間以内に生じるが，注射から2時間以上，さらには24時間以上経過してから生じる場合もある。そのため，Xolairを投与した後には，速やかに使用できるようアナフィラキシー反応治療用の薬剤を常に用意しておくべきである。患者には，これらの反応が生じる可能性があり，アレルギー反応が生じたら速やかに治療を受けるよう知らせておくべきである。 臨床試験ではアナフィラキシー反応はまれであった(副作用参照)。 すべての組み換えDNA由来ヒト化モノクローナル抗体と同じく，まれに抗オマリズマブ抗体が出現する可能性がある。 寄生虫（蠕虫）感染 IgEは，いくつかの蠕虫感染に対する免疫応答に関与していると考えられる。プラセボ対照試験では，蠕虫感染のリスクが慢性的に高い患者にオマリズマブを投与すると感染率がわずかに増加することが示されたが，感染の経過，重症度及び治療反応に影響は認められなかった。全臨床プログラム（このような感染を検出するようには計画されていない）における蠕虫感染率は1000例中1例未満であった。しかし，蠕虫感染のリスクが高い患者では注意を要する場合がある（特に蠕虫感染の流行地域に旅行する場合）。患者が推奨される駆虫薬に反応しない場合はXolairの投与中止を検討すること。 悪性腫瘍 臨床試験中には，Xolair投与群と対照群における癌の発生に数値上の不均衡が認められた。癌症例の観察頻度は，Xolair投与群及び対照群とも低頻度（＜1/100）であり，Xolair投与群5,015例中25例（0.5%），対照群2,854例中5例（0.18%）であった。観察された癌の種類は多岐にわたっていたこと，曝露期間が比較的短かったこと，及び各症例の臨床上の特徴から，投与との因果関係はないものと考えられる。Xolairの臨床試験プログラムで観察された悪性腫瘍の総発生率は，一般母集団で報告されている発生率と同様であった。 Churg-Strauss症候群と好酸球増多症 重度の喘息患者にはまれに，全身性好酸球増多症やアレルギー性好酸球性肉芽腫性血管炎（Churg-Strauss症候群）がみられることがあり，これらは両者とも，通常はステロイドの全身投与により治療する。 まれに，オマリズマブ等の抗喘息薬による治療中の患者に，全身性の好酸球増加及び血管炎がみられたり，発生することがある。これらの事象には通常経口ステロイド療法の減量が関連している。 これらの患者において，著しい好酸球増加，血管炎性の発疹，肺症状の悪化，心合併症及びニューロパシーの発現に対し，医師は警戒しておく。 **他の医薬品との相互作用及びその他の相互作用** オマリズマブのクリアランスにチトクロムP450酵素，排出ポンプ及びタンパク結合機序は関与しないため，薬物-薬物相互作用が生じる可能性はほとんどない。医薬品又はワクチンとXolairとの正式な相互作用試験は実施されていない。喘息治療に使用される処方頻度が高い薬物とオマリズマブとの相互作用を予測させる薬理学的知見はない。

1.6 外国における使用状況等に関する資料

使用上の注意

臨床試験では，吸入及び経口コルチコステロイド，短時間作用型及び長時間作用型吸入β刺激薬，ロイコトリエン拮抗薬，テオフィリン及び経口抗ヒスタミン薬をXolairと併用する場合が多かった。使用頻度が高いこれらの喘息治療薬と併用しても，Xolairの安全性が変化することを示す徴候は認められなかった。特異的免疫療法（減感作療法）との併用に関するデータはわずかしか得られていないため，特異的免疫療法と併用した場合のXolairの有効性は確立されていない。現在までのデータから，確立された減感作療法を受けている患者でXolairの用量を調節する必要はないことが示唆される。

妊婦及び授乳婦への投与

妊婦へのオマリズマブの投与に関する適切なデータは得られていない。動物実験では，妊娠，胚／胎児発生，分娩及び出生後の発育に対する直接的又は間接的な有害作用は示されていない。オマリズマブは胎盤関門を通過するが，胎児に有害な影響を及ぼすかどうかは不明である。ヒト以外の霊長類にオマリズマブを投与すると血液中の血小板数が年齢依存的に減少し，この影響に対する感受性は若年動物の方が相対的に高いことが示されている。妊娠中は，明らかに必要な場合を除きXolairを使用しないこと。

オマリズマブがヒト乳汁中に排出されるかどうかは不明である。オマリズマブはヒト以外の霊長類の乳汁中に排出されるため，乳児に影響が生じる可能性を除外することはできない。Xolairの投与中は授乳を行わないこと。

自動車の運転及び機械操作能力に対する影響

Xolairの投与を受ける患者には，めまい，疲労感，脱力や眠気が生じた場合には，運転や機械操作をしないよう警告すること。

副作用

臨床試験中に最も高頻度に報告された有害事象は，注射部位反応（注射部位の疼痛，腫脹，紅斑及びそう痒感を含む）と頭痛であった。これらの反応のほとんどは軽度又は中等度であった。

Xolairを投与した全安全性解析集団で臨床試験中に記録された副作用を器官大分類別及び発現頻度別にして表4に示す。発現頻度は以下の通り定義する：高頻度（＞1/100；＜1/10），低頻度（＞1/1,000；＜1/100）及びまれ（＜1/1,000）。市販後において報告された有害事象についての発現頻度は“不明”とした。

表4：副作用

血液及びリンパ系疾患 不明	 特発性重症血小板減少症
感染症および寄生虫症 まれ	 寄生虫感染
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症状
神経系障害 高頻度 低頻度	 頭痛 浮動性めまい，傾眠，錯感覚，失神
血管障害 低頻度	 体位性低血圧，潮紅
呼吸器，胸郭および縦隔障害 低頻度 まれ 不明	 咽頭炎，咳嗽，アレルギー性気管支痙攣 喉頭浮腫 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	

1.6 外国における使用状況等に関する資料

使用上の注意	

低頻度	悪心，下痢，消化不良徴候および症状
筋骨格及び結合組織疾患 不明	 関節痛，筋肉痛，関節腫脹
皮膚および皮下組織障害 低頻度 まれ 不明	 蕁麻疹，発疹，そう痒症，光線過敏 血管浮腫 脱毛症
全身障害および投与局所様態 高頻度 低頻度	 疼痛，紅斑，そう痒感及び腫脹などの注射部位反応 体重増加，疲労，腕の腫脹，インフルエンザ様疾患

悪性腫瘍

Xolair の臨床試験プログラムで観察された悪性腫瘍の総発生率は，一般母集団で報告されている発生率と同様であった（警告及び使用上の注意参照）。

血小板

臨床試験で血小板数が正常下限値を下回った患者はごく少数であった。これらの変化のうち，出血性の事象やヘモグロビン減少を伴っていたものはなかった。単独症例として特発性血小板減少症が市販後に報告されてはいるが，ヒト以外の霊長類で観察されたような血小板数の持続的な減少パターンは，ヒトでは報告されていない。

寄生虫感染

プラセボ対照試験では，蠕虫感染のリスクが慢性的に高い患者にオマリズマブを投与すると感染率がわずかに増加することが示されたが，統計学的に有意ではなかった。感染の経過，重症度及び治療反応に影響は認められなかった（警告及び使用上の注意参照）。

過量投与

過量投与症例は報告されていない。Xolair の最大耐容量は明らかにされていない。最大 4,000mg が患者に単回静脈内投与されているが，用量制限毒性は認められていない。また，患者への最高累積投与量は 20 週間かけて投与された 44,000mg であるが，この用量でも急性の有害な影響は認められなかった。

発行年月日	2007 年 5 月 30 日

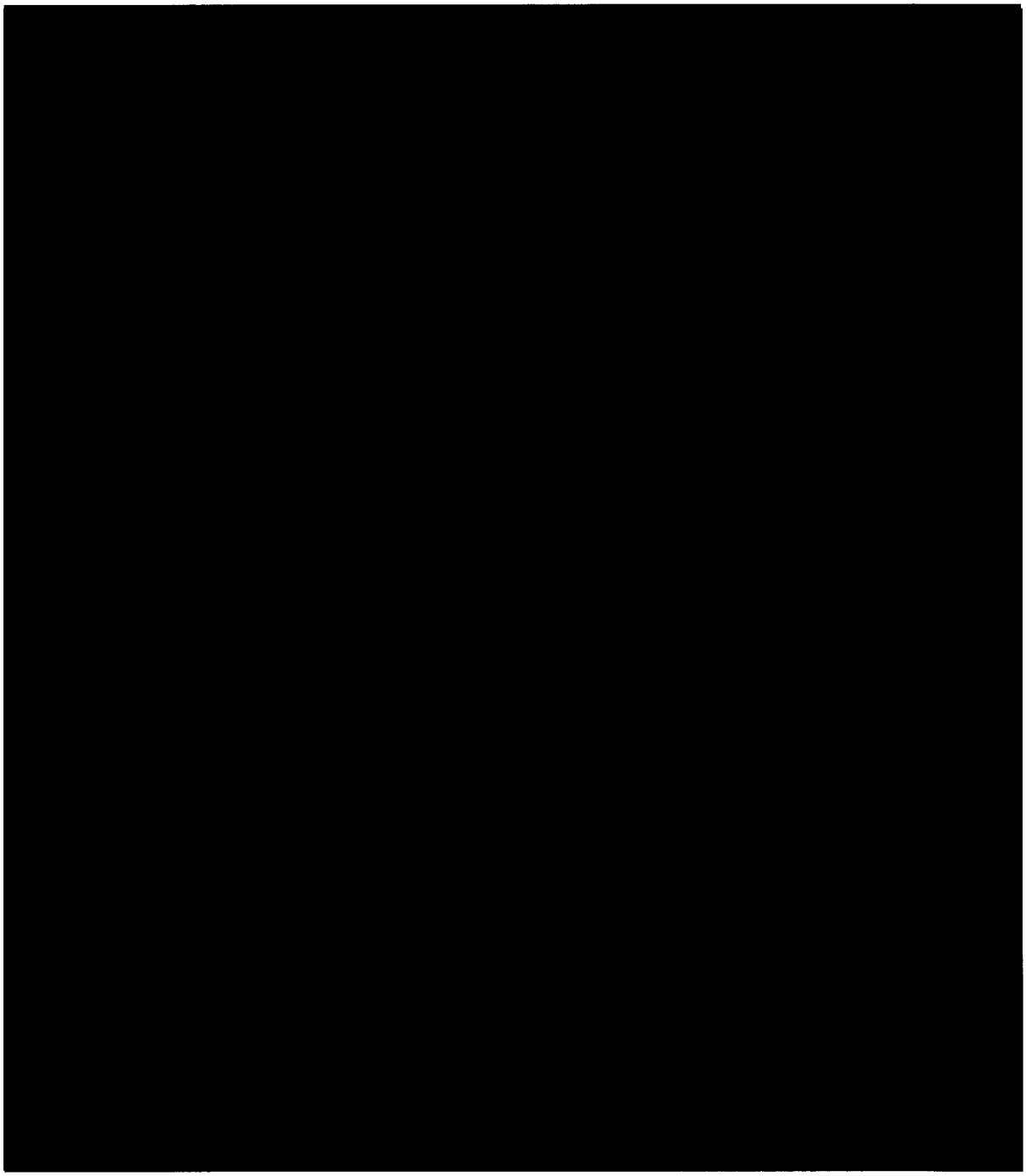
企業中核データシート

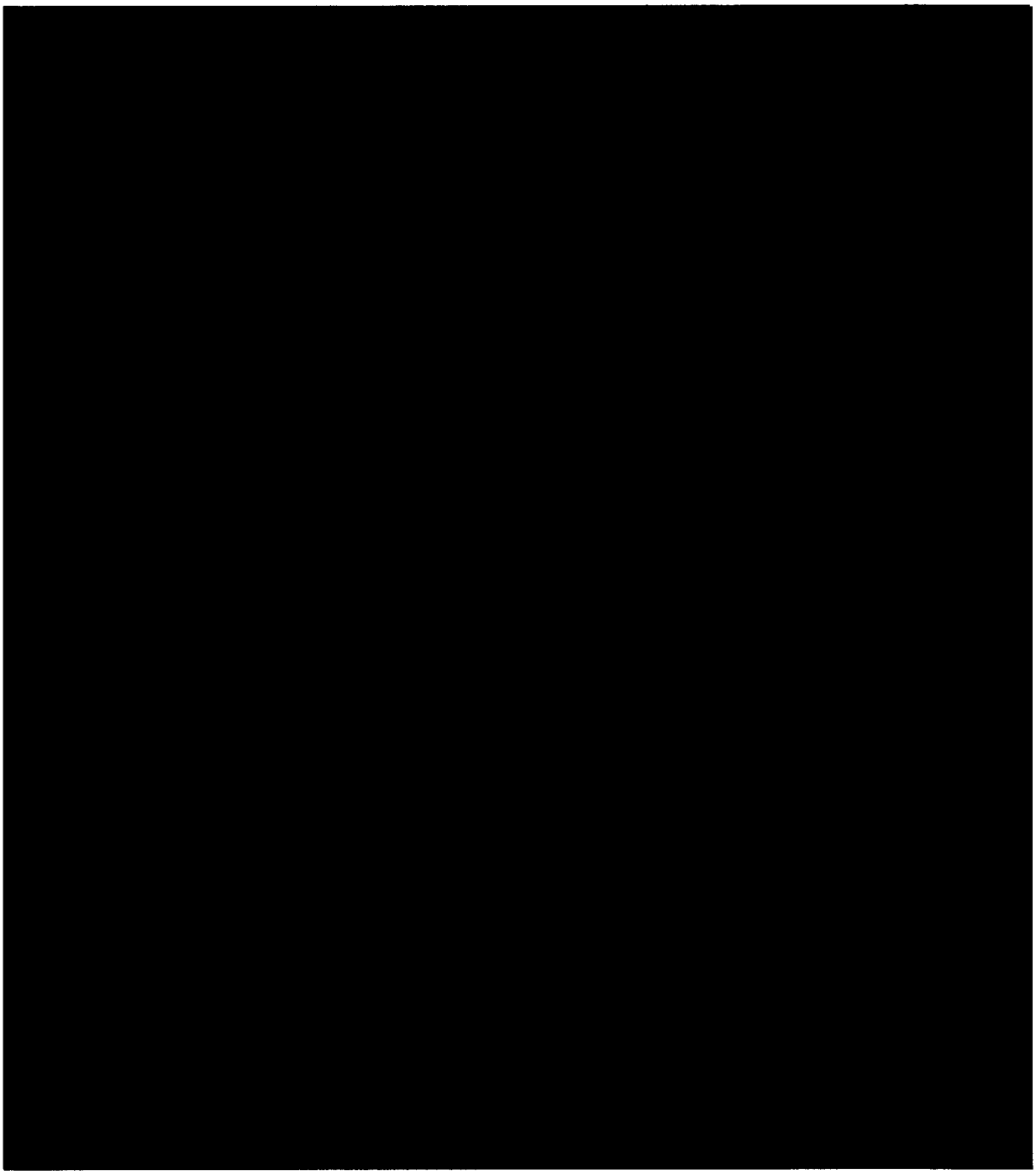
(CCDS/ Basic Prescribing Information)

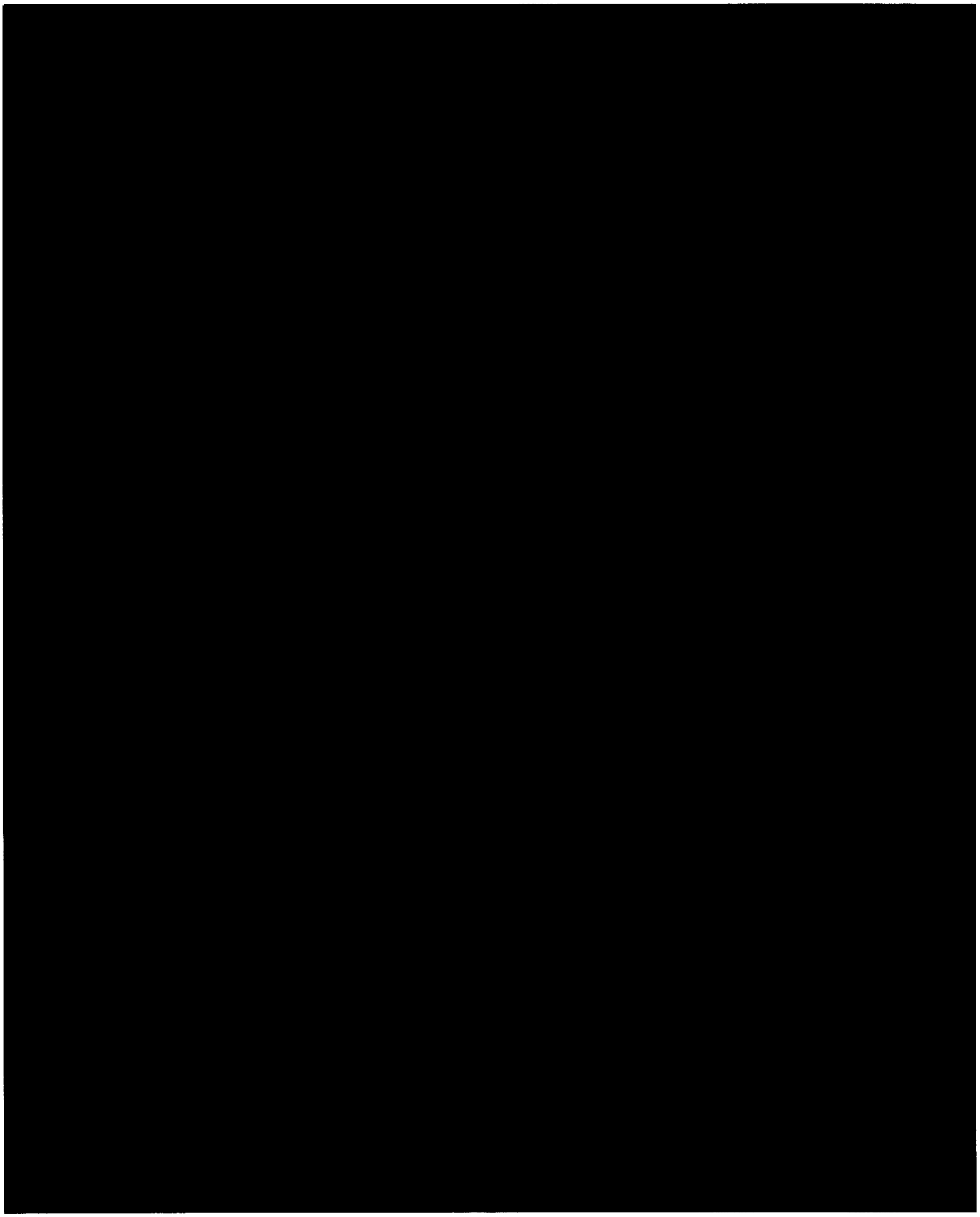
1 Name of the medicinal product

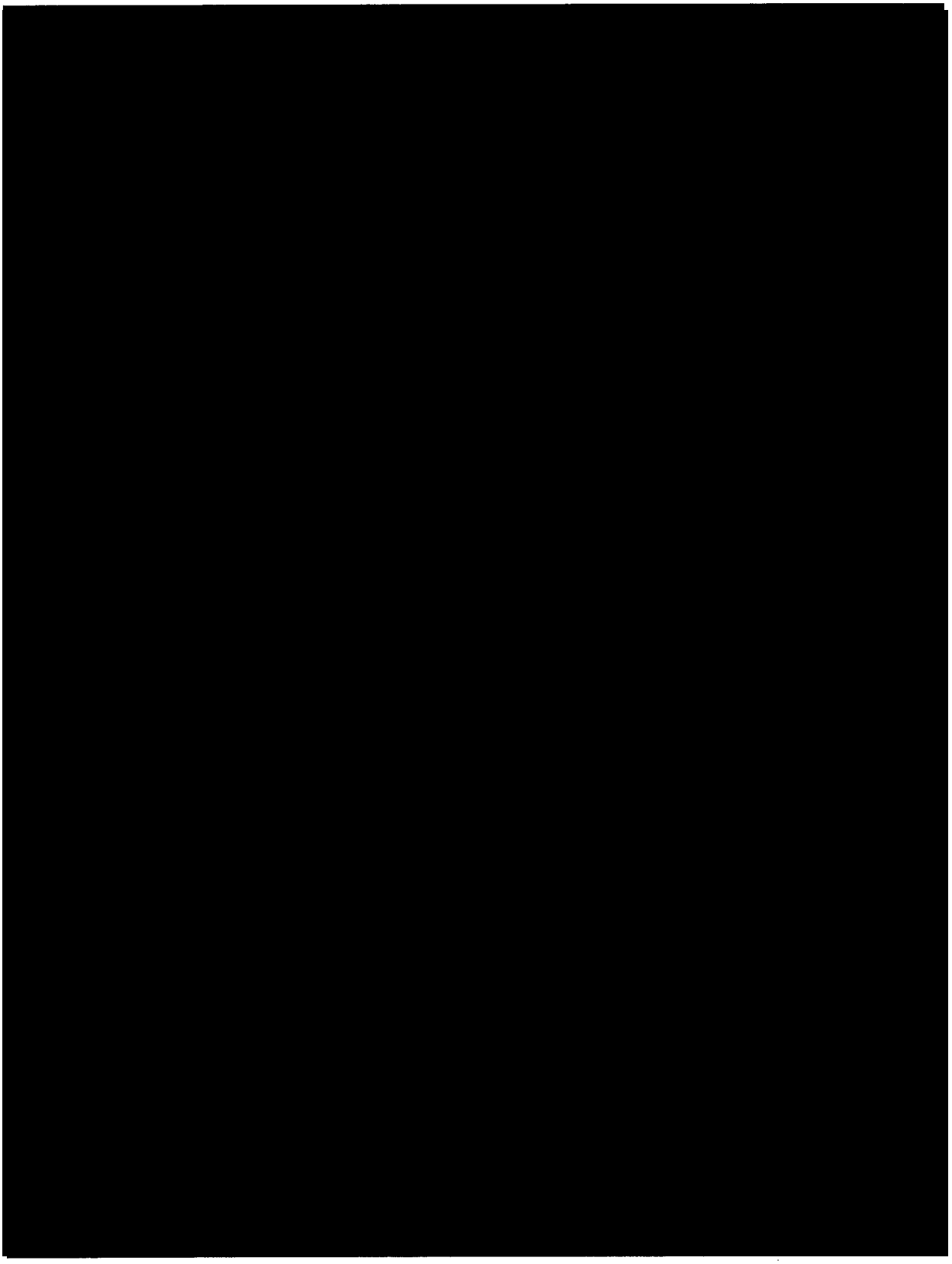
XOLAIR® 75 mg powder and solvent for solution for injection.

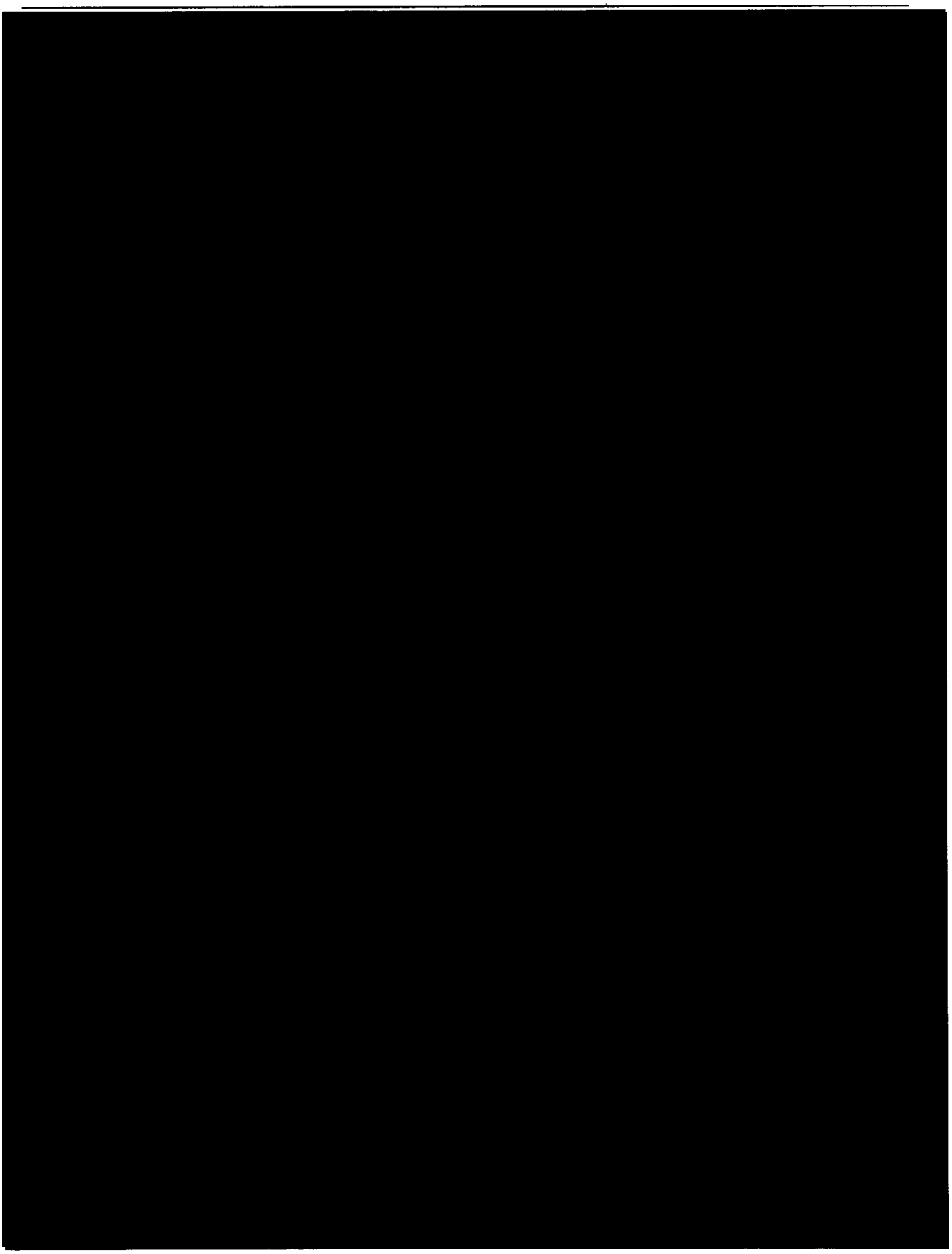
Xolair 150 mg powder and solvent for solution for injection.

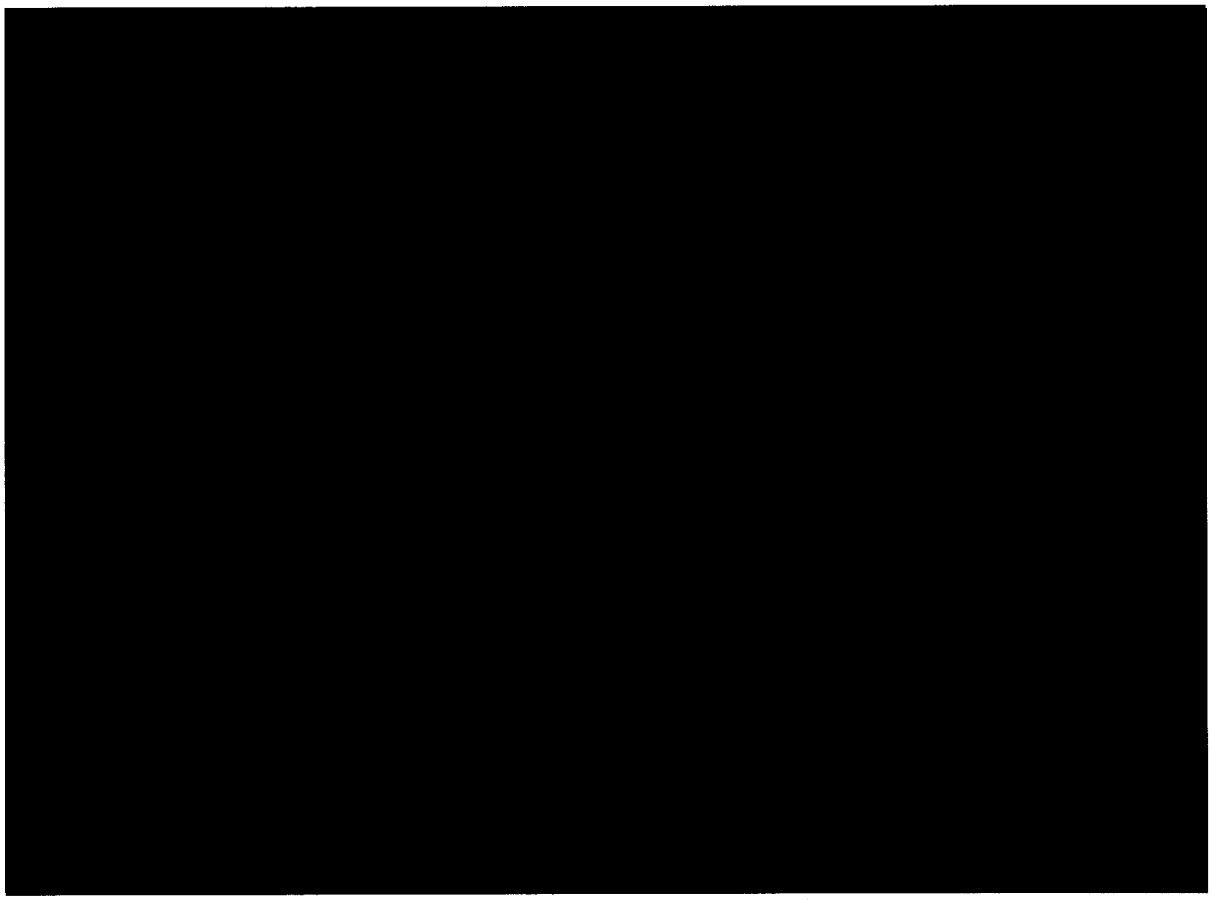


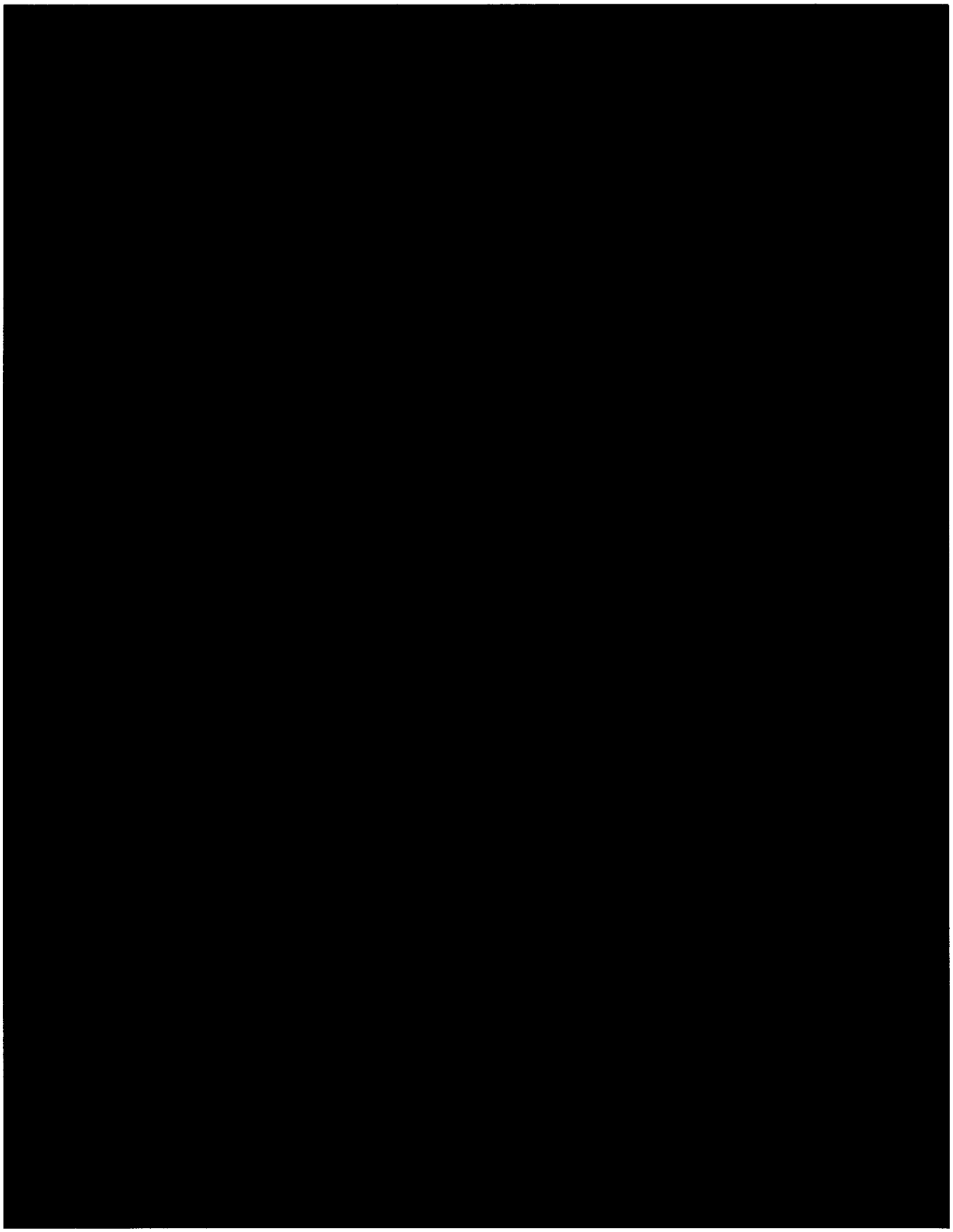


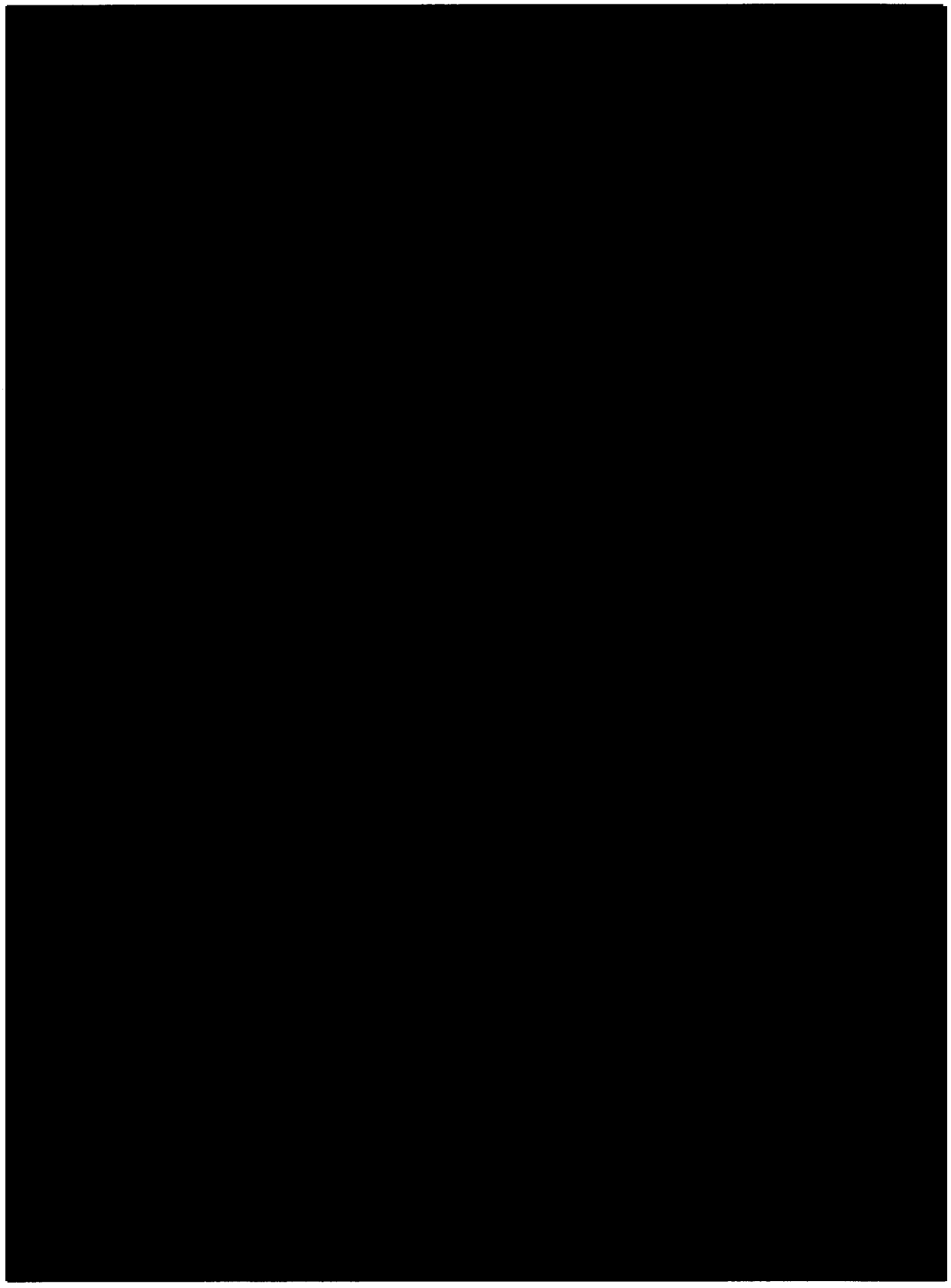


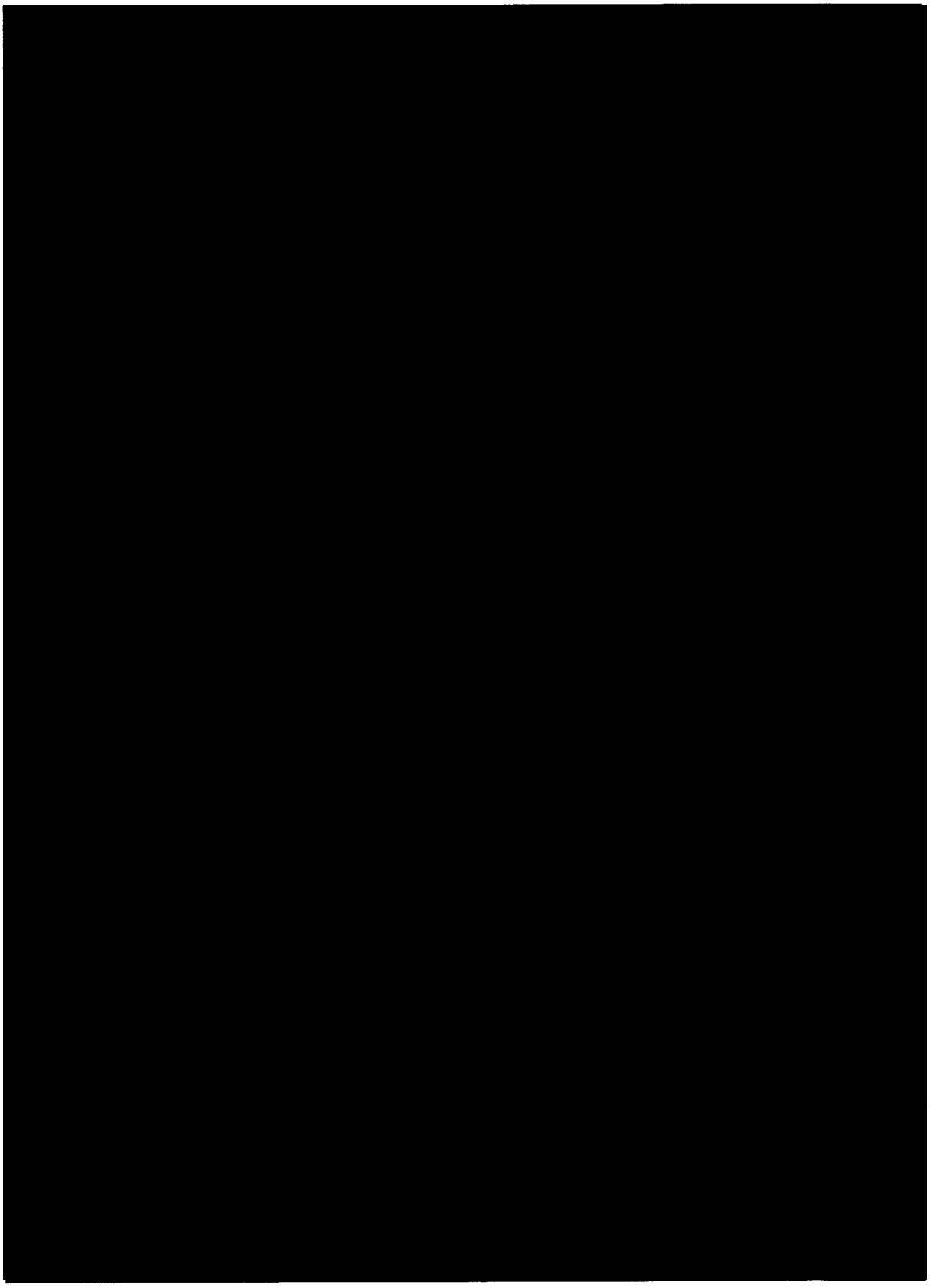


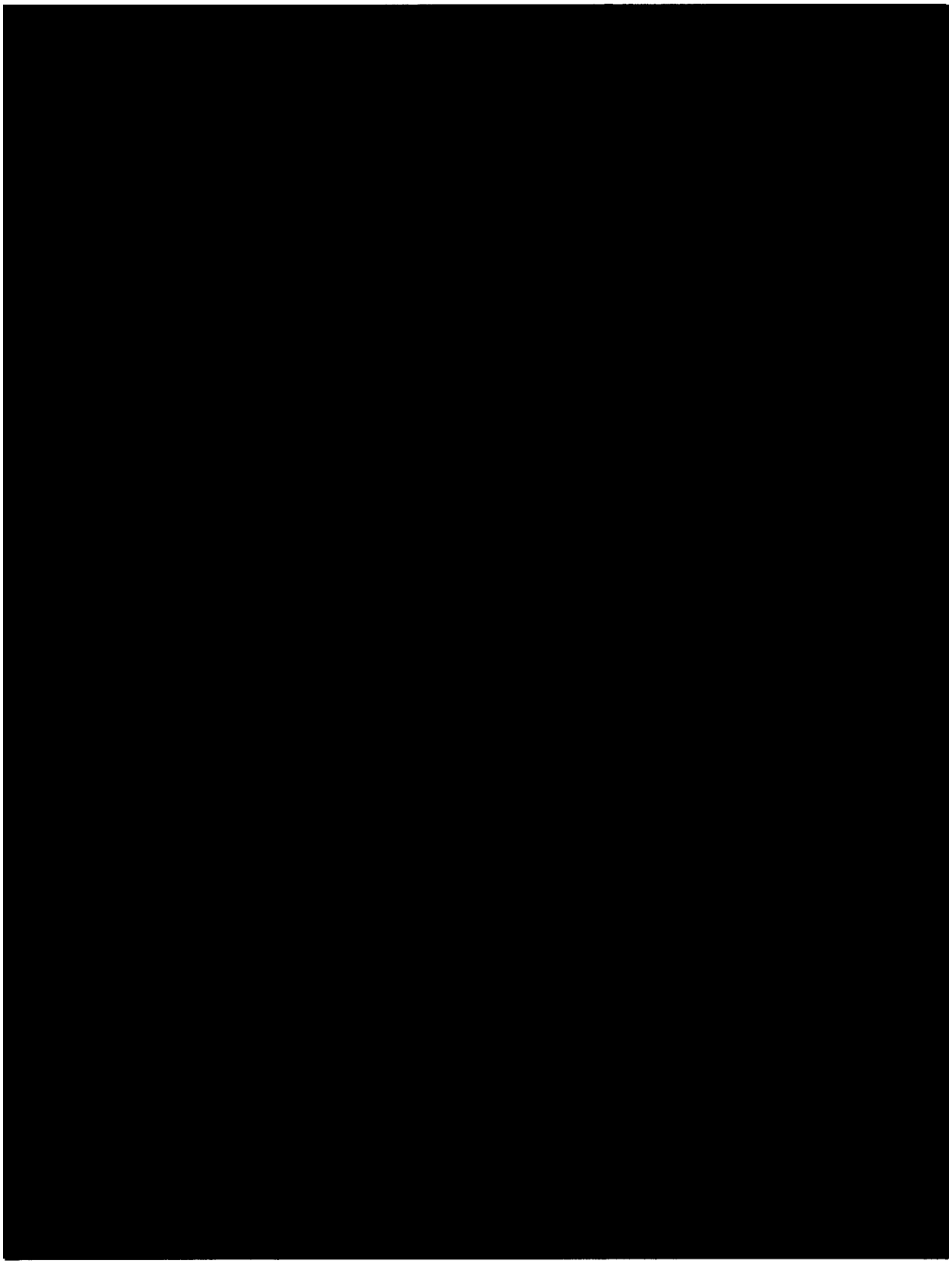


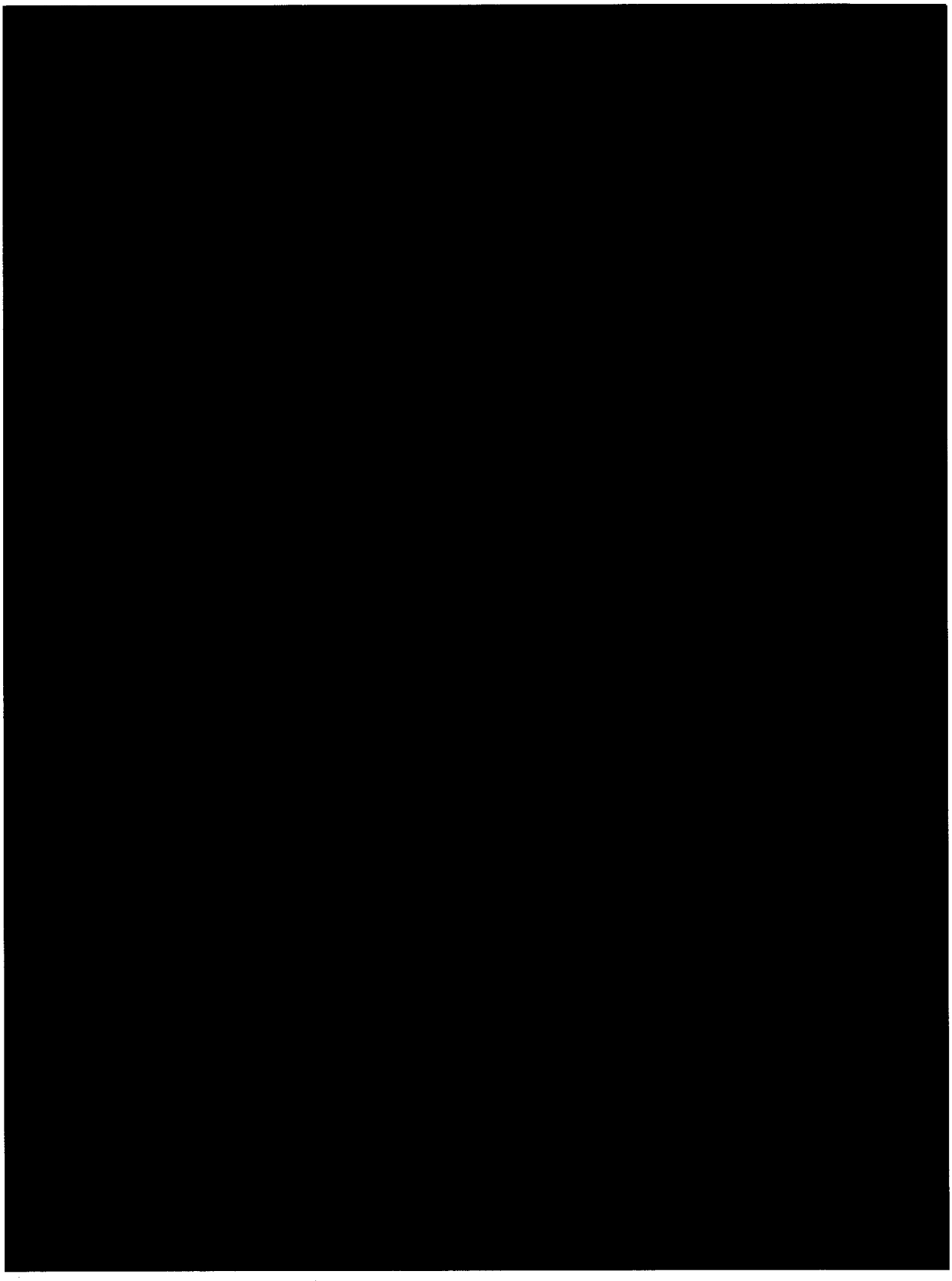


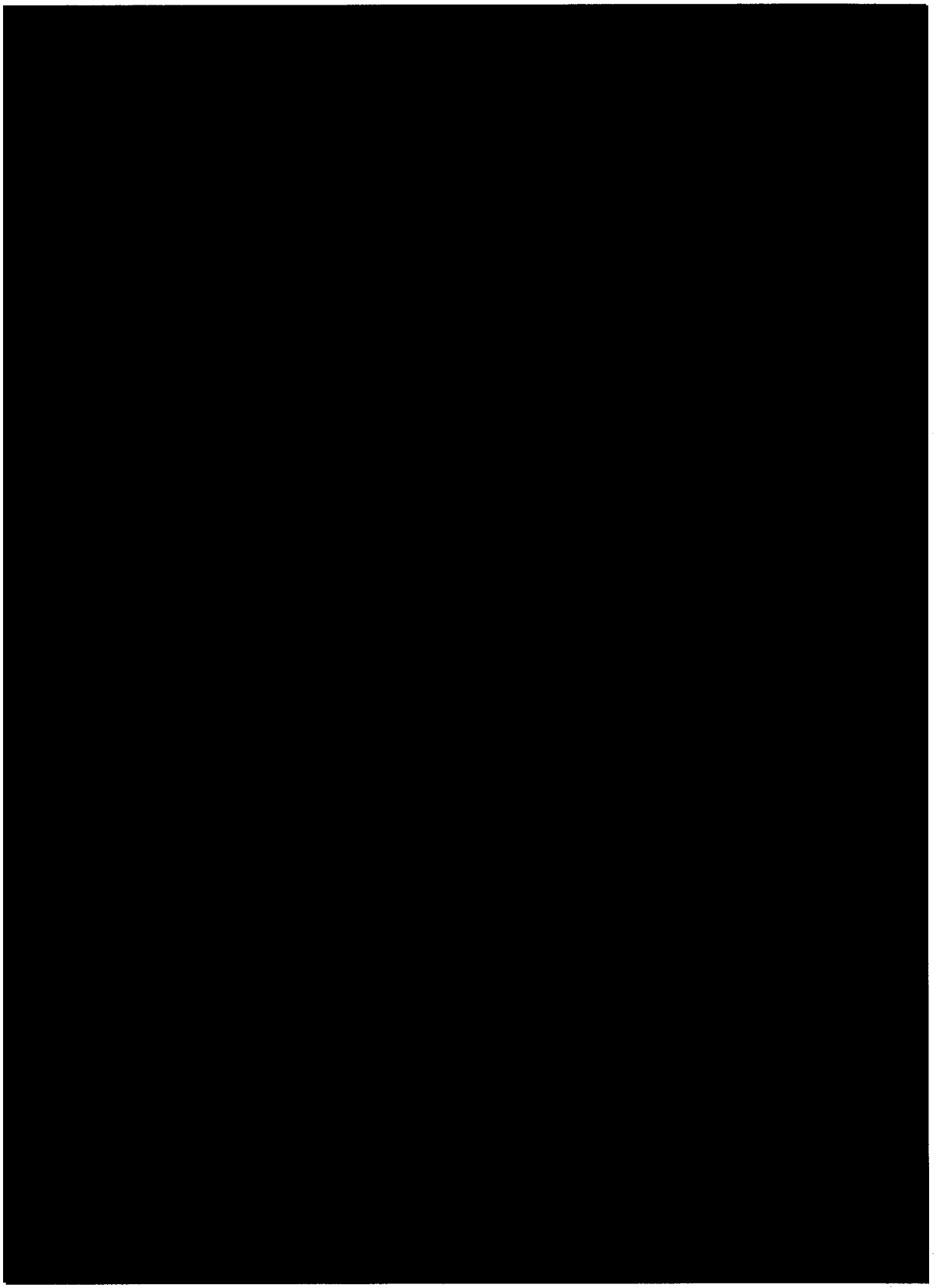


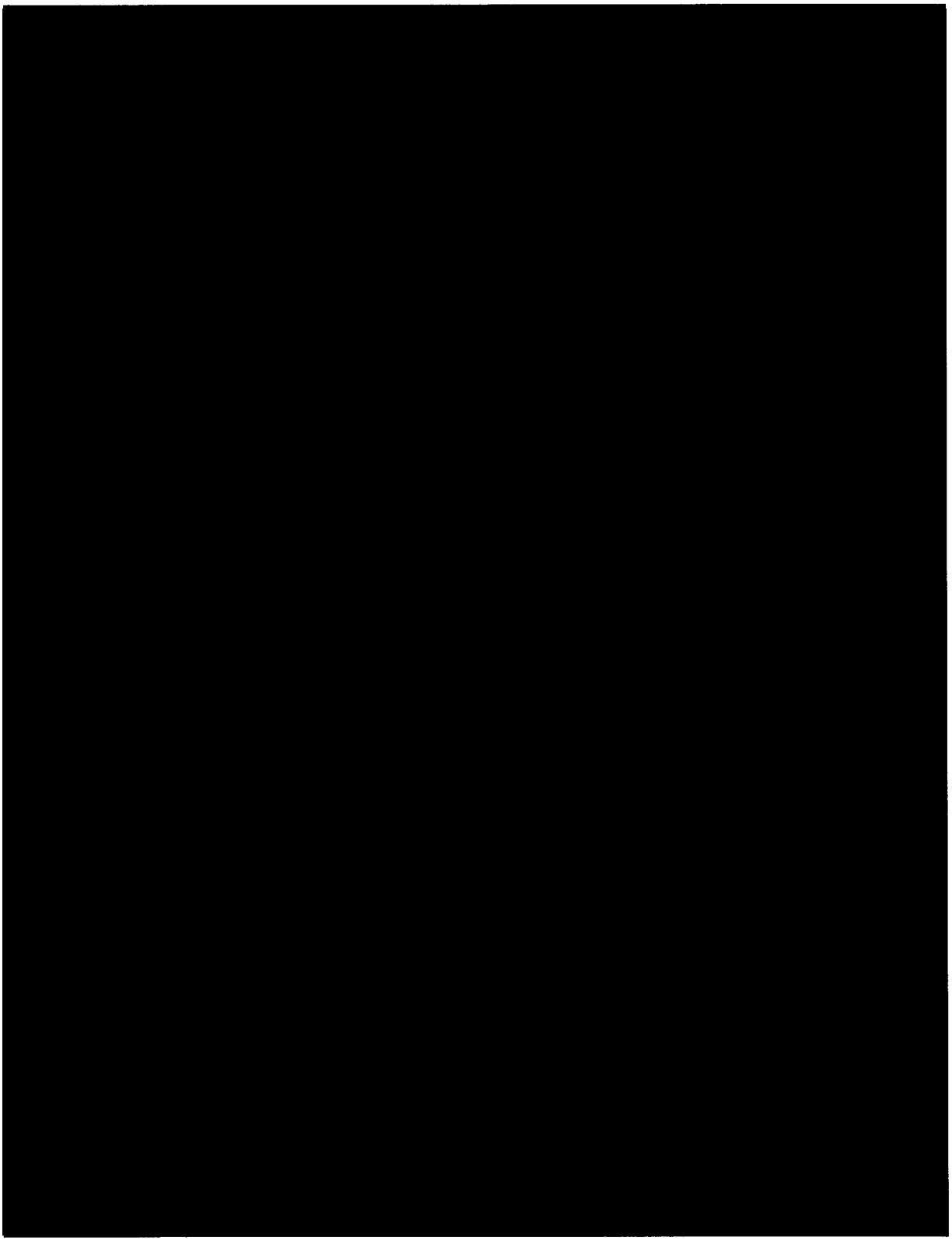


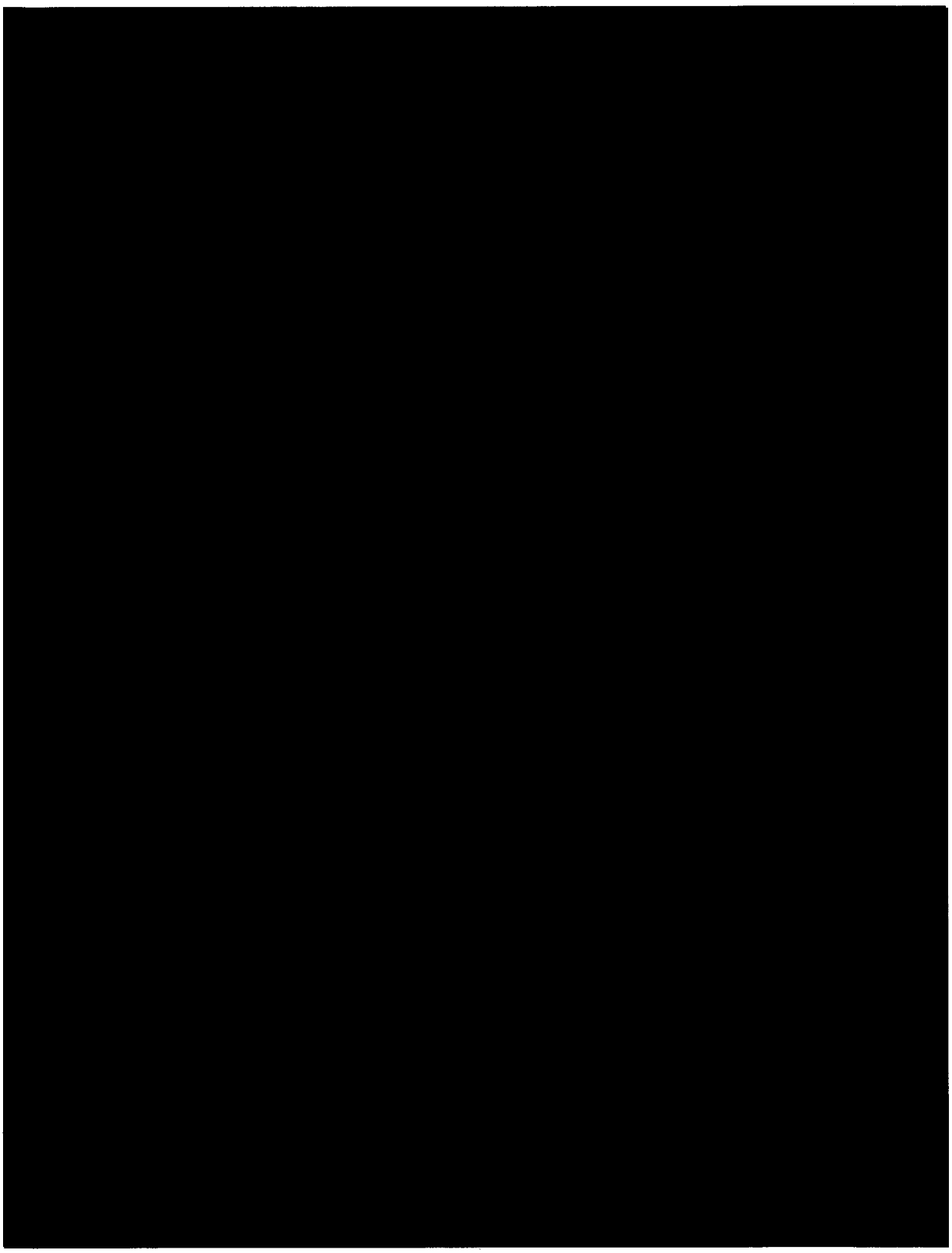


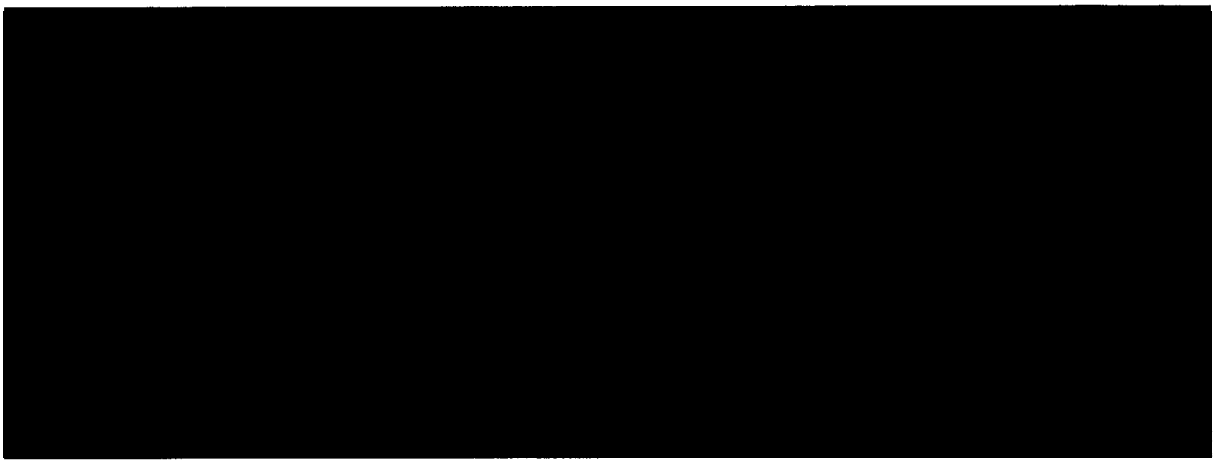












米国の添付文書

Xolair (omalizumab) Injection, Solution

For Subcutaneous Use

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 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, patients should be closely observed for an appropriate period of time after Xolair administration, and health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening. Patients should also be informed of the signs and symptoms of anaphylaxis and instructed to seek immediate medical care should symptoms occur (see WARNINGS, and PRECAUTIONS, Information for Patients).

DESCRIPTION

Xolair (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 containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Xolair is a sterile, white, preservative-free, lyophilized powder contained in a single-use vial that is reconstituted with Sterile Water for Injection (SWFI), USP, and administered as a subcutaneous (SC) injection. A Xolair vial contains 202.5 mg of Omalizumab, 145.5 mg sucrose, 2.8 mg L-histidine hydrochloride monohydrate, 1.8 mg L-histidine, and 0.5 mg polysorbate 20, and is designed to deliver 150 mg of Omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI, USP.

CLINICAL PHARMACOLOGY

Mechanism of Action

Xolair 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.

Pharmacokinetics

After SC administration, Omalizumab is 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. 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.

In vitro, Omalizumab forms complexes of limited size with IgE. Precipitating complexes and complexes larger than 1 million daltons in molecular weight are 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 in patients following SC administration was 78 ± 32 mL/kg.

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 liver reticuloendothelial system (RES) and endothelial cells. Intact IgG is 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. In addition, doubling body weight approximately doubled apparent clearance.

Pharmacodynamics

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.

Special Populations

The population pharmacokinetics of Xolair were analyzed to evaluate the effects of demographic characteristics. Analyses of these limited data suggest that no dose adjustments are necessary for age (12--76 years), race, ethnicity, or gender.

CLINICAL STUDIES

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. At screening, patients in Studies 1 and 2 had a forced expiratory volume in one second (FEV1) between 40% and 80% predicted, while in Study 3 there was no restriction on screening FEV1. All patients had a FEV1 improvement of at least 12% following beta-agonist administration. All patients were symptomatic and were being treated with inhaled corticosteroids (ICS) and short acting beta-agonists. In Study 3, long-acting beta-agonists were allowed. Study 3 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.

Each study was comprised of a run-in period to achieve a stable conversion to a common ICS (beclomethasone dipropionate, for Studies 1 and 2; fluticasone propionate for Study 3), followed by randomization to Xolair or placebo. In Study 3, 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 12 weeks (Studies 1 and 2) or 16 weeks (Study 3) during which ICS (or oral steroid in Study 3 subset) dose reduction was attempted in a step-wise manner.

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; patients who had a weight-IgE combination that yielded a dose greater than 750 mg were excluded from the studies. Patients who were to receive more than 300 mg within the 4-week period were administered half the total dose every 2 weeks.

The distribution of the number of asthma exacerbations per patient in each group during a study was analyzed separately for the stable steroid and steroid-reduction periods. In all three studies an exacerbation was defined as a worsening of asthma that required treatment with systemic corticosteroids or a doubling of the baseline ICS dose.

In both Studies 1 and 2 the number of exacerbations per patient was reduced in patients treated with Xolair compared with placebo (Table 1). In Study 3 the number of exacerbations in patients treated with Xolair was similar to that in placebo-treated patients (Table 2). The absence of an observed treatment effect in Study 3 may be related to differences in the patient population compared with Studies 1 and 2, study sample size, or other factors. In all three studies most exacerbations were managed in the out-patient setting and the majority were treated with systemic steroids. Hospitalization rates were not significantly different between Xolair and placebo-treated patients; however, the overall hospitalization rate was small. Among those patients who experienced an exacerbation, the distribution of exacerbation severity was similar between treatment groups.

Table 1: Frequency of Asthma Exacerbations per Patient by Phase in Studies 1 and 2

	Stable Steroid Phase (16 wks)			
	Study 1		Study 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

Table 2: Percentage of Patients with Asthma Exacerbations by Subgroup and Phase in Study 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	0.9		9.8	

(95% CI)	(−9.7, 13.7)		(−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 studies, a reduction of asthma exacerbations was not observed in the Xolair-treated patients who had FEV1> 80% at the time of randomization. Reductions in exacerbations were not seen in patients who required oral steroids as maintenance therapy.

In Studies 1 and 2 measures of airflow (FEV1) and asthma symptoms were evaluated (Table 3). The clinical relevance of the treatment-associated differences is unknown.

Table 3: Asthma Symptoms and Pulmonary Function During Stable Steroid Phase of Study 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†
FEV1 % 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 ($p < 0.05$).

Results from the stable steroid phase of Study 2 and the steroid reduction phases of both Studies 1 and 2 were similar to those presented in Table 3.

INDICATIONS AND USAGE

Xolair (Omalizumab) is indicated for adults and adolescents (12 years of age and above) 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. Safety and efficacy have not been established in other allergic conditions.

CONTRAINDICATIONS

Xolair should not be administered to patients who have experienced a severe hypersensitivity reaction to Xolair (see WARNINGS: Anaphylaxis).

WARNINGS

Anaphylaxis

Anaphylaxis has been reported to occur after administration of Xolair in premarketing clinical trials and

in postmarketing spontaneous reports. 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 the frequency of anaphylaxis attributed to Xolair use was estimated to be 0.1%. 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.

Xolair should only be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening. Patients should be closely observed 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). Patients should be informed of the signs and symptoms of anaphylaxis, and instructed to seek immediate medical care should signs or symptoms occur (See PRECAUTIONS, Information for Patients).

Xolair should be discontinued in patients who experience a severe hypersensitivity reaction (see CONTRAINDICATIONS).

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 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 (see ADVERSE REACTIONS: Clinical Trials Experience).

PRECAUTIONS

General

Xolair has not been shown to alleviate asthma exacerbations acutely and should not be used for the treatment of acute bronchospasm or status asthmaticus.

Information For Patients

Patients should be given and instructed 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.

Patients should be advised of the risk of life-threatening anaphylaxis with Xolair and that there have been reports of anaphylaxis 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 its 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. (See WARNINGS, Anaphylaxis).

Patients receiving Xolair should be told not to decrease the dose of, or stop taking any other asthma medications unless otherwise instructed by their physician. Patients should be told that they may not see immediate improvement in their asthma after beginning Xolair therapy.

Corticosteroid Reduction

Systemic or inhaled corticosteroids should not be abruptly discontinued upon initiation of Xolair therapy. Decreases in corticosteroids should be performed under the direct supervision of a physician and may need to be performed gradually.

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.

Parasitic (Helminth) Infection

In a one-year clinical trial conducted in Brazil in patients at high risk for geohelminthic infections (roundworm, hookworm, whipworm, threadworm), 53% (36/68) of omalizumab-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 Omalizumab 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. Patients at high risk of geohelminth infection should be monitored for such infections while on Xolair therapy. Insufficient data are available to determine the length of monitoring required for geohelminth infections after stopping Xolair treatment.

Laboratory Tests

Serum total IgE levels increase following administration of Xolair due to formation of Xolair:IgE complexes (see CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION). Elevated serum total IgE levels may persist for up to 1 year following discontinuation of Xolair. Serum total IgE levels obtained less than 1 year following discontinuation may not reflect steady state free IgE levels and should not be used to reassess the dosing regimen.

Drug Interactions

No formal drug interaction studies have been performed with Xolair. The concomitant use of Xolair and allergen immunotherapy has not been evaluated.

Carcinogenesis, Mutagenesis, Impairment Of Fertility

No long-term studies have been performed in animals to evaluate the carcinogenic potential of Xolair.

No evidence of mutagenic activity was observed in Ames tests using six different strains of bacteria with and without metabolic activation at Omalizumab concentrations up to 5000 μg/mL.

The effects of Omalizumab on male and female fertility have been assessed in cynomolgus monkey studies. Administration of Omalizumab at doses up to and including 75 mg/kg/week did not elicit reproductive toxicity in male cynomolgus monkeys and did not inhibit reproductive capability, including implantation, in female cynomolgus monkeys. These doses provide a 2- to 16-fold safety factor based on

total dose and 2- to 5-fold safety factor based on AUC over the range of adult clinical doses.

Pregnancy (Category B)

Reproduction studies in cynomolgus monkeys have been conducted with Omalizumab. Subcutaneous doses up to 75 mg/kg (12-fold the maximum clinical dose) of Omalizumab did not elicit maternal toxicity, embryotoxicity, or teratogenicity when administered throughout organogenesis and did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation, delivery, and nursing.

IgG molecules are known to cross the placental barrier. There are no adequate and well-controlled studies of Xolair in pregnant women. Because animal reproduction studies are not always predictive of human response, Xolair should be used during pregnancy only if clearly needed.

Pregnancy Exposure Registry

To monitor outcomes of pregnant women exposed to Xolair, including women who are exposed to at least one dose of Xolair within 8 weeks prior to conception or any time during pregnancy, a pregnancy exposure registry has been established. Healthcare providers should encourage their patients to call 1-866-4XOLAIR (1-866-496-5247) to enroll in the Xolair Pregnancy Exposure Registry. Healthcare providers can call this number to obtain further information about this registry.

Nursing Mothers

The excretion of Omalizumab in milk was evaluated in female cynomolgus monkeys receiving SC doses of 75 mg/kg/week. Neonatal plasma levels of Omalizumab after *in utero* exposure and 28 days of nursing were between 11% and 94% of the maternal plasma level. Milk levels of Omalizumab were 1.5% of maternal blood concentration. While Xolair presence in human milk has not been studied, IgG is excreted in human milk and therefore it is expected that Xolair will be present in human milk. The potential for Xolair absorption or harm to the infant are unknown; caution should be exercised when administering Xolair to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 have not been established.

Geriatric Use

In clinical trials 134 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.

ADVERSE REACTIONS

Clinical Trials Experience

The most serious adverse reactions occurring in clinical trials with Xolair were anaphylaxis and malignancies (see WARNINGS). Anaphylaxis was reported in 3 of 3507 (0.1%) patients in clinical trials. Anaphylaxis occurred with the first dose of Xolair in two patients and with the fourth dose in one patient. The time to onset of anaphylaxis was 90 minutes after administration in two patients and 2 hours after administration in one patient.

In clinical trials the observed incidence of malignancy among Xolair-treated patients (0.5%) was numerically higher than among patients in control groups (0.2%).

The adverse reactions most commonly observed among patients treated with Xolair in clinical studies included 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. These were also the most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Xolair, or the need for concomitant medication to treat an adverse reaction).

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of one drug cannot be directly compared with rates in the clinical studies of another drug and may not reflect the rates observed in medical practice.

The data described above reflect Xolair exposure for 2076 adult and adolescent patients ages 12 and older, including 1687 patients exposed for six months and 555 exposed for one year or more, in either placebo-controlled or other controlled asthma studies. The mean age of patients receiving Xolair was 42 years, with 134 patients 65 years of age or older; 60% were women, and 85% Caucasian. Patients received Xolair 150 to 375 mg every 2 or 4 weeks or, for patients assigned to control groups, standard therapy with or without a placebo.

Table 4 shows adverse events that occurred ≥ 1% more frequently in patients receiving Xolair than in those receiving placebo in the placebo controlled asthma studies. 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 and are described followingTable 4.

Table 4: Adverse Events ≥ 1% More Frequent in Xolair-Treated Patients

Adverse event	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

Age (among patients under age 65), race, and gender did not appear to affect the between group differences in the rates of adverse events.

Injection Site Reactions

Injection site reactions of any severity occurred at a rate of 45% in Xolair-treated patients compared with 43% in placebo-treated patients. The types of injection site reactions included: bruising, redness, warmth, burning, stinging, itching, hive formation, pain, indurations, mass, and inflammation.

Severe injection-site reactions occurred more frequently in Xolair-treated patients compared with patients in the placebo group (12% versus 9%).

The majority of injection site reactions occurred within 1 hour-post injection, lasted less than 8 days, and generally decreased in frequency at subsequent dosing visits.

Immunogenicity

Low titers of antibodies to Xolair were detected in approximately 1 / 1723 (< 0.1%) of patients treated with Xolair. The data reflect the percentage of patients whose test results were considered positive for antibodies to Xolair in an ELISA assay and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in the assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to Xolair with the incidence of antibodies to other products may be misleading.

Postmarketing Spontaneous Reports

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 in postapproval use of Xolair (see PRECAUTIONS: Eosinophilic Conditions).

Hematologic: Severe thrombocytopenia has been reported in postapproval use of Xolair.

Skin: Hair loss has been reported in postapproval use of Xolair.

OVERDOSAGE

The maximum tolerated dose of Xolair has not been determined. Single intravenous doses of up to 4000 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.

DOSAGE AND ADMINISTRATION

Xolair (Omalizumab) 150 to 375 mg is administered SC every 2 or 4 weeks. Because the solution is slightly viscous, the injection may take 5–10 seconds to administer. Doses (mg) and dosing frequency are determined by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See the dose determination charts below (Table 5 and Table 6) for appropriate dose assignment. Doses of more than 150 mg are divided among more than one injection site to limit injections to not more than 150 mg per site.

The need for continued therapy should be periodically reassessed based upon the patient's disease severity and level of asthma control.

Table 5: ADMINISTRATION EVERY 4 WEEKS Xolair Doses (milligrams) Administered by Subcutaneous Injection Every 4 Weeks for Adults and Adolescents (12 Years of Age and Older) with Asthma

<table>
<tr><th rowspan="2">Pre-treatment Serum IgE (IU/mL)</th><th colspan="4">Body Weight (kg)</th></tr>
<tr><th>30–60</th><th>> 60–70</th><th>> 70–90</th><th>> 90–150</th></tr>
<tr><td>≥ 30–100</td><td>150</td><td>150</td><td>150</td><td>300</td></tr>
<tr><td>> 100–200</td><td>300</td><td>300</td><td>300</td><td rowspan="5"></td></tr>
<tr><td>> 200–300</td><td>300</td><td colspan="3" rowspan="4">SEE TABLE 6</td></tr>
<tr><td>> 300–400</td></tr>
<tr><td>> 400–500</td></tr>
<tr><td>> 500–600</td></tr>
</table>

Table 6: ADMINISTRATION EVERY 2 WEEKS Xolair Doses (milligrams) Administered by Subcutaneous Injection Every 2 Weeks for Adults and Adolescents (12 Years of Age and Older) with Asthma

<table>
<tr><th rowspan="2">Pre-treatment Serum IgE (IU/mL)</th><th colspan="4">Body Weight (kg)</th></tr>
<tr><th>30–60</th><th>> 60–70</th><th>> 70–90</th><th>> 90–150</th></tr>
<tr><td>≥ 30–100</td><td colspan="3" rowspan="3">SEE TABLE 5</td><td rowspan="2">225</td></tr>
<tr><td>> 100–200</td></tr>
<tr><td>> 200–300</td><td>225</td><td>225</td><td>300</td></tr>
<tr><td>> 300–400</td><td>225</td><td>225</td><td>300</td><td rowspan="4"></td></tr>
<tr><td>> 400–500</td><td>300</td><td>300</td><td>375</td></tr>
<tr><td>> 500–600</td><td>300</td><td>375</td><td colspan="2" rowspan="2">DO NOT DOSE</td></tr>
<tr><td>> 600–700</td><td>375</td><td colspan="3"></td></tr>
</table>

Dosing Adjustments

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 1 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 Table 5 andTable 6.)

Preparation for Administration

Xolair for SC administration should be prepared using SWFI, USP, ONLY.

Xolair is for single use only and contains no preservatives. The solution should be used for SC administration within 8 hours following reconstitution when stored in the vial at 2–8°C (36–46°F), or within 4 hours of reconstitution when stored at room temperature.

The lyophilized product takes 15–20 minutes to dissolve. The fully reconstituted product will appear clear or slightly opalescent and may have a few small bubbles or foam around the edge of the vial. The reconstituted product is somewhat viscous; in order to obtain the full 1.2 mL dose, ALL OF THE PRODUCT MUST BE WITHDRAWN from the vial before expelling any air or excess solution from the syringe.

STEP 1: Draw 1.4 mL of SWFI, USP into a 3-cc syringe equipped with a 1-inch, 18-gauge needle.

STEP 2: 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.

STEP 3: Keeping the vial upright, gently swirl the upright vial for approximately 1 minute to evenly wet the powder. Do not shake.

STEP 4: After completing STEP 3, gently swirl the vial for 5–10 seconds approximately every 5 minutes in order to dissolve any remaining solids. There should be no visible gel-like particles in the solution. Do not use if foreign particles are present.

Note: Some vials may take longer than 20 minutes to dissolve completely. If this is the case, repeat STEP 4 until there are no visible gel-like particles in the solution. It is acceptable to have small bubbles or foam around the edge of the vial. Do not use if the contents of the vial do not dissolve completely by 40 minutes.

STEP 5: Invert the vial for 15 seconds in order to allow the solution to drain toward the stopper. Using a new 3-cc 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. 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.

STEP 6: Replace the 18-gauge needle with a 25-gauge needle for subcutaneous injection.

STEP 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, the injection may take 5–10 seconds to administer.

A 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 product (see Table 7).

Table 7: Number of Injections and Total Injection Volumes for Asthma

Dose (mg)	Number of Injections	Total Volume Injected (mL)*
150	1	1.2
225	2	1.8
300	2	2.4
375	3	3.0

* 1.2 mL maximum delivered volume per vial.

Stability and Storage

Xolair should be shipped at controlled ambient temperature (≤ 30°C [≤ 86°F]). Xolair should be stored under refrigerated conditions 2–8°C (36–46°F). Do not use beyond the expiration date stamped on

carton.

Xolair is for single-use only and contains no preservatives. The solution may be used for SC administration within 8 hours following reconstitution when stored in the vial at 2–8°C (36–46°F), or within 4 hours of reconstitution when stored at room temperature.

Reconstituted Xolair vials should be protected from direct sunlight.

HOW SUPPLIED

Xolair (Omalizumab) is supplied as a lyophilized, sterile powder in a single-use, 5-cc vial that is designed to deliver 150 mg of Xolair upon reconstitution with 1.4 mL SWFI, USP.

Each carton contains one single-use vial of Xolair® (Omalizumab) NDC 50242-040-62.

XOLAIR®
Omalizumab

For Subcutaneous Use

Manufactured by:

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

Jointly marketed by:

Genentech USA, Inc.
1 DNA Way
South San Francisco, CA 94080 4990

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

7390206/XOL-400050

LX1331

(4840203)
Initial US Approval: June 2003

Revision Date: TBD

MEDICATION GUIDE

XOLAIR®
(OMALIZUMAB)

IMPORTANT: XOLAIR SHOULD ALWAYS BE INJECTED IN YOUR DOCTOR'S OFFICE.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT XOLAIR?

A severe allergic reaction called anaphylaxis has happened in some patients after they received Xolair. Anaphylaxis is a life-threatening condition and can lead to death so get emergency medical treatment right away if symptoms occur.

Signs and Symptoms of anaphylaxis include:

- 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

Get emergency medical treatment right away if you have signs or symptoms of anaphylaxis after receiving Xolair.

Anaphylaxis from Xolair can happen:

- right after receiving a Xolair injection or hours later
- after any Xolair injection. Anaphylaxis has occurred after the first Xolair injection or after many Xolair injections.

Your healthcare provider should watch you for some time in the office for signs or symptoms of anaphylaxis after injecting Xolair. If you have signs or symptoms of anaphylaxis, tell your healthcare provider right away.

Your healthcare provider should instruct you about getting emergency medical treatment and further medical care if you have signs or symptoms of anaphylaxis after leaving the doctor's office.

WHAT IS XOLAIR?

Xolair is an injectable medicine for patients ages 12 and older with moderate to severe persistent allergic asthma whose asthma symptoms are not controlled by asthma medicines called inhaled corticosteroids. A skin or blood test is done to see if you have allergic asthma.

WHAT ELSE SHOULD I KNOW ABOUT XOLAIR?

- You should not receive Xolair if you have ever had an allergic reaction to a Xolair injection.
- Do not change or stop taking any of your other asthma medicines unless your healthcare provider tells you to do so.
- There are other possible side effects with Xolair. Talk to your doctor for more information. You can also go to www.xolair.com or call 1-866-4XOLAIR (1-866-496-5247).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

EU 加盟国での共通の添付文書

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.

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

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Xolair is an off-white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xolair is indicated as add-on therapy to improve asthma control in adult and adolescent patients (12 years of age and above) 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. Xolair treatment should only be considered for patients with convincing IgE mediated asthma (see section 4.2).

4.2 Posology and method of administration

Use in adolescents and adults (12 years of age and older)
Xolair treatment should be initiated by physicians experienced in the diagnosis and treatment of severe persistent asthma.

The appropriate dose and dosing frequency of Xolair is determined by baseline IgE (IU/ml), measured before the start of treatment, and body weight (kg). Prior to initial dosing, patients should have their IgE level determined by any commercial serum total IgE assay for their dose assignment. Based on these measurements 75–375 mg of Xolair in 1 to 3 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 patients with IgE below 76 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.

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

The maximum recommended dose is 375 mg omalizumab every two weeks.

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

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

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

For information on reconstitution of Xolair, see section 6.6.

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

[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		
>200–300	150	150	225	300	300					
>300–400	225	225	300							
>400–500	225	300								
>500–600	300	300								
>600–700	300									

ADMINISTRATION EVERY 2 WEEKS
SEE TABLE 3

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									225	300
>200–300						225	225	225	300	375
>300–400				225	225	225	300	300		
>400–500			225	225	300	300	375	375		
>500–600			225	300	300	375	DO NOT ADMINISTER – data is unavailable for dose recommendation			
>600–700		225	225	300	375					

Treatment duration, monitoring and dose adjustments
Discontinuation of Xolair treatment generally results in a return to elevated free IgE levels and associated symptoms.

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 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).

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).

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 dosage from younger adult patients.

Children (age below 12 years)
Safety and efficacy in paediatric patients below the age of 12 years have not been established and use of Xolair in such patients is therefore not recommended.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and special 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.

Xolair therapy has not been studied in patients with autoimmune diseases, immune complex-mediated conditions, or pre-existing renal or hepatic impairment. 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.

Patients with diabetes mellitus, the glucose-galactose malabsorption syndrome, fructose intolerance or sucrase-isomaltase deficiency should be warned that one 75 mg Xolair dose contains 54 mg of sucrose.

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

Anaphylactic reactions were rare in clinical trials (see section 4.8).

As with all recombinant DNA derived humanised monoclonal antibodies, patients may in rare cases develop antibodies to omalizumab.

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.

Malignancies
During clinical trials, there was a numerical imbalance in cancers arising in the Xolair treatment group compared with the control group. The frequency of observed cases was uncommon (<1/100) in both the active and the control group, i.e. 25 cancers in 5,015 patients treated with Xolair (0.5%) and 5 cancers in 2,854 patients in the control group (0.18%). The diversity in the type of cancers observed, the relatively short duration of exposure and the clinical features of the individual cases render a causal relationship unlikely. The overall observed incidence rate of malignancy in the Xolair clinical trial programme was comparable to that reported in the general population.

Churg-Strauss syndrome and hypereosinophilic syndrome
Patients with severe asthma may rarely present with 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 agents, 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, cardiac complications, and/or neuropathy.

4.5 Interaction with other medicinal products and other forms of interaction

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. No formal medicinal product or vaccine interaction studies have been performed with Xolair. There is no pharmacological reason to expect that commonly prescribed medications 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 asthma medications. Limited data are available on the use of Xolair in combination with specific immunotherapy (hypo-sensitisation therapy). Efficacy of Xolair treatment in combination with specific immunotherapy has not been established. Current data suggest that no dose adjustments of Xolair are needed in patients on established hypo-sensitisation therapy.

4.6 Pregnancy and lactation

There are no adequate data from the use of omalizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Omalizumab crosses the placental barrier and the potential for harm to the foetus is unknown. Omalizumab has been associated with age-dependent decreases in blood platelets in non-human primates, with a greater relative sensitivity in juvenile animals (see section 5.3). Xolair should not be used during pregnancy unless clearly necessary.

It is not known whether omalizumab is excreted in human breast milk. Omalizumab is excreted into non-human primate breast milk and an effect on the suckling child cannot be excluded. Nursing mothers should not breast-feed during Xolair therapy.

4.7 Effects on ability to drive and use machines

Patients receiving Xolair should be warned that if they experience dizziness, fatigue, faintness or drowsiness they should not drive or use machinery.

4.8 Undesirable effects

During clinical trials the most commonly reported adverse reactions were injection site reactions, including injection site pain, swelling, erythema and pruritus, and headaches. Most of the reactions were mild or moderate in severity.

Table 4 lists the adverse reactions recorded in clinical studies in the total safety population treated with Xolair by system organ class and by frequency. Frequencies are defined as: common (>1/100; <1/10), uncommon (>1/1,000; <1/100) and rare (<1/1,000). Events reported in the post-marketing setting are listed with frequency "unknown".

Table 4: Adverse reactions

Blood and lymphatic system disorders	
Unknown	Idiopathic severe thrombocytopenia
Infections and infestations	
Rare	Parasitic infection
Immune system disorders	
Rare	Anaphylactic reaction, other serious allergic conditions
Nervous system disorders	
Common	Headache
Uncommon	Dizziness, somnolence, paraesthesia, syncope
Vascular disorders	
Uncommon	Postural hypotension, flushing
Respiratory, thoracic and mediastinal disorders	
Uncommon	Pharyngitis, coughing, allergic bronchospasm
Rare	Laryngoedema
Unknown	Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome)
Gastrointestinal disorders	
Uncommon	Nausea, diarrhoea, dyspeptic signs and symptoms
Musculoskeletal and connective tissue disorders	
Unknown	Arthralgia, myalgia, joint swelling
Skin and subcutaneous tissue disorders	
Uncommon	Urticaria, rash, pruritus, photosensitivity
Rare	Angioedema
Unknown	Alopecia
General disorders and administration site conditions	
Common	Injection site reactions such as pain, erythema, pruritus, swelling
Uncommon	Weight increase, fatigue, swelling arms, influenza-like illness

Malignancies
The overall observed incidence rate of malignancy in the Xolair clinical trial programme was comparable to that reported in the general population (see section 4.4).

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 even though isolated cases of idiopathic thrombocytopenia 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 was unaltered (see section 4.4).

4.9 Overdose

No case of overdose has been reported. A 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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.

Omalizumab binds to IgE and prevents binding of IgE to the high-affinity FCεRI 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. Furthermore, 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 drug washout.

Clinical experience

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, 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.

5.2 Pharmacokinetic properties

The pharmacokinetics of omalizumab have been studied in 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.

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
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 (12–76 years), race, ethnicity or gender.

Renal and hepatic impairment
There are no pharmacokinetic or pharmacodynamic data in patients with renal or hepatic impairment (see section 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 was well tolerated in non-human primates, 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 (about 12-fold exposure ratio based on 28-day AUC values at 75 mg/kg versus the clinical maximum dose) 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.

Omalizumb is excreted in milk in cynomolgus monkeys. Milk levels of omalizumab were 1.5% of the maternal blood concentration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Sucrose
Histidine
Histidine hydrochloride monohydrate
Polysorbate 20

Solvent:
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

4 years

After reconstitution: The chemical and physical stability of the reconstituted 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 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 4 hours at 30°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package.

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.

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

6.6 Instructions for use, handling and disposal

The lyophilised product takes 15–20 minutes to dissolve, although in some cases it may take longer. The fully reconstituted product will appear clear or slightly opaque and may have a few small bubbles or foam around the edge of the vial. Because of the viscosity of the reconstituted product care must be taken to WITHDRAW ALL OF THE 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 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 product will appear clear or slightly opaque. 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 take 5–10 seconds to administer the solution by subcutaneous injection.

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

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

Xolair 75 mg powder for solution for injection is supplied in a single-use vial and contains no antibacterial preservatives.

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

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25.10.2005

10. DATE OF REVISION OF THE TEXT

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.

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

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Xolair is an off-white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xolair is indicated as add-on therapy to improve asthma control in adult and adolescent patients (12 years of age and above) 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. Xolair treatment should only be considered for patients with convincing IgE mediated asthma (see section 4.2).

4.2 Posology and method of administration

Use in adolescents and adults (12 years of age and older)
Xolair treatment should be initiated by physicians experienced in the diagnosis and treatment of severe persistent asthma.

The appropriate dose and dosing frequency of Xolair is determined by baseline IgE (IU/ml), measured before the start of treatment, and body weight (kg). Prior to initial dosing, patients should have their IgE level determined by any commercial serum total IgE assay for their dose assignment. Based on these measurements 75–375 mg of Xolair in 1 to 3 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 patients with IgE below 76 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.

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

The maximum recommended dose is 375 mg omalizumab every two weeks.

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

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

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

For information on reconstitution of Xolair, see section 6.6.

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

[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		
>200–300	150	150	225	300	300					
>300–400	225	225	300							
>400–500	225	300								
>500–600	300	300								
>600–700	300									

ADMINISTRATION EVERY 2 WEEKS
SEE TABLE 3

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									225	300
>200–300						225	225	225	300	375
>300–400				225	225	225	300	300		
>400–500			225	225	300	300	375	375		
>500–600			225	300	300	375	DO NOT ADMINISTER – data is unavailable for dose recommendation			
>600–700		225	225	300	375					

Treatment duration, monitoring and dose adjustments
Discontinuation of Xolair treatment generally results in a return to elevated free IgE levels and associated symptoms.

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 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).

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).

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 dosage from younger adult patients.

Children (age below 12 years)
Safety and efficacy in paediatric patients below the age of 12 years have not been established and use of Xolair in such patients is therefore not recommended.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and special 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.

Xolair therapy has not been studied in patients with autoimmune diseases, immune complex-mediated conditions, or pre-existing renal or hepatic impairment. 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.

Patients with diabetes mellitus, the glucose-galactose malabsorption syndrome, fructose intolerance or sucrase-isomaltase deficiency should be warned that one 150 mg Xolair dose contains 108 mg of sucrose.

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

Anaphylactic reactions were rare in clinical trials (see section 4.8).

As with all recombinant DNA derived humanised monoclonal antibodies, patients may in rare cases develop antibodies to omalizumab.

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.

Malignancies
During clinical trials, there was a numerical imbalance in cancers arising in the Xolair treatment group compared with the control group. The frequency of observed cases was uncommon (<1/100) in both the active and the control group, i.e. 25 cancers in 5,015 patients treated with Xolair (0.5%) and 5 cancers in 2,854 patients in the control group (0.18%). The diversity in the type of cancers observed, the relatively short duration of exposure and the clinical features of the individual cases render a causal relationship unlikely. The overall observed incidence rate of malignancy in the Xolair clinical trial programme was comparable to that reported in the general population.

Churg-Strauss syndrome and hypereosinophilic syndrome
Patients with severe asthma may rarely present with 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 agents, 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, cardiac complications, and/or neuropathy.

4.5 Interaction with other medicinal products and other forms of interaction

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. No formal medicinal product or vaccine interaction studies have been performed with Xolair. There is no pharmacological reason to expect that commonly prescribed medications 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 asthma medications. Limited data are available on the use of Xolair in combination with specific immunotherapy (hypo-sensitisation therapy). Efficacy of Xolair treatment in combination with specific immunotherapy has not been established. Current data suggest that no dose adjustments of Xolair are needed in patients on established hypo-sensitisation therapy.

4.6 Pregnancy and lactation

There are no adequate data from the use of omalizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Omalizumab crosses the placental barrier and the potential for harm to the foetus is unknown. Omalizumab has been associated with age-dependent decreases in blood platelets in non-human primates, with a greater relative sensitivity in juvenile animals (see section 5.3). Xolair should not be used during pregnancy unless clearly necessary.

It is not known whether omalizumab is excreted in human breast milk. Omalizumab is excreted into non-human primate breast milk and an effect on the suckling child cannot be excluded. Nursing mothers should not breast-feed during Xolair therapy.

4.7 Effects on ability to drive and use machines

Patients receiving Xolair should be warned that if they experience dizziness, fatigue, faintness or drowsiness they should not drive or use machinery.

4.8 Undesirable effects

During clinical trials the most commonly reported adverse reactions were injection site reactions, including injection site pain, swelling, erythema and pruritus, and headaches. Most of the reactions were mild or moderate in severity.

Table 4 lists the adverse reactions recorded in clinical studies in the total safety population treated with Xolair by system organ class and by frequency. Frequencies are defined as: common (>1/100; <1/10), uncommon (>1/1,000; <1/100) and rare (<1/1,000). Events reported in the post-marketing setting are listed with frequency "unknown".

Table 4: Adverse reactions

Blood and lymphatic system disorders	
Unknown	Idiopathic severe thrombocytopenia
Infections and infestations	
Rare	Parasitic infection
Immune system disorders	
Rare	Anaphylactic reaction, other serious allergic conditions
Nervous system disorders	
Common	Headache
Uncommon	Dizziness, somnolence, paraesthesia, syncope
Vascular disorders	
Uncommon	Postural hypotension, flushing
Respiratory, thoracic and mediastinal disorders	
Uncommon	Pharyngitis, coughing, allergic bronchospasm
Rare	Laryngoedema
Unknown	Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome)
Gastrointestinal disorders	
Uncommon	Nausea, diarrhoea, dyspeptic signs and symptoms
Musculoskeletal and connective tissue disorders	
Unknown	Arthralgia, myalgia, joint swelling
Skin and subcutaneous tissue disorders	
Uncommon	Urticaria, rash, pruritus, photosensitivity
Rare	Angioedema
Unknown	Alopecia
General disorders and administration site conditions	
Common	Injection site reactions such as pain, erythema, pruritus, swelling
Uncommon	Weight increase, fatigue, swelling arms, influenza-like illness

Malignancies
The overall observed incidence rate of malignancy in the Xolair clinical trial programme was comparable to that reported in the general population (see section 4.4).

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 even though isolated cases of idiopathic thrombocytopenia 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 was unaltered (see section 4.4).

4.9 Overdose

No case of overdose has been reported. A 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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.

Omalizumab binds to IgE and prevents binding of IgE to the high-affinity FCεRI 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. Furthermore, 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 drug washout.

Clinical experience
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.

Physicians 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, 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.

5.2 Pharmacokinetic properties

The pharmacokinetics of omalizumab have been studied in 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.

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
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 (12–76 years), race, ethnicity or gender.

Renal and hepatic impairment
There are no pharmacokinetic or pharmacodynamic data in patients with renal or hepatic impairment (see section 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 was well tolerated in non-human primates, 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 (about 12-fold exposure ratio based on 28-day AUC values at 75 mg/kg versus the clinical maximum dose) 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.

Omalizumb is excreted in milk in cynomolgus monkeys. Milk levels of omalizumab were 1.5% of the maternal blood concentration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Sucrose
Histidine
Histidine hydrochloride monohydrate
Polysorbate 20

Solvent:
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

4 years

After reconstitution: The chemical and physical stability of the reconstituted 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 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 4 hours at 30°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package.

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.

Xolair 150 mg powder and solvent for solution for injection is supplied as packs containing 1, 4 or 10 vials of powder and 1, 4 or 10 ampoules of water for injections, respectively. Not all pack sizes may be marketed.

6.6 Instructions for use, handling and disposal

The lyophilised product takes 15–20 minutes to dissolve, although in some cases it may take longer. The fully reconstituted product will appear clear or slightly opaque and may have a few small bubbles or foam around the edge of the vial. Because of the viscosity of the reconstituted product care must be taken to WITHDRAW ALL OF THE 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 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 product will appear clear or slightly opaque. Do not use if solid particles are present.

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

6. Replace the 18-gauge needle with a 25-gauge needle for subcutaneous injection.

7. Expel air, large bubbles, and any excess solution in order to obtain the required 1.2 ml dose. A thin layer of small bubbles may remain at the top of the solution in the syringe. Because the solution is slightly viscous, it may take 5–10 seconds to administer the solution by subcutaneous injection.

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

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

Xolair 150 mg powder for solution for injection is supplied in a single-use vial and contains no antibacterial preservatives.

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

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25.10.2005

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

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

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

- **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE 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, histidine, histidine hydrochloride monohydrate and polysorbate 20.

Solvent: Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 x 75 mg vial
1 x 2 ml solvent ampoule

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use immediately after reconstitution (it may be stored at 2°C – 8°C for up to 8 hours or at 30°C for 4 hours).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package.

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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/001

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Xolair 75 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

Xolair 75 mg powder for solution for injection
Omalizumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)

7. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MAH logo

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 ml

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

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, histidine, histidine hydrochloride monohydrate and polysorbate 20.

Solvent: Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 x 150 mg vial
1 x 2 ml solvent ampoule

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use immediately after reconstitution (it may be stored at 2°C – 8°C for up to 8 hours or at 30°C for 4 hours).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package.

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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/002

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Xolair 150 mg

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

CARTON CONTAINING 1 VIAL AND 1 AMPOULE AS INTERMEDIATE PACK (WITHOUT BLUE BOX) OF THE MULTIPACK CONTAINING 4 VIALS AND 4 AMPOULES

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, histidine, histidine hydrochloride monohydrate and polysorbate 20.

Solvent: Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 x 150 mg vial
1 x 2 ml solvent ampoule
Component of a multipack comprising 4 packs, each containing 1 vial and 1 ampoule.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use immediately after reconstitution (it may be stored at 2°C – 8°C for up to 8 hours or at 30°C for 4 hours).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package.

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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/003

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

CARTON CONTAINING 1 VIAL AND 1 AMPOULE AS INTERMEDIATE PACK (WITHOUT BLUE BOX) OF THE MULTIPACK CONTAINING 10 VIALS AND 10 AMPOULES

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, histidine, histidine hydrochloride monohydrate and polysorbate 20.

Solvent: Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 x 150 mg vial
1 x 2 ml solvent ampoule
Component of a multipack comprising 10 packs, each containing 1 vial and 1 ampoule.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use immediately after reconstitution (it may be stored at 2°C – 8°C for up to 8 hours or at 30°C for 4 hours).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package.

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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/004

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

WRAPPER LABEL ON MULTIPACKS CONTAINING 4 INTERMEDIATE PACKS 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, histidine, histidine hydrochloride monohydrate and polysorbate 20.

Solvent: Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use immediately after reconstitution (it may be stored at 2°C – 8°C for up to 8 hours or at 30°C for 4 hours).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package.

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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/003

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

WRAPPER LABEL ON MULTIPACKS CONTAINING 10 INTERMEDIATE PACKS 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, histidine, histidine hydrochloride monohydrate and polysorbate 20.

Solvent: Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use immediately after reconstitution (it may be stored at 2°C – 8°C for up to 8 hours or at 30°C for 4 hours).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package.

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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/319/004

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

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

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)

7. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MAH logo

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 ml

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

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using Xolair.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Xolair 75 mg powder and solvent for solution for injection
Omalizumab

- The active substance is omalizumab.
- The other ingredients are sucrose, histidine, histidine hydrochloride monohydrate and polysorbate 20.
- An ampoule containing 2 ml of water for injections, which is used to dissolve the powder before injection, is also provided in the pack.

Marketing Authorisation Holder
Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

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

1. WHAT XOLAIR IS AND WHAT IT IS USED FOR

Xolair is a powder and solvent for solution for injection.

Xolair is supplied as an 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 health professional. Each vial delivers 75 mg of omalizumab.

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.

Xolair is used to prevent your asthma getting worse and control your asthma symptoms when given in addition to your other asthma medication.

Xolair is used to control symptoms of severe allergic asthma in adults or adolescents (12 years of age and older) whose asthma symptoms are not well controlled by high-dose steroid inhalers or beta-agonist inhalers.

Xolair works by blocking a substance called immunoglobulin E (IgE), which is produced by your body. IgE plays a key role in causing allergic asthma. Your doctor will measure the amount of IgE in your blood before giving you Xolair injections.

2. BEFORE YOU USE XOLAIR

Do not use Xolair:
- if you are hypersensitive (allergic) to omalizumab or any of the other ingredients of Xolair. The ingredients are listed at the beginning of this leaflet.

Talk to your doctor before you have an injection.

Take special care with Xolair:
Do not use Xolair to treat acute asthma symptoms, such as a sudden asthma attack. You will have been given a separate medicine for this.

Watch out for allergic reactions to Xolair. Xolair contains a protein, and proteins can cause serious allergic reactions in some people. Signs include rash, difficulty in breathing, swelling or feeling faint. If you have an allergic reaction after taking Xolair, contact a doctor as soon as you can.

Do not use Xolair 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, allergic skin rash or hay fever.

Xolair will not harm you but you may need other medicines to treat these conditions.

Xolair in children and adolescents
Do not give Xolair to children under 12 years of age. Not enough is known about its effect on younger children.

Xolair and older people
Xolair may be given to people aged 65 years and over. There is no evidence to suggest that any special precautions are needed when older people are treated – although experience is still limited.

Patients with kidney or liver problems
If you have kidney or liver problems, please talk to your doctor about using Xolair.

Parasite infections
If you are living in a region where parasite infections are frequent or travelling to such a region, please tell your doctor. Xolair may weaken your resistance to such infections. If you are taking a treatment against parasite infection, please tell your doctor. Xolair may reduce the efficacy of your treatment.

Pregnancy
If you are pregnant or plan to become pregnant, tell your doctor before starting treatment with Xolair. Your doctor will discuss with you the benefits and potential risks of being given this medicine during pregnancy.

If you become pregnant while being treated with Xolair, tell your doctor straight away.

Breast-feeding
If you are breast-feeding or intend to breast-feed, get advice from your doctor before taking Xolair. Xolair may be passed in your breast milk to your baby.

Driving and using machines:
Xolair can make some people feel dizzy, sleepy or faint, although this is uncommon. Take care: make sure you are not affected before you drive or use machines.

Important information about some of the ingredients of Xolair:
If you are a diabetic or have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking Xolair. Xolair contains sucrose.

Taking other medicines:
Xolair can be used together with inhaled corticosteroids and other medicines for allergic asthma, but it is still important to tell your doctor that you are taking them before you are given Xolair.

You will need to carry on taking your current asthma medicine during Xolair treatment. Do not stop taking any asthma medications without talking to your doctor.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

3. HOW TO USE XOLAIR

Your doctor will give you Xolair as an injection just under the skin.

Before you start Xolair therapy, your doctor will do a blood test to measure the amount of IgE in your blood. The doctor will work out how much Xolair you need and how often you will be given it. This will depend on your body weight and the amount of IgE measured in your blood.

Follow your doctor's instructions carefully.

How much you will be given
You will be given 1–3 injections. The injections will be given every two weeks, or every four weeks.

You will need to carry on taking your current asthma medicine during Xolair treatment. Do not stop taking any asthma medications without talking to your doctor.

You may not see an immediate improvement in your asthma after beginning Xolair therapy. It usually takes several weeks to have the full effect.

If you use more Xolair than you should:
If you accidentally have been given more Xolair than prescribed, please contact your doctor for advice.

If you forget to use Xolair:
If you forget to use Xolair, use it as soon as you remember or contact your doctor. Do not take a double dose to make up for forgotten individual doses. Ask your doctor for advice.

Effects when treatment with Xolair is stopped:
Interrupting or ending the treatment with Xolair may cause your asthma symptoms to come back.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Xolair can have side effects. The side effects caused by Xolair are usually mild to moderate but occasionally can be serious.

Serious side effects include:

- Sudden severe allergic reactions (rare - *likely to affect between 1 and 10 in every 10,000 patients)*. If you notice sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, fast heart beat, dizziness and light-headedness, shortness of breath, wheezing or trouble breathing, or any other new symptoms, tell your doctor or nurse immediately.
- Joint appearance of some of the following symptoms: pain, numbness, tingling in the arms and legs, lumps or raised patches in the skin, weakness and fatigue, loss of appetite and weight loss (signs of so-called "Churg-Strauss syndrome").
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.

If you experience any of these, tell your doctor or nurse straight away.

Other side effects include:

Common side effects – likely *to affect up to 10 in every 100 patients*

- headache
- reactions at the injection site including pain, swelling, itching and redness.

Uncommon side effects – *likely to affect up to 1 in every 100 patients*

- 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, joint pain, muscle pain and joint swelling
- hair loss

If any of these affect you severely, tell your doctor. If you notice any side effects not mentioned in this leaflet or are concerned about those listed, please talk to your doctor or pharmacist.

5. STORING XOLAIR

Keep out of the reach and sight of children.
Store in the original package.
Store in a refrigerator (2°C – 8°C). Do not freeze.
Do not use after the expiry date stated on the label.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Luxembourg/Luxemburg
Novartis Pharma GmbH
Tél/Tel: +49 911 273 0

България
Novartis Pharma Services Inc.
Тел.: +359 2 489 98 28

Magyarország
Novartis Hungária Kft. Pharma
Tel.: +36 1 457 65 00

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Malta
Novartis Pharma Services Inc.
Tel: +356 2298 3217

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Nederland
Novartis Pharma B.V.
Tel: +31 26 37 82 111

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Eesti
Novartis Pharma Services Inc.
Tel: +372 60 62 400

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 550 8888

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

România
Novartis Pharma Services Inc.
Tel: +40 21 31299 01

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 77

Ísland
Vistor hf.
Sími: +354 535 7000

Slovenská republika
Novartis s.r.o.
Tel: +421 2 5542 5439

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 9 61 33 22 11

Κύπρος
Δημητριάδης και Παπαέλληνας Λτδ
Τηλ: +357 22 690 690

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

Latvija
Novartis Pharma Services Inc.
Tel: +371 7 887 070

Lietuva
Novartis Pharma Services Inc.
Tel: +370 5 269 16 50

United Kingdom
Novartis Pharmaceuticals UK Ltd.
Tel: +44 1276 698370

This leaflet was last approved on {date}

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

The following information is intended for medical or healthcare professionals only:

The lyophilised product takes 15–20 minutes to dissolve, although in some cases it may take longer. The fully reconstituted product will appear clear or slightly opaque and may have a few small bubbles or foam around the edge of the vial. Because of the viscosity of the reconstituted product care must be taken to WITHDRAW ALL OF THE 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 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 product will appear clear or slightly opaque. 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 take 5–10 seconds to administer the solution by subcutaneous injection.

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

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

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using Xolair.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Xolair 150 mg powder and solvent for solution for injection
Omalizumab

- The active substance is omalizumab.
- The other ingredients are sucrose, histidine, histidine hydrochloride monohydrate and polysorbate 20.
- An ampoule containing 2 ml of water for injections, which is used to dissolve the powder before injection, is also provided in the pack.

Marketing Authorisation Holder
Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

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

1. WHAT XOLAIR IS AND WHAT IT IS USED FOR

Xolair is a powder and solvent for solution for injection.

Xolair is supplied as an 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 health professional. Each vial delivers 150 mg of omalizumab.

Xolair is available in packs containing one, four or ten vials of powder for solution for injection and one, four or ten ampoules of 2 ml water for injections. Not all pack sizes may be marketed.

Xolair is also available in vials with 75 mg omalizumab.

Xolair is used to prevent your asthma getting worse and control your asthma symptoms when given in addition to your other asthma medication.

Xolair is used to control symptoms of severe allergic asthma in adults or adolescents (12 years of age and older) whose asthma symptoms are not well controlled by high-dose steroid inhalers or beta-agonist inhalers.

Xolair works by blocking a substance called immunoglobulin E (IgE), which is produced by your body. IgE plays a key role in causing allergic asthma. Your doctor will measure the amount of IgE in your blood before giving you Xolair injections.

2. BEFORE YOU USE XOLAIR

Do not use Xolair:
- if you are hypersensitive (allergic) to omalizumab or any of the other ingredients of Xolair. The ingredients are listed at the beginning of this leaflet.

Talk to your doctor before you have an injection.

Take special care with Xolair:
Do not use Xolair to treat acute asthma symptoms, such as a sudden asthma attack. You will have been given a separate medicine for this.

Watch out for allergic reactions to Xolair. Xolair contains a protein, and proteins can cause serious allergic reactions in some people. Signs include rash, difficulty in breathing, swelling or feeling faint. If you have an allergic reaction after taking Xolair, contact a doctor as soon as you can.

Do not use Xolair 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, allergic skin rash or hay fever.

Xolair will not harm you but you may need other medicines to treat these conditions.

Xolair in children and adolescents
Do not give Xolair to children under 12 years of age. Not enough is known about its effect on younger children.

Xolair and older people
Xolair may be given to people aged 65 years and over. There is no evidence to suggest that any special precautions are needed when older people are treated – although experience is still limited.

Patients with kidney or liver problems
If you have kidney or liver problems, please talk to your doctor about using Xolair.

Parasite infections
If you are living in a region where parasite infections are frequent or travelling to such a region, please tell your doctor. Xolair may weaken your resistance to such infections. If you are taking a treatment against parasite infection, please tell your doctor. Xolair may reduce the efficacy of your treatment.

Pregnancy
If you are pregnant or plan to become pregnant, tell your doctor before starting treatment with Xolair. Your doctor will discuss with you the benefits and potential risks of being given this medicine during pregnancy.

If you become pregnant while being treated with Xolair, tell your doctor straight away.

Breast-feeding
If you are breast-feeding or intend to breast-feed, get advice from your doctor before taking Xolair. Xolair may be passed in your breast milk to your baby.

Driving and using machines:
Xolair can make some people feel dizzy, sleepy or faint, although this is uncommon. Take care: make sure you are not affected before you drive or use machines.

Important information about some of the ingredients of Xolair:
If you are a diabetic or have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking Xolair. Xolair contains sucrose.

Taking other medicines:
Xolair can be used together with inhaled corticosteroids and other medicines for allergic asthma, but it is still important to tell your doctor that you are taking them before you are given Xolair.

You will need to carry on taking your current asthma medicine during Xolair treatment. Do not stop taking any asthma medications without talking to your doctor.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

3. HOW TO USE XOLAIR

Your doctor will give you Xolair as an injection just under the skin.

Before you start Xolair therapy, your doctor will do a blood test to measure the amount of IgE in your blood. The doctor will work out how much Xolair you need and how often you will be given it. This will depend on your body weight and the amount of IgE measured in your blood.

Follow your doctor's instructions carefully.

How much you will be given
You will be given 1–3 injections. The injections will be given every two weeks, or every four weeks.

You will need to carry on taking your current asthma medicine during Xolair treatment. Do not stop taking any asthma medications without talking to your doctor.

You may not see an immediate improvement in your asthma after beginning Xolair therapy. It usually takes several weeks to have the full effect.

If you use more Xolair than you should:
If you accidentally have been given more Xolair than prescribed, please contact your doctor for advice.

If you forget to use Xolair:
If you forget to use Xolair, use it as soon as you remember or contact your doctor. Do not take a double dose to make up for forgotten individual doses. Ask your doctor for advice.

Effects when treatment with Xolair is stopped:
Interrupting or ending the treatment with Xolair may cause your asthma symptoms to come back.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Xolair can have side effects. The side effects caused by Xolair are usually mild to moderate but occasionally can be serious.

Serious side effects include:

- Sudden severe allergic reactions (rare - *likely to affect between 1 and 10 in every 10,000 patients)*. If you notice sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, fast heart beat, dizziness and light-headedness, shortness of breath, wheezing or trouble breathing, or any other new symptoms, tell your doctor or nurse immediately.
- Joint appearance of some of the following symptoms: pain, numbness, tingling in the arms and legs, lumps or raised patches in the skin, weakness and fatigue, loss of appetite and weight loss (signs of so-called "Churg-Strauss syndrome").
- Low blood platelet count with symptoms such as bleeding or bruising more easily than normal.

If you experience any of these, tell your doctor or nurse straight away.

Other side effects include:

Common side effects – likely *to affect up to 10 in every 100 patients*

- headache
- reactions at the injection site including pain, swelling, itching and redness.

Uncommon side effects – *likely to affect up to 1 in every 100 patients*

- 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, joint pain, muscle pain and joint swelling
- hair loss

If any of these affect you severely, tell your doctor. If you notice any side effects not mentioned in this leaflet or are concerned about those listed, please talk to your doctor or pharmacist.

5. STORING XOLAIR

Keep out of the reach and sight of children.
Store in the original package.
Store in a refrigerator (2°C – 8°C). Do not freeze.
Do not use after the expiry date stated on the label.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Pharma Services Inc.
Тел.: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
Novartis Pharma Services Inc.
Tel: +372 60 62 400

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Κύπρος
Δημητριάδης και Παπαέλληνας Λτδ
Τηλ: +357 22 690 690

Luxembourg/Luxemburg
Novartis Pharma GmbH
Tél/Tel: +49 911 273 0

Magyarország
Novartis Hungária Kft. Pharma
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2298 3217

Nederland
Novartis Pharma B.V.
Tel: +31 26 37 82 111

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 550 8888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Inc.
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 77

Slovenská republika
Novartis s.r.o.
Tel: +421 2 5542 5439

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 9 61 33 22 11

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

Latvija
Novartis Pharma Services Inc.
Tel: +371 7 887 070

Lietuva
Novartis Pharma Services Inc.
Tel: +370 5 269 16 50

United Kingdom
Novartis Pharmaceuticals UK Ltd.
Tel: +44 1276 698370

This leaflet was last approved on {date}

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

The following information is intended for medical or healthcare professionals only:

The lyophilised product takes 15–20 minutes to dissolve, although in some cases it may take longer. The fully reconstituted product will appear clear or slightly opaque and may have a few small bubbles or foam around the edge of the vial. Because of the viscosity of the reconstituted product care must be taken to WITHDRAW ALL OF THE 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 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 product will appear clear or slightly opaque. Do not use if solid particles are present.

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

6. Replace the 18-gauge needle with a 25-gauge needle for subcutaneous injection.

7. Expel air, large bubbles, and any excess solution in order to obtain the required 1.2 ml dose. A thin layer of small bubbles may remain at the top of the solution in the syringe. Because the solution is slightly viscous, it may take 5–10 seconds to administer the solution by subcutaneous injection.

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

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