ヒュミラ皮下注 40 mg シリンジ 0.4 mL
同皮下注 20 mg シリンジ 0.2 mL
同皮下注 80 mg シリンジ 0.8 mL
同皮下注 40 mg ペン 0.4 mL
同皮下注 80 mg ペン 0.8 mL
に関する資料

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アッヴィ合同会社

1.5 起原又は発見の経緯及び開発の経緯

起原又は発見の経緯及び開発の経緯については，平成 13 年 6 月 21 日付け医薬審発第 899 号医薬局審査管理課長通知「新医薬品の製造又は輸入の承認申請に際し承認申請書に添付すべき資料の作成要領について」の別紙 2 の 5（1）に作成要領が示されているが，その中の「当該内容が第 2 部（5）に記載できる場合は，第 1 部において提出を省略することができる。」との記述を基に，当該内容（1.5 起源又は発見の経緯及び開発の経緯）を主に第 2 部（5）（臨床に関する概括評価）に記載した。表 1.5-1 に，第 2 部（5）での当該内容の記載場所を示す。

アダリムマブは遺伝子組換えモノクローナル抗体であり，ヒトの塩基配列のみを含む最初の TNFα モノクローナル抗体製剤である。アダリムマブは，TNFα に選択的かつ特異的に結合する。

Knoll 社は，ヒトモノクローナル抗体作製技術を Cambridge Antibody Technology 社より導入し，ファージディスプレイ法を用いてヒトの TNFα に対して非常に高い親和性と選択性を持つヒトモノクローナル抗体を作製した。

本剤の臨床開発は，Knoll 社により 1997 年から欧州で開発され，2001 年に Abbott Laboratories 社が Knoll 社を吸収合併したことから，それ以降は Abbott Laboratories 社が，2013 年からは Abbott Laboratories 社から分社独立した AbbVie Inc.社が本剤の開発を引き継いだ。

本剤は，2002 年 12 月に米国，2003 年 9 月に欧州で関節リウマチの治療薬として承認された。その後，早期関節リウマチ，関節症性乾癬，強直性脊椎炎，クローン病（成人及び小児），尋常性乾癬（成人），多関節若年性特発性関節炎（2 歳以上），潰瘍性大腸炎（成人），化膿性汗腺炎（成人及び青年期），非感染性ぶどう膜炎（成人及び小児）の効能追加が米国及び欧州で承認された。また，X 線所見が認められない体軸性脊椎関節炎，小児腱付着部炎関連関節炎及び小児尋常性乾癬が欧州で承認され，広くこれらの疾患の治療に用いられている。

表 1.5-1 に第 1 部（5）に記載すべき内容の第 2 部（5）での当該内容の記載場所を示す。

表 1.5-1. 第 1 部（5）に関する内容の第 2 部（5）（臨床に関する概括評価）における記載場所

第 1 部（5）に記載すべき内容	第 2 部（5）での記載場所
治験相談，申請に至った経緯，申請の妥当性	2.5.1 製品開発の根拠
本剤の有効性及び安全性	2.5.4 有効性の概括評価 2.5.5 安全性の概括評価
本剤の有効性及び安全性に基づく有用性に関する記載	2.5.6 ベネフィットとリスクに関する結論

日本における開発

本邦での開発は，Knoll 社の日本法人であるクノールジャパン株式会社とエーザイ株式会社の共同開発により 1999 年より開始されたが，その後，クノールジャパン株式会社からアボット ジャパン株式会社へ引き継がれた。アボット ジャパン株式会社とエーザイ株式会社の共同開発により進められ，2013 年以降は，アボットジャパン株式会社から分社独立したアッヴィ合同会社が本剤の開発業務を引き継いだ。2020 年 11 月現在，以下の効能・効果及び用法・用量の申請を行い，承認されている。

【効能又は効果追加，用法及び用量変更追加等の年月及びその内容】

- 関節リウマチ（関節の構造的損傷の防止を含む） 2008 年 4 月（「関節の構造的損傷の防止を含む」の追加は 2012 年 8 月）
- 既存治療で効果不十分な下記疾患
  - 尋常性乾癬，関節症性乾癬 2010 年 1 月
  - 強直性脊椎炎 2010 年 10 月
  - 多関節に活動性を有する若年性特発性関節炎 2011 年 7 月
  - 腸管型ベーチェット病 2013 年 5 月
  - 非感染性の中間部，後部又は汎ぶどう膜炎 2016 年 9 月
  - 膿疱性乾癬 2018 年 3 月
- 中等症又は重症の活動期にあるクローン病の寛解導入及び維持療法（既存治療で効果不十分な場合に限る） 2010 年 10 月
- 中等症又は重症の潰瘍性大腸炎の治療（既存治療で効果不十分な場合に限る） 2013 年 6 月
- クローン病の用法・用量 効果が減弱した場合には 1 回 80mg に増量できる 2016 年 6 月
- 化膿性汗腺炎 2019 年 2 月
- 化膿性汗腺炎の用法・用量（下線部を追加） 初回投与 4 週間後以降は，40mg を毎週 1 回 80mg を 2 週に 1 回，皮下注射する． 2020 年 5 月

本剤の最初の剤型は，「ヒュミラ® 皮下注 40mg シリンジ 0.8 mL」 であり，2008 年に承認された。高濃度製剤（ヒュミラ® 皮下注 40 mg シリンジ 0.4 mL 及び同皮下注 80 mg シリンジ 0.8 mL）の剤形追加を 2015 年に申請し，2016 年 6 月に承認された。更に，ペン製剤である「ヒュミラ® 皮下注 40 mg ペン 0.4 mL」及び「ヒュミラ® 皮下注 80 mg ペン 0.8 mL」の剤形追加がそれぞれ 2017 年 7 月及び 12 月に承認された。なお，「ヒュミラ® 皮下注 20mg シリンジ 0.2mL」は 2018 年 3 月に承認された。

今般，中等症から重症の成人潰瘍性大腸炎患者に対する高用量の維持療法用量追加及び中等症から重症の小児潰瘍性大腸炎の適応拡大を目的に，以下に示す国内試験（第 III 相試験）を実施した。表 1.5-2 及び図 1.5-1 に，本申請における臨床データパッケージ及び開発の経緯図を示す。

表 1.5-2.　　臨床データパッケージ

試験番号	資料区分	評価項目			内容
		有効性	安全性	PK	
M14-033	評価	X	X	X	中等症から重症の活動性潰瘍性大腸炎患者を対象として高用量のアダリムマブでの導入療法及び維持療法を標準用量と比較する多施設共同無作為化二重盲検比較試験
M11-290	評価	X	X	X	中等症から重症の小児潰瘍性大腸炎患者を対象としてヒト型抗ヒトTNFモノクローナル抗体アダリムマブの有効性及び安全性を評価する第III相多施設共同無作為化二重盲検比較試験
M10-870	評価	X	X	-	M11-290試験を完了した小児潰瘍性大腸炎患者を対象とした安全性及び忍容性を評価する第III相多施設共同非盲検試験

図 1.5-1.　　開発の経緯図

試験の種類		対象患者	国内	海外	20[redacted]	20[redacted]	20[redacted]	20[redacted]	20[redacted]	20[redacted]	20[redacted]
第 III 相試験	M14-033	中等症から重症の活動性潰瘍性大腸炎患者	○	○	[redacted]						
第 III 相試験	M11-290	中等症から重症の小児潰瘍性大腸炎患者	○	○							
第 III 相試験	M10-870	M11-290 試験を完了した小児潰瘍性大腸炎患者	○	○							

1.6 外国における使用状況等に関する資料

1.6.1 外国における使用状況等

本剤は，2002 年 12 月に米国，2003 年 9 月に欧州で関節リウマチの治療薬として承認された。その後，早期関節リウマチ，関節症性乾癬，強直性脊椎炎，クローン病（成人及び小児），尋常性乾癬（成人），多関節若年性特発性関節炎（2 歳以上），潰瘍性大腸炎（成人及び小児），化膿性汗腺炎（成人及び青年期），非感染性ぶどう膜炎（成人及び小児）の効能追加が米国及び欧州で承認された。また，X 線所見が認められない体軸性脊椎関節炎，小児腱付着部炎関連関節炎及び小児尋常性乾癬の効能追加が欧州で承認され，広くこれらの疾患の治療に用いられている。2021 年 6 月の時点では，本剤は世界 100 ヵ国以上において，少なくとも 1 つの適応症で承認を取得している。

潰瘍性大腸炎に関して以下に承認されている国の概要を記す。

	承認国数
成人 UC に対する 40 mg 週 1 回投与の用法・用量が承認されている国又は地域の数	63*
成人 UC に対する 80 mg 隔週投与の用法・用量が承認されている国又は地域の数	53*
小児 UC に対する用法・用量が承認されている国又は地域の数	15*

*EU は個々の国としてではなく，1 地域として計上する。

小児の潰瘍性大腸炎は EU では 2020 年 4 月 8 日に製造販売承認申請が行われており，2020 年 11 月 24 日に製造販売承認を取得した。米国では，2020 年 4 月 23 日に製造販売承認申請が行われており，2021 年 2 月 24 日に製造販売承認を取得した。

主要国の承認状況（2021 年 6 月現在）を表 1 に示す。

海外において本剤は，医師の指導及び監視下で投与することとされ，医師が適切と判断した患者については自己注射が可能となっている。自己注射を開始する前には，注射方法の技術的なトレーニングを十分に行い，必要に応じて医師が追跡調査を行うこととしている。

表 1. 主要国の承認状況（海外における販売名：HUMIRA® ）

国名 (関節リウマチ承認年月)	剤形・含量	効能・効果	用法・用量
米国 (2002 年 12 月)	単回投与用皮下注射用剤 プレフィルドガラスシリンジ 80 mg/0.8 mL 40 mg/0.8 mL 40 mg/0.4 mL 20 mg/0.4 mL 20 mg/0.2 mL 10 mg/0.2 mL 10 mg/0.1 mL 単回投与用プレフィルドペン(ヒュミラペン) 80 mg/0.8 mL 40 mg/0.8 mL 40 mg/0.4 mL 単回投与医療機関用バイアル 40 mg/0.8 mL	関節リウマチ 中等症から重症の活動性関節リウマチ成人患者の徴候及び症状を緩和し，主要な臨床的効果の誘導，関節の構造的損傷の進展抑制及び身体機能を改善する。HUMIRA は，単独あるいは MTX 又は他の非生物学的疾患修飾性抗リウマチ薬(DMARDs)と併用できる。	40 mg 隔週投与 関節リウマチ患者で MTX を併用していない患者では，HUMIRA の投与頻度を週 1 回 40 mg に増やすことで更なる効果が得られることがある。
		関節症性乾癬 活動性関節症性乾癬成人患者に対し活動性関節炎の徴候及び症状を緩和し，関節の構造的損傷の進展抑制及び身体機能を改善する。HUMIRA は単独又は非生物学的 DMARDs と併用できる。	
		強直性脊椎炎 活動性強直性脊椎炎の成人患者の徴候及び症状を緩和する。	
		若年性特発性関節炎 中等症から重症の 2 歳以上の活動性多関節型若年性特発性関節炎患者の徴候及び症状を緩和する。HUMIRA は，単独又は MTX と併用できる。	10 kg (22 ポンド) から 15 kg (33 ポンド) 未満：10 mg 隔週投与 15 kg (33 ポンド) から 30 kg (66 ポンド) 未満：20 mg 隔週投与 30 kg (66 ポンド) 以上：40 mg 隔週投与
		クローン病 中等症から重症の活動性クローン病における成人及び 6 歳以上の小児患者の治療	成人：Day 1 160 mg (1 日に投与又は連続した 2 日で分割投与)，Day 15 80 mg。Day 29 から 40 mg 隔週投与の維持用量を開始。 6 歳以上の小児： 17 kg (37 ポンド) から 40 kg (88 ポンド) 未満： Days 1 および Day15 Day 1: 80 mg Day 15: 40 mg Day 29 から 20 mg 隔週投与開始 40 kg (88 ポンド) 以上

国名 (関節リウマチ承認年月)	剤形・含量	効能・効果	用法・用量
			Days 1 and 15 Day 1: 160 mg (1日に投与又は連続した2日で分割投与) Day 15: 80 mg Day 29 から 80 mg 隔週 or 40 mg 週 1 回
		潰瘍性大腸炎 中等症から重症の活動性潰瘍性大腸炎の成人患者及び 5 歳以上の小児患者の治療 TNF 阻害薬の効果が消失若しくは不耐の患者では，HUMIRA の有効性は確立されていない。	成人：初回投与 (Day 1) は 160 mg (1 日に投与又は連続した 2 日で分割投与), Day 15 に 80 mg。Day 29 から 40 mg 隔週投与の維持用量を開始。 8 週 (Day 57) までに臨床的寛解が得られなかった患者は HUMIRA の投与を中止する。

国名 (関節リウマチ承認年月)	剤形・含量	効能・効果	用法・用量
			5 歳以の小児: 20 kg (44 ポンド) から 40 kg (88 ポンド) 未満: Days 1 から Day 15 Day 1: 80 mg Day 8: 40 mg Day 15: 40 mg Day 29 から 40 mg 隔週投与 or 20 mg 週 1 回投与 (18 歳を迎え，投与された投与レジメンで十分にコントロールされている患者は小児の推奨用量を継続する。) 40 kg (88 ポンド) 以上: Days 1 から Day 15 Day 1:160 mg (単回又は連続した 2 日で分割投与) Day 8: 80 mg Day 15: 80 mg 80 mg 隔週投与 or 40 mg 週 1 回投与 (18 歳を迎え，投与された投与レジメンで十分にコントロールされている患者は小児の推奨用量を継続する。)
		乾癬 全身療法又は光線療法の対象で，他の全身療法に効果が見られない中等症から重症の慢性尋常性乾癬の成人患者の治療。HUMIRA は，投与中患者を注意深く観察し，医師の定期的な診察を受けることができる場合にのみ投与すること。	成人：初回 80 mg 投与，初回投与後 1 週時から 40 mg を隔週投与。
		化膿性汗腺炎 12 歳以上の中等症から重症の化膿性汗腺炎患者の治療。	成人 成人： Day1：160 mg (1 日で投与若しくは連続 2 日間に分けて投与)

国名 (関節リウマチ承認年月)	剤形・含量	効能・効果	用法・用量
			Day15：80 mg Day29 及びその後の投与：週 1 回 40 mg 投与。 青年期（12 歳以上） ・30 kg (66 ポンド) 以上 60 kg (132 ポンド) 未満： Day1 ：80 mg Day 8 ：及びその後の投与：40 mg 隔週投与 ・60 kg (132 ポンド) 以上： Day1：160 mg (1 日で投与若しくは連続 2 日間に分けて投与) Day15：80 mg Day29 及びその後の投与：週 1 回 40 mg 投与又は 80 ㎎隔週投与
		ぶどう膜炎 成人及び 2 歳以上の小児における非感染性の中間部，後部，又は汎ぶどう膜炎の治療	成人 初回 80 mg 投与，初回投与後 1 週時から 40 mg を隔週投与。 2 歳以上の小児 ・10 kg (22 ポンド) から 15 kg (33 ポンド) 未満：10 mg 隔週投与 ・15 kg (33 ポンド) から 30 kg (66 ポンド) 未満：20 mg 隔週投与 ・30 kg (66 ポンド) 以上：40 mg 隔週投与
スイス (2003 年 4 月)	皮下注射用剤 40 mg/0.8 mL バイアル プレフィルドシリンジ	関節リウマチ DMARDs の効果不十分な中等症から重症の活動性関節リウマチ成人患者の徴候及び症状を緩和し，関節の構造的損傷の進展抑制及び身体機能を改善する。 HUMIRA は，単独投与あるいは MTX 又は他の DMARDs と併用できるが，HUMIRA とシクロスポリン，アザチオプリン及び他の抗 TNF-α 療法との併用については検討されていない。 中等症から重症の関節リウマチが最近診断され(病歴 3 年未満)，かつ MTX による治療歴のない患者において，MTX 併用下での HUMIRA の有	40 mg 隔週投与 グルココルチコイド，サリチル酸，非ステロイド性抗炎症薬，鎮痛薬又は DMARDs(シクロスポリン，アザチオプリン及び他の抗 TNF-α 療法を除く)は HUMIRA の治療中も投与を継続することは可能である。 効果が減弱した患者では，HUMIRA 40 mg 週 1 回又は 80 ㎎ 隔週投与することにより，効果を得られる可能性がある。

5

国名 (関節リウマチ承認年月)	剤形・含量	効能・効果	用法・用量
	80 mg/0.8 mL 40 mg/0.4 mL 20 mg/0.2 mL プレフィルドペン 80 mg/0.8 mL 40 mg/0.4 mL	効性が示されている。	
		多関節型若年性特発性関節炎 MTX との併用において，1 剤以上の DMARDs の効果不十分な，活動性多関節型若年性特発性関節炎の 4~17 歳以上の患者に対する治療。MTX 不耐容の場合又は MTX の治療継続が適切でない場合，HUMIRA を単独投与する。	体表面積あたり 24 mg/m^2 の皮下注射による隔週投与。アダリムマブ最大単独用量は 40 mg。 注射量は患者の身長及び体重に基づき選択される。 通常，治療 12 週間以内に臨床的効果が得られる。この時期まで効果が得られない患者においては，治療の継続を慎重に再検討すること。
		関節症性乾癬 DMARDs の効果が不十分な，関節症性乾癬患者の徴候及び症状を緩和する。 対称性多関節型の患者において関節の構造的損傷の進展抑制及び身体機能を改善する。 HUMIRA は単独又は疾患修飾性 DMARDs と併用できる。	40 mg 隔週投与 グルココルチコイド，サリチル酸，非ステロイド性抗炎症薬，鎮痛薬又は DMARDs は HUMIRA の治療中も投与を継続することは可能である。
		強直性脊椎炎 通常療法で効果不十分な活動性強直性脊椎炎の成人患者の治療。	40 mg 隔週投与 12 週以内に効果が得られない場合は，本剤の治療の継続を検討すること。 非ステロイド性抗炎症薬は HUMIRA の治療中も投与を継続することは可能である。
		クローン病 通常の治療では十分な効果が得られない又はインフリキシマブの効果消失若しくは不耐容の中等症から重症の活動性クローン病の成人患者の治療。	0 週時で 160 mg (160mg を 1 日で投与若しくは 80mg を連続 2 日間に分けて投与)，2 週時で 80 mg 投与，その後 40 mg 隔週投与。 アミノサリチル酸，副腎皮質ステロイド及び免疫抑制剤(6-メルカプトプリン，アザチオプリン等)は HUMIRA の治療中も投与を継続することは可能である。 効果が減弱した患者では，HUMIRA の投与頻度を 40 mg 週 1 回投与へ増加することにより，効果を得られる可能性がある。 8 週までに効果が得られた患者のみ HUMIRA を継続投与。

国名 (関節リウマチ承認年月)	剤形・含量	効能・効果	用法・用量
		小児クローン病 栄養療法，グルココルチコイド，免疫抑制剤を含む既存治療で効果不十分若しくは不耐容，又はこれらの治療が禁忌である，重症の活動性クローン病の 6 歳以上の患者の徴候及び症状を緩和し，臨床的寛解を導入及び維持する。	小児クローン病患者<40 kg： 推奨導入用量は，0 週時で 80 mg（1 日 2 回投与），続いて 2 週時で 40 mg 投与。導入療法後，推奨維持用量（4 週時から開始）は 20 mg 投与。 30 kg 以下の小児患者での HUMIRA 投与データは限られている。別の用量スキームは国際的ガイダンスを推奨する。 小児及び青年期クローン病患者 >40kg: 推奨導入用量は，0 週時で 160mg，続いて 2 週時で 80mg 投与。導入療法後，推奨維持用量（4 週時から開始）は 40mg 又は 20mg 隔週投与。 維持療法期間に再燃又は効果不十分な場合には，週 1 回に投与頻度を増やすことにより，効果を得られる可能性がある。 40kg 未満の患者： 20mg 週 1 回投与 40kg 以上の患者： 40mg 隔週投を行っていた場合には，40mg 週 1 回投与又は 80mg 隔週投与 又は 20mg の隔週投与を行っていた場合には，20mg の週 1 回投与 寛解が持続する場合，減量を検討すること。12 週以内に治療反応が得られない場合は，投与の継続を慎重に再考すること。
		潰瘍性大腸炎 副腎皮質ステロイド，6-メルカプトプリン又はアザチオプリンを含む通常の治療法で効果不十分，又はこの治療に不耐容又は禁忌である中等症から重症の活動性潰瘍性大腸炎の成人患者に対する治療。	0 週時で 160 mg（160mg を 1 日で投与若しくは 80mg を連続 2 日間に分けて投与）及び 2 週時で 80 mg 投与。導入療法後，40 mg 隔週投与。 維持療法期間中，標準的治療法ガイドラインに従い，副腎皮質ステロイドの投与量を徐々に減らすことができる。

国名 (関節リウマチ承認年月)	剤形・含量	効能・効果	用法・用量
			有効性の減弱が認められた場合には，HUMIRA40mg 週 1 回投与又は 80mg 隔週投与に増量することで効果が得られる可能性がある。治療の継続について定期的に再評価する。通常，投与開始後 2~8 週間以内に臨床的改善が得られることを示唆するデータが得られている。この期間中に効果が認められない患者には HUMIRA の投与を継続するべきではない。
		尋常性乾癬 全身療法又は光線療法の対象となる中等症から重症の慢性尋常性乾癬の成人患者の治療。	初回 80 mg 投与，初回投与後 1 週時より 40 mg を隔週投与。 16 週以内に効果が得られない場合は，本剤の治療は継続しないこと。 この期間中に効果が認められない患者に対しては，16 週時点で投与を中止すること。16 週後に少なくとも部分奏効の最初の二次的な消失が認められた患者では，40mg 週 1 回投与又は 80mg の隔週投与への投与頻度の増加が有効である可能性がある。高頻度の投与で十分な効果が得られた場合，新たに 40mg 隔週投与への減量を考慮する。また，増量後 16 週以内に 40mg 週 1 回投与又は 80mg 隔週投与で効果不十分な場合には，投与継続を中止すること。 最初に奏効が認められた患者では，33 週から 52 週で投与を中止した後，投与中止後に再発が認められた患者は 1/4 強にすぎなかった。33 週以降は休薬を考慮すること。 この治療のベネフィット・リスクは定期的にモニタリングすること。
		小児乾癬 全身療法又は光線療法の効果不十分又はこれらの治療が適切でない重症の慢性尋常性乾癬の小児，青年期（6 歳以上）	15kg 以上 30kg 未満: 初回 20 mg 投与，初回投与後 1 週時より 20 mg を隔週投与。 30kg 以上: 初回 40 mg 投与，初回投与後 1 週時より 40 mg を隔週投与。16 週以内に効果が得られない場合は，本剤の治療を慎重に検討すること。投与再開する際の用法・用量，投与期間は上記に記載のとおり。

国名 (関節リウマチ承認年月)	剤形・含量	効能・効果	用法・用量
		化膿性汗腺炎（Acne inversa） 既存治療では十分な効果が得られない中等症から重症の活動性化膿性汗腺炎の成人患者の治療。	0 週に 160 mg（160mg を 1 日で投与若しくは 80mg を連続 2 日間に分けて投与），2 週後に 80 mg，4 週以降は 40 mg 週 1 回投与又は 80mg 隔週投与する。 必要な場合，HUMIRA による治療期間中に抗生物質の継続使用が可能である。日常の治療においてはその病変に局所消毒洗浄液を使用する。 12 週間以内に効果が得られない場合は，本剤の治療の継続を慎重に再検討すること。 治療のリスク・ベネフィットを定期的に評価すること。臨床試験では，抗生物質と併用又は非併用で HUMIRA を投与した。HUMIRA による治療を中断する必要がある場合でも，治療の再開は可能である。
		非感染性ぶどう膜炎 免疫調節薬の併用有無にかかわらず副腎皮質ステロイドで効果不十分，副腎皮質ステロイドによる温存治療を必要とする，副腎皮質ステロイド依存性の非感染性の中間部，後部，又は汎ぶどう膜炎成人患者の寛解導入（副腎皮質ステロイド併用）及び寛解維持治療。 副腎皮質ステロイド及び/又は免疫調節薬の併用は，解剖学的及び機能的進行に依存する。	初回 80 mg 投与（40mg を 2 回投与），初回投与後 1 週時から 40 mg（40mg を 1 回投与）を隔週投与 副腎皮質ステロイドと併用により治療を開始することができる。また非生物学免疫調整薬を併用することもできる。 併用した副腎皮質ステロイドは，本剤による治療開始後に徐々に減量することができる。治療開始 6 ヵ月後期待された効果が認められない場合，ベネフィットとリスクを考慮の上，本剤の治療の継続について注意深く再検討すること
EU [1)] (2003 年 9 月)	皮下注射用剤 プレフィルドシリンジ 80 mg/0.8 mL 40 mg/0.8 mL 40 mg/0.4 mL 20 mg/0.2 mL	関節リウマチ MTX と HUMIRA の併用において， ・MTX を含む DMARDs の効果が不十分な中等症から重症の活動性関節リウマチの成人患者に対する治療。 ・MTX の治療歴のない重症の活動性及び進行性関節リウマチの成人患者に対する治療。 MTX 不耐容の場合，又は MTX 治療	40 mg 隔週投与 HUMIRA 投与中は MTX の投与を継続すること。 副腎皮質ステロイド，サリチル酸塩，NSAIDs 又は鎮痛剤は HUMIRA による治療中も継続可能。 単独療法で効果が減弱した患者では，40 mg 週 1 回又は 80 mg 隔週投与で更なる効果が得られることがあ

国名 (関節リウマチ承認年月)	剤形・含量	効能・効果	用法・用量
	プレフィルドペン 80 mg/0.8 mL 40 mg/0.8 mL 40 mg/0.4 mL バイアル 40 mg/0.8 mL	の継続が適切でない場合，HUMIRA を単独投与する。HUMIRA は，MTX との併用において，X 線検査により測定される関節の構造的損傷の進展抑制及び身体機能の改善がみられた。	る。 手術前又は重篤な感染症が発症したなど，投与の中断が必要な場合がある。
		多関節型若年性特発性関節炎 MTX との併用において，1 剤以上の DMARDs の効果不十分な，活動性多関節型若年性特発性関節炎の 2 歳以上の患者に対する治療。MTX 不耐容の場合又は MTX の治療継続が適切でない場合，HUMIRA を単独投与する。	10 kg から 30 kg 未満：20 mg 隔週投与 30 kg 以上：40 mg 隔週投与 治療 12 週間以内に臨床的効果が得られない患者においては，治療の継続を慎重に再検討すること。
		腱付着部炎関連関節炎 通常の治療法で効果不十分，又は不耐容である活動性腱付着部炎関連関節炎の 6 歳以上の患者に対する治療。	10 kg から 30 kg 未満：20 mg 隔週投与 30 kg 以上：40 mg 隔週投与
		関節症性乾癬 DMARDs の効果が不十分な，活動性及び進行性の関節症性乾癬の成人患者に対する治療。HUMIRA 投与により，対称性多関節型の患者において X 線検査により末梢関節の構造的損傷の進展抑制及び身体機能の改善がみられた。	40 mg 隔週投与。 12 週以内に効果が得られない場合は，本剤の治療の継続を検討すること。
		強直性脊椎炎 通常の治療法の効果が不十分な重症の活動性強直性脊椎炎の成人患者に対する治療。	

国名 (関節リウマチ 承認年月)	剤形・含量	効能・効果	用法・用量
		強直性脊椎炎の証拠となるX線像が認められない体軸性脊椎関節炎 HUMIRAは，非ステロイド性抗炎症薬で十分な効果が得られなかった又は不耐容であった，強直性脊椎炎の証拠となるX線像は認められず，CRP の上昇及び/又はMRIにより炎症の客観的兆候が認められる重症の体軸性脊椎関節炎の成人の治療に適応される。	

国名 (関節リウマチ承認年月)	剤形・含量	効能・効果	用法・用量
		クローン病 副腎皮質ステロイド及び免疫抑制剤による治療の効果が不十分又はこの治療に不耐容又は禁忌である重症の活動性クローン病患者に対する治療。	導入用量は，0 週時で 80 mg 続いて 2 週時で 40 mg 投与。より速やかな効果が必要な場合，導入期間中に有害事象のリスクが高まることを考慮の上，0 週時で 160 mg (1 日 4 回に分けて投与若しくは連続 2 日間で 2 回ずつ投与が可能)，2 週時で 80 mg 投与が可能である。 導入療法後，推奨用量は隔週 40 mg 皮下投与。患者が HUMIRA の投与を中止し，疾患の徴候や症状が再発した場合，HUMIRA を再度投与できる。前回の投与から 8 週間以上経過後の再投与の報告はほとんどない。 維持療法期間中，標準的治療法ガイドラインに従い，副腎皮質ステロイドの投与量を徐々に減らすことができる。 効果が減弱した患者では，HUMIRA の投与頻度を 40 mg 週 1 回又は 80 mg 隔週投与へ増加することにより，効果を得られる可能性がある。 4 週時までに効果が現れない患者は，12 週時まで維持療法の継続により，効果が得られる可能性がある。この時期まで効果が得られない患者に対する継続投与については，慎重に再検討すること。
		小児クローン病 一次栄養療法，副腎皮質ステロイド及び免疫調節薬を含む通常の治療法で効果不十分，又はこれらの治療に不耐容又は禁忌である重症の活動性クローン病の小児患者 (6 歳以上) に対する治療。	小児クローン病患者<40 kg： 重症の小児クローン病患者に対する推奨導入用量は，0 週時で 40 mg，続いて 2 週時で 20 mg 投与。より速やかな効果が必要な場合，より高い導入用量により有害事象のリスクが高まる可能性があることを考慮の上，0 週時で 80 mg (1 日 2 回に分けて投与)，2 週時で 40 mg 投与が可能である。 導入療法後，推奨用量は 20 mg の隔週皮下投与。十分な効果が得られな

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			い患者では，HUMIRA の投与頻度を 20 mg 週 1 回投与へ増加することにより，効果を得られる可能性がある。 小児クローン病患者≥40 kg： 重症の小児クローン病患者に対する推奨導入用量は，0 週時で 80 mg，続いて 2 週時で 40 mg 投与。より速やかな効果が必要な場合，より高い導入用量により有害事象のリスクが高まる可能性があることを考慮の上，0 週時で 160 mg (160mg を 1 日で投与若しくは 80mg を連続 2 日間に分けて投与)，2 週時で 80 mg 投与が可能である。 導入療法後，推奨用量は 40 mg の隔週皮下投与。十分な効果が得られない患者では，HUMIRA の投与頻度を 40 mg 週 1 回投与又は 80 mg 隔週投与へ増加することにより，効果を得られる可能性がある。12 週時までに効果が現れない患者に対する継続投与については，慎重に検討すること。
		乾癬 全身療法の候補となる中等症から重症の慢性尋常性乾癬の成人患者に対する治療。	初回 80 mg，初回投与後 1 週時より 40 mg 隔週投与。 16 週以上投与後，十分な効果が得られない患者では，HUMIRA を 40 mg 週 1 回投与又は 80 mg 隔週投与に増加することができる。 16 週以内に効果が得られなかった患者においては，治療の継続を注意深く再検討すること。用量を増量しても効果が不十分な患者に対しては，40 mg 週 1 回投与又は 80 mg 隔週投与の継続の効果とリスクを注意深く再検討すべきである。40 mg 週 1 回投与又は 80 mg 隔週投与で十分な反応が達成される場合，その後 40 mg 隔週投与に減量することも可能である。
		小児尋常性乾癬 局所療法及び光線療法で効果不十分，又はこれらの治療に不耐容であ	15 kg から 30 kg 未満：20 mg で初回投与し，続いて初回投与の 1 週間後より 20 mg を隔週投与

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		る重症の慢性尋常性乾癬を有する 4 歳以上の小児及び若年患者に対する治療。	30 kg 以上：40 mg で初回投与し，続いて初回投与の 1 週間後より 40 mg を隔週投与 16 週以内に効果が得られない患者に対する継続投与については，慎重に検討すること。 HUMIRA の再治療が検討された場合は，用量および治療期間に関する上記ガイダンスに従うこと。 HUMIRA の尋常性乾癬の小児患者における安全性は 13 ヵ月間評価された。 本適応症について，4 歳未満の小児に対する HUMIRA の使用経験はない。
		潰瘍性大腸炎 副腎皮質ステロイド，6-メルカプトプリン又はアザチオプリンを含む通常の治療法で効果不十分，又はこの治療に不耐容又は禁忌である中等症から重症の活動性潰瘍性大腸炎の成人患者に対する治療。	中等症から重症の潰瘍性大腸炎成人患者に対する導入用量は，0 週時で 160 mg（1 日 4 回投与若しくは連続 2 日間で 2 回ずつ投与が可能）及び 2 週時で 80 mg 投与。導入療法後，推奨用量は隔週 40 mg 皮下投与。 維持療法期間中，標準的治療法ガイドラインに従い，副腎皮質ステロイドの投与量を徐々に減らすことができる。 効果が減弱した患者では，HUMIRA の投与頻度を 40 mg 週 1 回投与又は 80 mg 隔週投与へ増加することにより，効果を得られる可能性がある。 通常，治療 2-8 週間以内に臨床的効果が得られることを示唆するデータはある。この時期に効果が得られない患者においては，治療を継続しないこと。
		小児の潰瘍性大腸炎 副腎皮質ステロイド，6-メルカプトプリン又はアザチオプリンを含む通常の治療法で効果不十分，又はこの治療に不耐容又は禁忌である中等症から重症の活動性潰瘍性大腸炎の小児患者(6 歳以上)に対する治療。	中等症から重症の潰瘍性大腸炎小児患者 40 ㎏未満： 患者に対する導入用量は，0 週時で 80 mg（40 ㎎の 1 日 2 回投与として投与される）及び 2 週時で 40 mg 投与（40 ㎎の 1 日 1 回投与として投与される）。導入療法後，推奨用量は隔週 40 mg 皮下投与。 18 歳を迎えた小児患者は小児の推奨用量を継続する。

国名 (関節リウマチ 承認年月)	剤形・含量	効能・効果	用法・用量
			投与 8 週までの期間に改善の兆候が見られない患者に対して 8 週を超えて投与を継続するか注意深く検討すべきである。 この対象疾患における 6 歳以下の患者に対する投与経験はない。 個々の治療ニーズに応じて異なった剤型や規格を利用することができる 中等症から重症の潰瘍性大腸炎小児患者 40 ㎏以上： 患者に対する導入用量は，0 週時で 160 mg（40 ㎎の 1 日 4 回投与として投与される又は 1 日 40 ㎎を 2 日間で投与される）及び 2 週時で 40 mg 投与（40 ㎎の 1 日 1 回投与として投与される）。導入療法後，推奨用量は隔週 80 mg 皮下投与 18 歳を迎えた小児患者は小児の推奨用量を継続する。
		化膿性汗腺炎 従来の全身療法では十分な効果が得られない中等症から重症の活動性化膿性汗腺炎の成人患者の治療。	初回投与（Day1）は 160 mg 投与 (1 日に 40 mg を 4 回投与又は連続した 2 日で 40 mg を 2 回投与)，続いて 2 週間後 (Day15) に 80 mg (1 日に 40 mg を 2 回投与)。 更に 2 週間後 (Day29)及びそれ以降は，週 1 回 40 mg 投与，又は 80 mg 隔週投与(1 日に 40 mg を 2 回投与)。 HUMIRA の治療中，必要に応じて抗生物質を継続できる。日常の治療においてはその病変に局所消毒洗浄液を使用する。 12 週間以内に効果が得られない場合は，本剤の治療の継続を慎重に再検討すること。 HUMIRA の治療中断後も週 1 回 40 mg 若しくは隔週 80mg の再投与ができる (Section 5.1 参照) 。 長期治療における効能とリスクについて定期的に評価すること (Section 5.1 参照) 。

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国名 (関節リウマチ 承認年月)	剤形・含量	効能・効果	用法・用量
		青年期化膿性汗腺炎 従来の全身療法では十分な効果が得られない 12 歳以上の青少年における中等症から重症の活動性化膿性汗腺炎の治療。	化膿性汗腺炎の青少年患者を対象とした HUMIRA による臨床試験はない。これらの患者における HUMIRA の投与量は，薬物動態的モデリングとシミュレーションから決定されている。 HUMIRA の推奨用量は，0 週時に 80 mg を投与後，40 mg の隔週皮下注射を 1 週時に開始する。 HUMIRA 40 mg の隔週投与で十分な効果が得られない青少年患者においては，40 mg 週 1 回又は 80 mg 隔週への投与頻度の増加を考慮することができる。 HUMIRA の治療中，必要に応じて抗生物質を継続できる。日常の治療においてはその病変に局所消毒洗浄液を使用する。 12 週間以内に効果が得られない場合は，本剤の治療の継続を慎重に再検討すること。 HUMIRA の治療中断後も必要に応じて再投与ができる。 長期治療における効能とリスクについて定期的に評価すること。 12 歳未満の小児においては，この適応に関連する HUMIRA の使用経験はない。
		ぶどう膜炎 副腎皮質ステロイドで効果不十分，副腎皮質ステロイドによる治療が不適切，若しくは副腎皮質ステロイド依存性で副腎皮質ステロイドの減量を必要とする非感染性の中間部，後部，又は汎ぶどう膜炎の成人患者に対する治療。	成人ぶどう膜炎病患者に対する推奨初回用量は 80 mg，続いて初回投与後 1 週時から 40 mg を隔週投与。導入療法時における HUMIRA 単剤投与経験は限られている。導入療法時における HUMIRA と副腎皮質ステロイド及び／若しくは非生物学製剤である免疫調整薬との併用投与は可能である。 併用中の副腎皮質ステロイドは HUMIRA の導入療法 2 週後以降，患者の臨床症状により漸減される場合がある。

国名 (関節リウマチ承認年月)	剤形・含量	効能・効果	用法・用量
		小児ぶどう膜炎 従来の治療で効果不十分，若しくは不耐容，又は従来の治療が不適切であった 2 歳以上の非感染性の前部小児ぶどう膜炎患者に対する治療。	小児ぶどう膜炎患者＜30 kg： 20 mg を隔週投与。 小児ぶどう膜炎患者≥30 kg： 40 mg を隔週投与。 HUMIRA 初回投与時は負荷投与量として体重 30 kg 未満は 40 mg，30 kg 以上は 80 mg を維持療法開始の 1 週間前に投与することがある。 HUMIRA は MTX と併用することを推奨する。 2 歳未満の小児においては，この適応に関連する HUMIRA の使用経験はない。 長期治療の継続のベネフィット及びリスクを年に一度，評価することが推奨される。
オーストラリア (2003 年 12 月)	皮下注射用剤 プレフィルドシリンジ 80 mg/0.8 mL 40 mg/0.8 mL 40 mg/0.4 mL 20 mg/0.4 mL 20 mg/0.2 mL	関節リウマチ 中等症から重症の活動性 RA の成人患者における徴候及び症状の緩和，関節の構造的損傷の進展抑制。 MTX の治療歴がなく，直近に中等症から重症の活動性 RA と診断された患者の治療。	40 mg 隔週投与。 グルココルチコイド，サリチル酸，非ステロイド性抗炎症薬，鎮痛薬又は DMARDs は HUMIRA の治療中も投与を継続することは可能である。 MTX を併用していない患者では，HUMIRA の投与頻度を 40 mg 週 1 回投与若しくは 80mg 隔週投与へ増加することにより，効果を得られる可能性がある。
	プレフィルドペン 80 mg/0.8 mL 40 mg/0.8 mL 40 mg/0.4 mL	関節症性乾癬 DMARDs で効果不十分な中等症から重症の活動性 PsA の成人患者における徴候及び症状の緩和，関節の構造的損傷の進展抑制。	40 mg 隔週投与。 グルココルチコイド，サリチル酸，非ステロイド性抗炎症薬，鎮痛薬又は DMARDs は HUMIRA の治療中も投与を継続することは可能である。
		強直性脊椎炎 活動性 AS 患者の徴候及び症状の緩和。	

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		成人及び小児 (6 歳以上) クローン病 通常の治療では十分な効果が得られない又はインフリキシマブの効果消失若しくは不耐容の中等症から重症の CD 患者における徴候及び症状の緩和，寛解の導入及び維持。	<u>クローン病</u> 導入用量 160 mg：初回投与(Day 0)として 80mg を 1 日で 2 回投与，若しくは 80mg を連続する 2 日間で 1 回ずつ投与，又は 40mg を 1 日で 4 回投与，若しくは 40mg を連続する 2 日間で 2 回ずつ投与。 80 mg：2 回目投与(Day 14)として 80mg を 1 回投与，若しくは 40mg を 2 回投与。 維持用量 40 mg：Day 28 から隔週投与を開始。 効果が減弱した患者では，HUMIRA の投与頻度を 40 mg 週 1 回投与又は 80 mg 隔週投与へ増加することにより，効果を得られる可能性がある。 アミノサリチル酸，副腎皮質ステロイド/免疫抑制剤(6-メルカプトプリン，アザチオプリン等)は HUMIRA の治療中も投与を継続することは可能である。 <u>小児クローン病（6-17 歳）</u> 体重 40 kg 未満の患者： 中等症～重症のクローン病 導入用量 • 80 mg：初回投与(Day0)として 80mg を 1 回投与，若しくは 40 mg を 2 回投与。 • 40 mg：2 回目投与(Day 14)として 40 mg を 1 回投与，若しくは 20 mg を 2 回投与。 維持用量 • 20 mg：Day 28 から隔週投与を開始。 体重 40 kg 以上の患者： 中等症～重症のクローン病 導入用量 • 160 mg：初回投与(Day 0)として 80mg を 1 日で 2 回投与，若しくは 80mg を連続する 2 日間で 1 回

			ずつ投与，又は 40mg を 1 日で 4 回投与，若しくは 40mg を連続する 2 日間で 2 回ずつ投与。 • 80 mg：2 回目投与(Day 14)として 80mg を 1 回投与，若しくは 40 mg を 2 回投与。 維持用量 • 40 mg：Day 28 から隔週投与を開始。 維持療法中，疾患の再燃をきたした場合又は十分な効果が得られない場合，増量により効果を得られる可能性がある。 40kg 未満の患者：20mg 週 1 回投与。 40kg 以上の患者：40mg 週 1 回投与若しくは 80mg 隔週投与。 12 週時までに効果が現れない患者に対する継続投与については，慎重に検討すること。 適切な発育を可能にするため，薬物療法と並行して栄養状態を良好にするよう奨励すること。

国名 (関節リウマチ承認年月)	剤形・含量	効能・効果	用法・用量
		乾癬 全身療法又は光線療法の対象となる中等症から重症の慢性尋常性乾癬の成人患者の治療。 局所療法及び光線療法で十分な効果が得られない又は対象外の 4 歳以上の小児及び青少年患者における重症の慢性尋常性乾癬の治療。	成人 成人患者における HUMIRA の推奨用量は，80 mg の初回投与後，40 mg の隔週投与を初回投与 1 週間後に開始する。 16 週間以内に効果が得られない患者においては，治療の継続を慎重に再検討すること。 16 週以降，効果不十分な患者に対しては，40mg 週 1 回投与又は 80mg 隔週投与への増量により効果が得られる可能性がある。効果を定期的に評価すること（例えば， 12 週ごと）。効果不十分が持続する患者では投与を中止すること。投与回数を増やして十分な効果が得られた場合は，その後の用量を 40mg 隔週投与に減量することができる。 小児乾癬（4 歳~17 歳） HUMIRA の推奨用量は体重に基づく。 40kg 未満:20mg 隔週投与 40kg 以上:40mg 隔週投与 最初の 2 回は週 1 回，その後は 2 週に 1 回皮下投与する。この期間中に効果が認められない患者については，16 週以降の治療継続を慎重に検討すること。HUMIRA の再投与を行う場合は，上記の用量及び投与期間に関するガイダンスに従うこと。 4 歳未満の小児に対する HUMIRA の使用経験はない。小児乾癬患者に対する 52 週を超える HUMIRA の有効性又は安全性に関するデータは限られている。
		多関節型若年性特発性関節炎 MTX との併用において，1 剤以上の DMARDs の効果不十分な，中等症から重症の活動性多関節型若年性特発性関節炎患者(2 歳以上)の徴候及び症	10 kg 以上 30 kg 未満：20 mg 隔週投与。

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国名 (関節リウマチ承認年月)	剤形・含量	効能・効果	用法・用量
		状の緩和。MTX 不耐容の場合又は MTX の治療継続が適切でない場合，HUMIRA を単独投与する。	30 kg 以上：40 mg 隔週投与。 HUMIRA の投与中は，MTX，グルココルチコイド，NSAIDs 及び鎮痛薬の投与を継続してもよい。投与後 12 週以内に効果が認められなかった患者については，投与継続の可否を慎重に再考すること。 2 歳未満の若年性特発性関節炎患者又は体重 10kg 未満の患者を対象とした HUMIRA の試験は実施されていない。腱付着部炎関連関節炎患者（6 歳未満）又は小児（体重 10kg 未満）を対象とした HUMIRA の試験は実施されていない。
		潰瘍性大腸炎 通常療法で効果不十分，若しくは不耐容又は禁忌である中等症から重症の潰瘍性大腸炎成人患者に対する治療。8 週以内に臨床的効果が得られた患者でのみ継続投与すること。	導入用量 160 mg：初回投与(Day 0)として 80mg を 1 日で 2 回投与，若しくは 80mg を連続する 2 日間で 1 回ずつ投与，又は 40mg を 1 日で 4 回投与，若しくは 40mg を連続する 2 日間で 2 回ずつ投与。 80 mg：2 回目投与(Day 14)として 80mg を 1 回投与，若しくは 40 mg を 2 回投与。 維持用量 40 mg：Day 28 から隔週投与を開始。 維持療法中，標準的治療法ガイドラインに従い，副腎皮質ステロイドの投与量を徐々に減らすことができる。 効果が減弱した患者では，HUMIRA の投与頻度を 40 mg 週 1 回投与若しくは 80mg 隔週投与へ増加することにより，効果を得られる可能性がある。 8 週間時までに効果が得られない患者は，HUMIRA の投与を継続しないこと。抗 TNF 療法で効果が得られない患者における潰瘍性大腸炎に対する HUMIRA の有効性は確認されていない。

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		化膿性汗腺炎 HUMIRA は，従来の化膿性汗腺炎の全身治療に対して十分に奏功しない，活動性が中等度から重度の 12 歳以上患者の化膿性汗腺炎（又は acne inversa）の治療に適応される。	初回（Day 1）に 160 mg（80mg を 1 日で 2 回投与，若しくは 80mg を連続する 2 日間で 1 回ずつ投与，又は 40 mg を 1 日で 4 回投与，若しくは 40 mg を連続する 2 日間で 2 回ずつ投与），2 週後（Day 15）に 80 mg（80mg を 1 回，若しくは 40 mg を 2 回）を投与。更に，その 2 週後（Day 29）以降，40 mg 週 1 回投与若しくは 80mg 隔週投与を継続する。 必要な場合，HUMIRA による治療期間中に抗生物質の継続使用が可能である。 HUMIRA による治療を中断する必要がある場合でも，治療の再開は可能である。 投与 12 週後にいかなる改善も認められない患者は，治療を中止する。 12 週以降，アダリムマブ投与を継続中の患者について，改善の継続，効果喪失の可能性，及び治療のリスクを定期的に評価する必要がある（例えば，更に 12 週後及びその後 6 ヵ月毎）。 2 本の主要試験において，有効性の主要評価項目は化膿性汗腺炎の臨床反応（HiSCR）とし，HiSCR は膿瘍数及び炎症性結節数の総和（AN 数）が投与前より 50%以上低下し，かつ膿瘍数及び排膿性瘻孔数の増加が認められないことと定義した（臨床試験参照）。 30 kg 以上の 12 歳以上の青年期患者 初回投与時に 80 mg を投与後，40 mg の隔週皮下注射を 1 週時に開始する。 HUMIRA 40 mg の隔週投与で十分な効果が得られない青少年患者においては，40 mg 週 1 回投与若しくは 80mg 隔週投与への投与頻度の増加を考慮することができる。 HUMIRA の治療中，必要に応じて抗生物質を継続できる。日常の治療においてはその病変に局所消毒洗浄液を使用する。 12 週間以内に効果が得られない場合は，本剤の治療を中止または中断す

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国名 (関節リウマチ承認年月)	剤形・含量	効能・効果	用法・用量
			ること。HUMIRA は適宜再開できる。長期にわたる治療継続のベネフィット・リスクは定期的に評価すること。 12 歳未満の化膿性汗腺炎患者に対する HUMIRA の使用経験はない。
		腱付着部炎関連関節炎 通常の治療法で効果不十分，又は不耐容である活動性腱付着部炎関連関節炎の小児患者に対する治療。	10 kg to < 30 kg: 20 mg 隔週 ≥ 30 kg: 40 mg 隔週 HUMIRA の投与中は，MTX，グルココルチコイド，NSAIDs 及び鎮痛薬の投与を継続してもよい。この期間中に効果が認められなかった患者については，投与継続の可否を慎重に再考すること。 2 歳未満の若年性特発性関節炎患者又は体重 10kg 未満の患者を対象とした HUMIRA の試験は実施されていない。腱付着部炎関連関節炎患者（6 歳未満）又は小児（体重 10kg 未満）を対象とした HUMIRA の試験は実施されていない。
		ぶどう膜炎 副腎皮質ステロイドで効果不十分，副腎皮質ステロイドによる治療が不適切，若しくは副腎皮質ステロイド依存性で副腎皮質ステロイドの減量を必要とする非感染性の中間部，後部，又は汎ぶどう膜炎の成人患者に対する治療。	眼科医は HUMIRA 投与開始前に適切な専門家に相談することを勧める。ぶどう膜炎に対する HUMIRA の使用は眼科医又は適切な専門家が監督するべきである。HUMIRA を処方された患者は特別な注意カードを受け取る必要がある。 HUMIRA の成人ぶどう膜炎患者に対する推奨用量は，初回 80 mg（80mg を 1 回投与，若しくは 40 mg を 2 回投与），その後初回投与から 1 週間後より 40 mg 隔週とする。 HUMIRA による治療はコルチコステロイド及び/又は他の非生物学的免疫調節剤と併用して開始できる。HUMIRA 単独投与での治療開始経験は多くない。 併用しているコルチコステロイドの漸減は，HUMIRA の治療開始後 2 週間以降に日常診療の方法に従い実施可能である。 1 年ごとに継続の長期投与のベネフィットとリスクを評価することが推

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国名 (関節リウマチ承認年月)	剤形・含量	効能・効果	用法・用量
			奨される。
カナダ (2004 年 9 月)	皮下注射用剤 プレフィルドシリンジ 80 mg/0.8 mL 40 mg/0.8 mL 40 mg/0.4 mL 20 mg/0.2 mL 10 mg/0.1 mL プレフィルドペン 40 mg/0.8 mL 40 mg/0.4 mL 80mg/0.8mL バイアル 40 mg/0.8 mL	関節リウマチ 中等症から重症の活動性 RA の成人患者における徴候及び症状の緩和，主要な臨床的効果及び寛解の誘導，関節の構造的損傷の進展抑制及び身体機能の改善。単独，MTX との併用，他の DMARDs との併用のいずれも可能。MTX の治療歴がなく，直近に診断された患者で第一選択薬として使用する際は MTX と併用すること。MTX 不耐容又は禁忌の場合，単独投与も可能。	40 mg 隔週投与 12 週以内に効果が得られない患者に対する継続投与については，慎重に再検討すること。
		関節症性乾癬 成人関節症性乾癬における活動性関節炎の徴候及び症状の緩和，関節の構造的損傷の進展抑制及び身体機能の改善。MTX 単独で十分な効果が得られない場合，MTX と併用可能。	40 mg 隔週投与 12 週以内に効果が得られない患者に対する継続投与については，慎重に再検討すること。
		強直性脊椎炎 通常の療法で効果不十分な活動性強直性脊椎炎患者の徴候及び症状の緩和。	40 mg 隔週投与 グルココルチコイド，サリチル酸，非ステロイド性抗炎症薬，鎮痛薬又は DMARDs は HUMIRA の治療中も投与を継続することは可能である。
		多関節型若年性特発性関節炎 MTX との併用において，1 剤以上の DMARDs の効果不十分な，中等症から重症の活動性多関節型若年性特発性関節炎患者(2～17 歳)の徴候及び症状の緩和。MTX 不耐容の場合又は MTX の治療継続が適切でない場合，HUMIRA を単独投与する。	2 歳以上の HUMIRA の推奨用量は体重に基づく。 20mg 隔週投与（体重 10kg 以上 30kg 未満の患者*) 40mg 隔週投与（体重 30kg 以上の患者) *体重 10kg 以上 15kg 未満の患者では 10mg 隔週投与を検討してもよい。 HUMIRA は，MTX に不耐容である場合又は MTX の継続投与が適切でない場合に，MTX との併用又は単剤投与として使用することができる。 これまでに入手されたデータから，通常，治療 12 週間以内に臨床的効果が得られる。16 週時までに効果が得られない患者における有効性及び安全性は確立されていない。
		クローン病 副腎皮質ステロイド/免疫抑制剤を含	初回投与は 160 mg (80mg を 1 日で 2 回投与，若しくは 80mg を連続する

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国名 (関節リウマチ 承認年月)	剤形・含量	効能・効果	用法・用量
		む通常の治療では十分な効果が得られない中等症から重症の活動性クローン病の成人患者における徴候及び症状の緩和，寛解の導入及び維持。インフリキシマブの効果消失若しくは不耐容の患者における，徴候及び症状の緩和，寛解の導入。	2 日間で 1 回ずつ投与，又は 40mg を 1 日で 4 回投与，若しくは 40mg を連続する 2 日間で 2 回ずつ投与)，2 週後に 80 mg(80mg を 1 回投与，若しくは 40 mg を 2 回投与)。維持療法として，4 週後から 40 mg 隔週投与。 HUMIRA 投与中，他の併用薬(副腎皮質ステロイド/免疫抑制剤)の投与を最適化すること。 再発した患者では，投与量を増量することができる。 4 週までに効果が得られない患者で，12 週まで維持療法の継続により効果が得られることがある。4 週以内に効果が得られない患者に対する継続投与については，慎重に再検討すること。
		小児クローン病 通常療法(副腎皮質ステロイド及び/又はアミノサリチル酸)や TNF 阻害薬で十分な効果が得られない又は不耐容の重症のクローン病の体重 40 kg 以上の 13～17 歳の小児患者における徴候及び症状の緩和，寛解の導入及び維持。	0 週時で 160 mg(80mg を 1 日で 2 回投与，若しくは 80mg を連続する 2 日間で 1 回ずつ投与，又は 40mg を 1 日で 4 回投与，若しくは 40mg を連続する 2 日間で 2 回ずつ投与)，2 週後に 80 mg 投与(80mg を 1 回投与，若しくは 40 mg を 2 回投与)。維持用量は，4 週時から 20 mg 隔週投与。 再発又は効果が得られない小児患者では，40 mg 隔週投与まで投与量を z 増量することができる。 12 週時までに効果が得られない患者に対する継続投与については，慎重に検討すること。
		潰瘍性大腸炎 副腎皮質ステロイド，アザチオプリン及び 6-メルカプトプリン(6-MP)を含む通常療法で効果不十分又は不耐容の中等症から重症の活動性潰瘍性大腸炎成人患者に対する治療。TNF 阻害薬の効果が消失若しくは不耐容の患者では，HUMIRA の有効性は確立されていない。	導入用量は，0 週時で 160 mg(80mg を 1 日で 2 回投与，若しくは 80mg を連続する 2 日間で 1 回ずつ投与，又は 40mg を 1 日で 4 回投与，若しくは 40mg を連続する 2 日間で 2 回ずつ投与)，2 週後に 80 mg(80mg を 1 回投与，若しくは 40 mg を 2 回投与)。4 週時より 40 mg 隔週投与の維持用量を開始。 8 週までに効果が得られた患者のみ HUMIRA を継続投与。

国名 (関節リウマチ承認年月)	剤形・含量	効能・効果	用法・用量
			アミノサリチル酸及び/又は副腎皮質ステロイドは HUMIRA の治療中も投与を継続することは可能である。必要であれば，アザチオプリン及び 6-メルカプトプリン(6-MP)は HUMIRA の治療中も投与を継続することは可能である。 維持療法中，標準的治療法ガイドラインに従い，副腎皮質ステロイドの投与量を減らすことができる。
		乾癬 全身療法の対象となり，中等症から重症の慢性乾癬成人患者の治療。中等症の慢性尋常性乾癬患者では，光線療法で効果がない又は不適切な場合に使用。	初回 80 mg，初回投与後 1 週時より 40 mg 隔週投与。16 週以内に効果が得られなかった患者においては，治療の継続を注意深く再検討すること。
		化膿性汗腺炎 既存治療で十分な効果が得られない中等症から重症の活動性化膿性汗腺炎患者の治療（抗生物質を含む）	初回投与は 160 mg 投与，続いて 2 週間後に 80 mg 投与する。160 mg の初回投与は，80mg を 1 日で 2 回投与，若しくは 80mg を連続する 2 日間で 1 回ずつ投与，又は 40mg を 1 日で 4 回投与，若しくは 40mg を連続する 2 日間で 2 回ずつ投与することができる。80 mg の投与は，80mg を 1 回投与，若しくは 40 mg を 2 回投与することができる。
		青年期化膿性汗腺炎 中等症から重症の青年期の活動性化膿性汗腺炎患者（30 kg 以上の 12 歳から 17 歳）で，既存治療で十分な効果が得られない患者の治療（抗生物質を含む）	体重≥ 30 kg（12 歳から 17 歳）は初回 80 mg 投与する。初回投与後 1 週間後以降 40 mg 隔週投与を開始する。 40 mg 隔週投与で効果不十分の患者は，40 mg 週 1 回投与に頻度を変更することを検討できる。

国名 (関節リウマチ承認年月)	剤形・含量	効能・効果	用法・用量
		ぶどう膜炎 副腎皮質ステロイドで効果不十分，副腎皮質ステロイドによる治療が不適切，若しくは副腎皮質ステロイド依存性で副腎皮質ステロイドの減量を必要とする非感染性の中間部，後部，又は汎ぶどう膜炎の成人患者に対する治療。	非感染性ぶどう膜炎の成人患者における HUMIRA の推奨用量は，80 mg の初回皮下投与後，40 mg の隔週皮下投与を初回投与 1 週間後に開始する。 HUMIRA は，副腎皮質ステロイド及び／若しくは非生物学製剤である免疫調整薬との併用投与は可能である。副腎皮質ステロイドは，HUMIRA での治療開始 2 週間後に診察を開始し，それに応じて徐々に減量ことができる。HUMIRA 単剤投与の導入経験は限られている。 継続な長期治療の効能とリスクについて年 1 回評価することが推奨される。
		小児ぶどう膜炎 既存治療で効果不十分若しくは不耐容，又は既存治療が不適切な 2 歳以上の小児慢性非感染性前部ぶどう膜炎患者。	2 歳以上の小児の慢性非感染性前部ぶどう膜炎患者に対する HUMIRA と MTX の併用投与の推奨用量は体重に基づく。 MTX 製剤併用 20mg 隔週投与（体重 30kg 未満の場合） MTX 製剤併用時:40mg 隔週投与（体重 30kg 以上の場合） 小児のぶどう膜炎では，MTX を併用せずに HUMIRA を投与した経験はない。6 歳以上の患者に HUMIRA の投与を開始する場合，体重 30kg 未満の患者には 40mg，体重 30kg 以上の患者には 80mg の負荷用量を維持療法開始の 1 週間前に投与することができる。

1) EU において承認されているのは次の国である：オーストリア，ベルギー，デンマーク，フィンランド，フランス，ドイツ，ギリシャ，アイルランド，イタリア，ルクセンブルグ，ポルトガル，スペイン，スロバキア，スウェーデン，オランダ，英国，キプロス，チェコ，エストニア，ハンガリー，ラトビア，リトアニア，マルタ，ポーランド，スロベニア，ブルガリア，ルーマニア，クロアチア（EU 28 カ国）並びにノルウェイ，リヒテンシュタイン及びアイスランド

1.6.2 海外における添付文書

1.6.2.1 米国における添付文書

Humira®（adalimumab）（原文）

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HUMIRA safely and effectively. See full prescribing information for HUMIRA.

HUMIRA® (adalimumab) injection, for subcutaneous use
Initial U.S. Approval: 2002

WARNING: SERIOUS INFECTIONS AND MALIGNANCY
See full prescribing information for complete boxed warning.

SERIOUS INFECTIONS (5.1, 6.1):
- **Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.**
- **Discontinue HUMIRA if a patient develops a serious infection or sepsis during treatment.**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting HUMIRA.**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative.**

MALIGNANCY (5.2):
- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA.**
- **Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescent and young adults with inflammatory bowel disease treated with TNF blockers including HUMIRA.**

RECENT MAJOR CHANGES

Indications and Usage, Ulcerative Colitis (1.6)	2/2021
Dosage and Administration, Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis (2.1)	12/2020
Dosage and Administration, Ulcerative Colitis (2.4)	2/2021
Dosage and Administration, Hidradenitis Suppurativa (2.6)	12/2020

INDICATIONS AND USAGE

HUMIRA is a tumor necrosis factor (TNF) blocker indicated for:
- **Rheumatoid Arthritis (RA) (1.1):** reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
- **Juvenile Idiopathic Arthritis (JIA) (1.2):** reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 2 years of age and older.
- **Psoriatic Arthritis (PsA) (1.3):** reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
- **Ankylosing Spondylitis (AS) (1.4):** reducing signs and symptoms in adult patients with active AS.
- **Crohn's Disease (CD) (1.5):** treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.
- **Ulcerative Colitis (UC) (1.6):** treatment of moderately to severely active ulcerative colitis in adults and pediatric patients 5 years of age and older. Limitations of Use: Effectiveness has not been established in patients who have lost response to or were intolerant to TNF blockers.
- **Plaque Psoriasis (Ps) (1.7):** treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.
- **Hidradenitis Suppurativa (HS) (1.8):** treatment of moderate to severe hidradenitis suppurativa in patients 12 years of age and older.
- **Uveitis (UV) (1.9):** treatment of non-infectious intermediate, posterior, and panuveitis in adults and pediatric patients 2 years of age and older.

DOSAGE AND ADMINISTRATION

- Administer by subcutaneous injection (2)

Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis (2.1):
- *Adults* 40 mg every other week.
  - Some patients with RA not receiving methotrexate may benefit from increasing the dosage to 40 mg every week or 80 mg every other week.

Juvenile Idiopathic Arthritis or Pediatric Uveitis (2.2):

Pediatric Weight 2 Years of Age and Older	Recommended Dosage
10 kg (22 lbs) to less than 15 kg (33 lbs)	10 mg every other week
15 kg (33 lbs) to less than 30 kg (66 lbs)	20 mg every other week
30 kg (66 lbs) and greater	40 mg every other week

Crohn's Disease (2.3):
- *Adults* 160 mg on Day 1 (given in one day or split over two consecutive days); 80 mg on Day 15; and 40 mg every other week starting on Day 29.
- *Pediatric Patients 6 Years of Age and Older*:

Pediatric Weight	Recommended Dosage	
	Days 1 and 15	Starting on Day 29
17 kg (37 lbs) to less than 40 kg (88 lbs)	Day 1: 80 mg Day 15: 40 mg	20 mg every other week
40 kg (88 lbs) and greater	Day 1: 160 mg (single dose or split over two consecutive days) Day 15: 80 mg	40 mg every other week

Ulcerative Colitis (2.4):
- *Adults* 160 mg on Day 1 (given in one day or split over two consecutive days), 80 mg on Day 15 and 40 mg every other week starting on Day 29. Discontinue in patients without evidence of clinical remission by eight weeks (Day 57).
- *Pediatric Patients 5 Years of Age and Older*:

Pediatric Weight	Recommended Dosage	
	Days 1 through 15	Starting on Day 29*
20 kg (44 lbs) to less than 40 kg (88 lbs)	Day 1: 80 mg Day 8: 40 mg Day 15: 40 mg	40 mg every other week or 20 mg every week
40 kg (88 lbs) and greater	Day 1: 160 mg (single dose or split over two consecutive days) Day 8: 80 mg Day 15: 80 mg	80 mg every other week or 40 mg every week

* Continue the recommended pediatric dosage in patients who turn 18 years of age and who are well-controlled on their HUMIRA regimen.

Plaque Psoriasis or Adult Uveitis (2.5):
- *Adults*: 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose.

Hidradenitis Suppurativa (2.6):
- *Adults*
  - Day 1: 160 mg (given in one day or split over two consecutive days)
  - Day 15: 80 mg
  - Day 29 and subsequent doses: 40 mg every week or 80 mg every other week
- *Adolescents 12 years of age and older*

Adolescent Weight	Recommended Dosage
30 kg (66 lbs) to less than 60 kg (132 lbs)	Day 1: 80 mg Day 8 and subsequent doses: 40 mg every other week
60 kg (132 lbs) and greater	Day 1: 160 mg (given in one day or split over two consecutive days) Day 15: 80 mg Day 29 and subsequent doses: 40 mg every week or 80 mg every other week

DOSAGE FORMS AND STRENGTHS

Injection:
- Single-dose prefilled pen (HUMIRA Pen): 80 mg/0.8 mL, 40 mg/0.8 mL, and 40 mg/0.4 mL (3)
- Single-dose prefilled glass syringe: 80 mg/0.8 mL, 40 mg/0.8 mL, 40 mg/0.4 mL, 20 mg/0.4 mL, 20 mg/0.2 mL, 10 mg/0.2 mL, 10 mg/0.1 mL (3)
- Single-dose glass vial for institutional use only: 40 mg/0.8 mL (3)

CONTRAINDICATIONS

None (4)

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WARNINGS AND PRECAUTIONS

- *Serious infections* Do not start HUMIRA during an active infection. If an infection develops, monitor carefully, and stop HUMIRA if infection becomes serious. (5.1)
- *Invasive fungal infections* For patients who develop a systemic illness on HUMIRA, consider empiric antifungal therapy for those who reside or travel to regions where mycoses are endemic. (5.1)
- *Malignancies* Incidence of malignancies was greater in HUMIRA-treated patients than in controls (5.2)
- *Anaphylaxis or serious hypersensitivity reactions* may occur (5.3)
- *Hepatitis B virus reactivation* Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop HUMIRA and begin anti-viral therapy. (5.4)
- *Demyelinating disease* Exacerbation or new onset, may occur. (5.5)
- *Cytopenias, pancytopenia* Advise patients to seek immediate medical attention if symptoms develop, and consider stopping HUMIRA. (5.6)
- *Heart failure* Worsening or new onset, may occur. (5.8)
- *Lupus-like syndrome* Stop HUMIRA if syndrome develops. (5.9)

ADVERSE REACTIONS

Most common adverse reactions (>10%) are: infections (e.g. upper respiratory, sinusitis), injection site reactions, headache and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- *Abatacept* Increased risk of serious infection. (5.1, 5.11, 7.2)
- *Anakinra* Increased risk of serious infection. (5.1, 5.7, 7.2)
- *Live vaccines* Avoid use with HUMIRA. (5.10, 7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 2/2021

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1)]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA *[see Warnings and Precautions (5.2)]*. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF

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blocker in combination with these other immunosuppressants *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

1.2 Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

1.3 Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. HUMIRA can be used alone or in combination with non-biologic DMARDs.

1.4 Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

1.5 Crohn's Disease

HUMIRA is indicated for the treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.

1.6 Ulcerative Colitis

HUMIRA is indicated for the treatment of moderately to severely active ulcerative colitis in adults and pediatric patients 5 years of age and older.

Limitations of Use
The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers *[see Clinical Studies (14.7, 14.8)]*.

1.7 Plaque Psoriasis

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who

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will be closely monitored and have regular follow-up visits with a physician *[see Warnings and Precautions (5)]*.

1.8 Hidradenitis Suppurativa

HUMIRA is indicated for the treatment of moderate to severe hidradenitis suppurativa in patients 12 years of age and older.

1.9 Uveitis

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior, and panuveitis in adults and pediatric patients 2 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis

The recommended subcutaneous dosage of HUMIRA for adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS) is 40 mg administered every other week. Methotrexate (MTX), other non-biologic DMARDS, glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or analgesics may be continued during treatment with HUMIRA. In the treatment of RA, some patients not taking concomitant MTX may derive additional benefit from increasing the dosage of HUMIRA to 40 mg every week or 80 mg every other week.

2.2 Juvenile Idiopathic Arthritis or Pediatric Uveitis

The recommended subcutaneous dosage of HUMIRA for patients 2 years of age and older with polyarticular juvenile idiopathic arthritis (JIA) or pediatric uveitis is based on weight as shown below. MTX, glucocorticoids, NSAIDs, and/or analgesics may be continued during treatment with HUMIRA.

Pediatric Weight (2 Years of Age and older)	**Recommended Dosage**
10 kg (22 lbs) to less than 15 kg (33 lbs)	10 mg every other week
15 kg (33 lbs) to less than 30 kg (66 lbs)	20 mg every other week
30 kg (66 lbs) and greater	40 mg every other week

HUMIRA has not been studied in patients with polyarticular JIA or pediatric uveitis less than 2 years of age or in patients with a weight below 10 kg.

2.3 Crohn's Disease

Adults

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The recommended subcutaneous dosage of HUMIRA for adult patients with Crohn's disease (CD) is 160 mg initially on Day 1 (given in one day or split over two consecutive days), followed by 80 mg two weeks later (Day 15). Two weeks later (Day 29) begin a dosage of 40 mg every other week. Aminosalicylates and/or corticosteroids may be continued during treatment with HUMIRA. Azathioprine, 6-mercaptopurine (6-MP) *[see Warnings and Precautions (5.2)]* or MTX may be continued during treatment with HUMIRA if necessary.

Pediatrics

The recommended subcutaneous dosage of HUMIRA for pediatric patients 6 years of age and older with Crohn's disease (CD) is based on body weight as shown below:

Pediatric Weight	**Recommended Dosage**	
	Days 1 through 15	**Starting on Day 29**
17 kg (37 lbs) to less than 40 kg (88 lbs)	Day 1: 80 mg Day 15: 40 mg	20 mg every other week
40 kg (88 lbs) and greater	Day 1: 160 mg (single dose or split over two consecutive days) Day 15: 80 mg	40 mg every other week

2.4 Ulcerative Colitis

Adults

The recommended subcutaneous dosage of HUMIRA for adult patients with ulcerative colitis is 160 mg initially on Day 1 (given in one day or split over two consecutive days), followed by 80 mg two weeks later (Day 15). Two weeks later (Day 29) continue with a dosage of 40 mg every other week.

Discontinue HUMIRA in adult patients without evidence of clinical remission by eight weeks (Day 57) of therapy. Aminosalicylates and/or corticosteroids may be continued during treatment with HUMIRA. Azathioprine and 6-mercaptopurine (6-MP) *[see Warnings and Precautions (5.2)]* may be continued during treatment with HUMIRA if necessary.

Pediatrics

The recommended subcutaneous dosage of HUMIRA for pediatric patients 5 years of age and older with ulcerative colitis is based on body weight as shown below:

Pediatric Weight	**Recommended Dosage**	
	Days 1 through 15	**Starting on Day 29***
20 kg (44 lbs) to less than 40 kg (88 lbs)	Day 1: 80 mg Day 8: 40 mg Day 15: 40 mg	40 mg every other week or 20 mg every week

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40 kg (88 lbs) and greater	Day 1: 160 mg (single dose or split over two consecutive days) Day 8: 80 mg Day 15: 80 mg	80 mg every other week or 40 mg every week

* Continue the recommended pediatric dosage in patients who turn 18 years of age and who are well-controlled on their HUMIRA regimen.

2.5 Plaque Psoriasis or Adult Uveitis

The recommended subcutaneous dosage of HUMIRA for adult patients with plaque psoriasis (Ps) or Uveitis (UV) is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. The use of HUMIRA in moderate to severe chronic Ps beyond one year has not been evaluated in controlled clinical studies.

2.6 Hidradenitis Suppurativa

Adults

The recommended subcutaneous dosage of HUMIRA for adult patients with hidradenitis suppurativa (HS) is an initial dose of 160 mg (given in one day or split over two consecutive days), followed by 80 mg two weeks later (Day 15). Begin 40 mg weekly or 80 mg every other week dosing two weeks later (Day 29).

Adolescents

The recommended subcutaneous dosage of HUMIRA for adolescent patients 12 years of age and older weighing at least 30 kg with hidradenitis suppurativa (HS) is based on body weight as shown below *[see Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)]*:

Body Weight of Adolescent Patients (12 years of age and older)	**Recommended Dosage**
30 kg (66 lbs) to less than 60 kg (132 lbs)	• Day 1: 80 mg • Day 8 and subsequent doses: 40 mg every other week
60 kg (132 lbs) and greater	• Day 1: 160 mg (given in one day or split over two consecutive days); • Day 15: 80 mg • Day 29 and subsequent doses: 40 mg every week or 80 mg every other week

2.7 Monitoring to Assess Safety

Prior to initiating HUMIRA and periodically during therapy, evaluate patients for active tuberculosis and test for latent infection *[see Warnings and Precautions (5.1)]*.

2.8 General Considerations for Administration

HUMIRA is intended for use under the guidance and supervision of a physician. A patient may self-inject HUMIRA or a caregiver may inject HUMIRA using either the HUMIRA Pen or

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prefilled syringe if a physician determines that it is appropriate, and with medical follow-up, as necessary, after proper training in subcutaneous injection technique.

HUMIRA can be taken out of the refrigerator for 15 to 30 minutes before injecting to allow the liquid to come to room temperature. Do not remove the cap or cover while allowing it to reach room temperature. Carefully inspect the solution in the HUMIRA Pen, prefilled syringe, or single-dose institutional use vial for particulate matter and discoloration prior to subcutaneous administration. If particulates and discolorations are noted, do not use the product. HUMIRA does not contain preservatives; therefore, discard unused portions of drug remaining from the syringe. NOTE: Instruct patients sensitive to latex not to handle the needle cover of the HUMIRA 40 mg/0.8 mL Pen and 40 mg/0.8 mL, 20 mg/0.4 mL and 10 mg/0.2 mL prefilled syringe because it may contain natural rubber latex *[see How Supplied/Storage and Handling (16)]*.

Instruct patients using the HUMIRA Pen or prefilled syringe to inject the full amount in the syringe, according to the directions provided in the Instructions for Use *[see Instructions for Use]*.

Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites and do not give injections into areas where the skin is tender, bruised, red or hard.

If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.

The HUMIRA single-dose institutional use vial is for administration within an institutional setting only, such as a hospital, physician's office or clinic. Withdraw the dose using a sterile needle and syringe and administer promptly by a healthcare provider within an institutional setting. Only administer one dose per vial. The vial does not contain preservatives; therefore, discard unused portions.

3 DOSAGE FORMS AND STRENGTHS

HUMIRA is a clear and colorless solution available as:

- **Pen** (HUMIRA Pen)
  Injection: 80 mg/0.8 mL in a single-dose pen.
  Injection: 40 mg/0.8 mL in a single-dose pen.
  Injection: 40 mg/0.4 mL in a single-dose pen.
- **Prefilled Syringe**
  Injection: 80 mg/0.8 mL in a single-dose prefilled glass syringe.
  Injection: 40 mg/0.8 mL in a single-dose prefilled glass syringe.
  Injection: 40 mg/0.4 mL in a single-dose prefilled glass syringe.
  Injection: 20 mg/0.4 mL in a single-dose prefilled glass syringe.
  Injection: 20 mg/0.2 mL in a single-dose prefilled glass syringe.
  Injection: 10 mg/0.2 mL in a single-dose prefilled glass syringe.
  Injection: 10 mg/0.1 mL in a single-dose prefilled glass syringe.
- **Single-Dose Institutional Use Vial**
  Injection: 40 mg/0.8 mL in a single-dose, glass vial for institutional use only.

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4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA *[see Warnings and Precautions (5.7, 5.11) and Drug Interactions (7.2)]*.

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients 65 years of age and older, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis

Cases of reactivation of tuberculosis and new onset tuberculosis infections have been reported in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating HUMIRA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating HUMIRA, assess if treatment for latent tuberculosis is needed; and consider an induration of $\geq$ 5 mm a positive tuberculin skin test result, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed,

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and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Strongly consider tuberculosis in the differential diagnosis in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with HUMIRA.

Discontinue HUMIRA if a patient develops a serious infection or sepsis. For a patient who develops a new infection during treatment with HUMIRA, closely monitor them, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider appropriate empiric antifungal therapy, taking into account both the risk for severe fungal infection and the risks of antifungal therapy, while a diagnostic workup is being performed. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

5.2 Malignancies

Consider the risks and benefits of TNF-blocker treatment including HUMIRA prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy.

Malignancies in Adults

In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 39 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), plaque psoriasis (Ps), hidradenitis suppurativa (HS) and uveitis (UV), malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.48, 1.03) per 100 patient-years among 7973 HUMIRA-treated patients versus a rate of 0.7 (0.41, 1.17) per 100 patient-years among 4848 control-treated patients (median duration of

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treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).[1]

In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener's granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

Non-Melanoma Skin Cancer

During the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate (95% confidence interval) of NMSC was 0.8 (0.52, 1.09) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.10, 0.59) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment for the presence of NMSC prior to and during treatment with HUMIRA.

Lymphoma and Leukemia

In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, 2 lymphomas occurred among 7973 HUMIRA-treated patients versus 1 among 4848 control-treated patients. In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV with a median duration of approximately 0.7 years, including 24,605 patients and over 40,215 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).[1] Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

<u>Malignancies in Pediatric Patients and Young Adults</u>

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy $\leq$ 18 years of age), of which HUMIRA is a member. Approximately half the cases were lymphomas, including Hodgkin's and

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non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants. The potential risk with the combination of azathioprine or 6-mercaptopurine and HUMIRA should be carefully considered.

5.3 Hypersensitivity Reactions

Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, immediately discontinue administration of HUMIRA and institute appropriate therapy. In clinical trials of HUMIRA, hypersensitivity reactions (e.g., rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed.

5.4 Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy. Exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. For patients who are carriers of HBV and require treatment with TNF blockers, closely monitor such patients for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, stop HUMIRA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, exercise caution when considering resumption of HUMIRA therapy in this situation and monitor patients closely.

5.5 Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous

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system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of HUMIRA should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders.

5.6 Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA. Consider discontinuation of HUMIRA therapy in patients with confirmed significant hematologic abnormalities.

5.7 Increased Risk of Infection when Used with Anakinra

Concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater proportion of serious infections and neutropenia and no added benefit compared with the TNF-blocker alone in patients with RA. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions (7.2)]*.

5.8 Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. HUMIRA has not been formally studied in patients with CHF; however, in clinical trials of another TNF blocker, a higher rate of serious CHF-related adverse reactions was observed. Exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

5.9 Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, discontinue treatment *[see Adverse Reactions (6.1)]*.

5.10 Immunizations

In a placebo-controlled clinical trial of patients with RA, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Similar proportions of patients developed protective levels of anti-influenza antibodies between HUMIRA and placebo treatment groups; however, titers in aggregate to influenza antigens were moderately lower in patients receiving HUMIRA. The clinical significance of this is unknown. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

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It is recommended that pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants *[see Use in Specific Populations (8.1, 8.4)]*.

5.11 Increased Risk of Infection When Used with Abatacept

In controlled trials, the concurrent administration of TNF-blockers and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of abatacept with TNF-blockers including HUMIRA is not recommended *[see Drug Interactions (7.2)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Serious Infections *[see Warnings and Precautions (5.1)]*
- Malignancies *[see Warnings and Precautions (5.2)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Hepatitis B Virus Reactivation *[see Warnings and Precautions (5.4)]*
- Neurologic Reactions *[see Warnings and Precautions (5.5)]*
- Hematological Reactions *[see Warnings and Precautions (5.6)]*
- Heart Failure *[see Warnings and Precautions (5.8)]*
- Autoimmunity *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

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

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of studies in patients with RA (i.e., Studies RA-I, RA-II, RA-III and RA-IV) was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of HUMIRA in these RA studies were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

<u>Infections</u>

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In the controlled portions of the 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate of serious infections was 4.3 per 100 patient-years in 7973 HUMIRA-treated patients versus a rate of 2.9 per 100 patient-years in 4848 control-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis *[see Warnings and Precautions (5.1)]*.

Tuberculosis and Opportunistic Infections

In 52 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD, UC, Ps, HS and UV that included 24,605 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.20 per 100 patient-years and the rate of positive PPD conversion was 0.09 per 100 patient-years. In a subgroup of 10,113 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.05 per 100 patient-years and the rate of positive PPD conversion was 0.07 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB. Most of the TB cases occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. In these global clinical trials, cases of serious opportunistic infections have been reported at an overall rate of 0.05 per 100 patient-years. Some cases of serious opportunistic infections and TB have been fatal *[see Warnings and Precautions (5.1)]*.

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of HUMIRA (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations $\geq$ 3 x ULN occurred in 3.5% of HUMIRA-treated patients and 1.5% of control-treated patients. Since many of these patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear. In a controlled Phase 3 trial of HUMIRA in patients with polyarticular JIA who were 4 to 17 years, ALT elevations $\geq$ 3 x ULN occurred in 4.4% of HUMIRA-treated patients and 1.5% of control-treated patients (ALT more common than AST); liver enzyme test elevations were more frequent among those treated with the combination of HUMIRA and MTX than those treated with HUMIRA alone. In general, these elevations did not lead to discontinuation of HUMIRA treatment. No ALT elevations $\geq$ 3 x ULN occurred in the open-label study of HUMIRA in patients with polyarticular JIA who were 2 to <4 years.

In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in adult patients with Crohn's Disease with a control period duration ranging from 4 to 52 weeks, ALT elevations $\geq$ 3 x ULN occurred in 0.9% of HUMIRA-treated patients and 0.9% of control-treated patients. In

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the Phase 3 trial of HUMIRA in pediatric patients with Crohn's disease which evaluated efficacy and safety of two body weight based maintenance dose regimens following body weight based induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients, of whom 4 were receiving concomitant immunosuppressants at baseline; none of these patients discontinued due to abnormalities in ALT tests. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week) in adult patients with UC with control period duration ranging from 1 to 52 weeks, ALT elevations ≥3 x ULN occurred in 1.5% of HUMIRA-treated patients and 1.0% of control-treated patients. In the controlled Phase 3 trial of HUMIRA in patients with pediatric ulcerative colitis (N=93), which evaluated efficacy and safety of a maintenance dose of 0.6 mg/kg (maximum of 40 mg) every other week (N=31) and a maintenance dose of 0.6 mg/kg (maximum of 40 mg) every week (N=32), following body weight based induction doses of 2.4 mg/kg (maximum of 160 mg) at Week 0 and Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2 (N=63), or an induction dose of 2.4 mg/kg (maximum of 160 mg) at Week 0, placebo at Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2 (N=30), ALT elevations ≥ 3 X ULN occurred in 1.1% (1/93) of patients. In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week) in patients with Ps with control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of HUMIRA-treated patients and 1.8% of control-treated patients. In controlled trials of HUMIRA (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in subjects with HS with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of HUMIRA-treated subjects and 0.6% of control-treated subjects. In controlled trials of HUMIRA (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in adult patients with uveitis with an exposure of 165.4 PYs and 119.8 PYs in HUMIRA-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of HUMIRA-treated patients and 2.4% of control-treated patients.

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies RA-I, RA-II, RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week *[see Clinical Studies (14.1)]*.

Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. In Study RA-III, the types and frequencies of adverse reactions in the second year open-label extension were similar to those observed in the one-year double-blind portion.

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Table 1. Adverse Reactions Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Pooled RA Studies (Studies RA-I, RA-II, RA-III, and RA-IV)

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
	(N=705)	(N=690)
Adverse Reaction (Preferred Term)		
Respiratory		
Upper respiratory infection	17%	13%
Sinusitis	11%	9%
Flu syndrome	7%	6%
Gastrointestinal		
Nausea	9%	8%
Abdominal pain	7%	4%
Laboratory Tests*		
Laboratory test abnormal	8%	7%
Hypercholesterolemia	6%	4%
Hyperlipidemia	7%	5%
Hematuria	5%	4%
Alkaline phosphatase increased	5%	3%
Other		
Headache	12%	8%
Rash	12%	6%
Accidental injury	10%	8%
Injection site reaction **	8%	1%
Back pain	6%	4%
Urinary tract infection	8%	5%
Hypertension	5%	3%

* Laboratory test abnormalities were reported as adverse reactions in European trials
** Does not include injection site erythema, itching, hemorrhage, pain or swelling

Less Common Adverse Reactions in Rheumatoid Arthritis Clinical Studies

Other infrequent serious adverse reactions that do not appear in the Warnings and Precautions or Adverse Reaction sections that occurred at an incidence of less than 5% in HUMIRA-treated patients in RA studies were:

Body As A Whole: Pain in extremity, pelvic pain, surgery, thorax pain

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Cardiovascular System: Arrhythmia, atrial fibrillation, chest pain, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, tachycardia

Digestive System: Cholecystitis, cholelithiasis, esophagitis, gastroenteritis, gastrointestinal hemorrhage, hepatic necrosis, vomiting

Endocrine System: Parathyroid disorder

Hemic And Lymphatic System: Agranulocytosis, polycythemia

Metabolic And Nutritional Disorders: Dehydration, healing abnormal, ketosis, paraproteinemia, peripheral edema

Musculo-Skeletal System: Arthritis, bone disorder, bone fracture (not spontaneous), bone necrosis, joint disorder, muscle cramps, myasthenia, pyogenic arthritis, synovitis, tendon disorder

Neoplasia: Adenoma

Nervous System: Confusion, paresthesia, subdural hematoma, tremor

Respiratory System: Asthma, bronchospasm, dyspnea, lung function decreased, pleural effusion

Special Senses: Cataract

Thrombosis: Thrombosis leg

Urogenital System: Cystitis, kidney calculus, menstrual disorder

Juvenile Idiopathic Arthritis Clinical Studies

In general, the adverse reactions in the HUMIRA-treated patients in the polyarticular juvenile idiopathic arthritis (JIA) trials (Studies JIA-I and JIA-II) *[see Clinical Studies (14.2)]* were similar in frequency and type to those seen in adult patients *[see Warnings and Precautions (5), Adverse Reactions (6)]*. Important findings and differences from adults are discussed in the following paragraphs.

In Study JIA-I, HUMIRA was studied in 171 patients who were 4 to 17 years of age, with polyarticular JIA. Severe adverse reactions reported in the study included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia, and appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with HUMIRA and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

In Study JIA-I, 45% of patients experienced an infection while receiving HUMIRA with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in HUMIRA-treated patients were generally similar to those commonly seen in polyarticular JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in this patient population treated with HUMIRA were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in patients receiving HUMIRA was granuloma annulare which did not lead to discontinuation of HUMIRA treatment.

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In the first 48 weeks of treatment in Study JIA-I, non-serious hypersensitivity reactions were seen in approximately 6% of patients and included primarily localized allergic hypersensitivity reactions and allergic rash.

In Study JIA-I, 10% of patients treated with HUMIRA who had negative baseline anti-dsDNA antibodies developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.

Approximately 15% of patients treated with HUMIRA developed mild-to-moderate elevations of creatine phosphokinase (CPK) in Study JIA-I. Elevations exceeding 5 times the upper limit of normal were observed in several patients. CPK concentrations decreased or returned to normal in all patients. Most patients were able to continue HUMIRA without interruption.

In Study JIA-II, HUMIRA was studied in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with polyarticular JIA. The safety profile for this patient population was similar to the safety profile seen in patients 4 to 17 years of age with polyarticular JIA.

In Study JIA-II, 78% of patients experienced an infection while receiving HUMIRA. These included nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, and were mostly mild to moderate in severity. Serious infections were observed in 9% of patients receiving HUMIRA in the study and included dental caries, rotavirus gastroenteritis, and varicella.

In Study JIA-II, non-serious allergic reactions were observed in 6% of patients and included intermittent urticaria and rash, which were all mild in severity.

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

HUMIRA has been studied in 395 patients with psoriatic arthritis (PsA) in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis (AS) in two placebo-controlled studies *[see Clinical Studies (14.3, 14.4)]*. The safety profile for patients with PsA and AS treated with HUMIRA 40 mg every other week was similar to the safety profile seen in patients with RA, HUMIRA Studies RA-I through IV.

Crohn's Disease Clinical Studies

Adults: The safety profile of HUMIRA in 1478 adult patients with Crohn's disease from four placebo-controlled and two open-label extension studies *[see Clinical Studies (14.5)]* was similar to the safety profile seen in patients with RA.

Pediatric Patients 6 Years to 17 Years: The safety profile of HUMIRA in 192 pediatric patients from one double-blind study (Study PCD-I) and one open-label extension study *[see Clinical Studies (14.6)]* was similar to the safety profile seen in adult patients with Crohn's disease.

During the 4-week open label induction phase of Study PCD-I, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (6% and 5%, respectively).

A total of 67% of children experienced an infection while receiving HUMIRA in Study PCD-I. These included upper respiratory tract infection and nasopharyngitis.

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A total of 5% of children experienced a serious infection while receiving HUMIRA in Study PCD-I. These included viral infection, device related sepsis (catheter), gastroenteritis, H1N1 influenza, and disseminated histoplasmosis.

In Study PCD-I, allergic reactions were observed in 5% of children which were all non-serious and were primarily localized reactions.

Ulcerative Colitis Clinical Studies

Adults: The safety profile of HUMIRA in 1010 adult patients with ulcerative colitis (UC) from two placebo-controlled studies and one open-label extension study *[see Clinical Studies (14.7)]* was similar to the safety profile seen in patients with RA.

Pediatric Patients 5 Years to 17 Years: The safety profile of HUMIRA in 93 pediatric patients with ulcerative colitis from one double-blind study and one open-label extension study *[see Clinical Studies (14.8)]* was similar to the safety profile seen in adult patients with ulcerative colitis.

Plaque Psoriasis Clinical Studies

HUMIRA has been studied in 1696 subjects with plaque psoriasis (Ps) in placebo-controlled and open-label extension studies *[see Clinical Studies (14.9)]*. The safety profile for subjects with Ps treated with HUMIRA was similar to the safety profile seen in subjects with RA with the following exceptions. In the placebo-controlled portions of the clinical trials in Ps subjects, HUMIRA-treated subjects had a higher incidence of arthralgia when compared to controls (3% *vs.* 1%).

Hidradenitis Suppurativa Clinical Studies

HUMIRA has been studied in 727 subjects with hidradenitis suppurativa (HS) in three placebo-controlled studies and one open-label extension study *[see Clinical Studies (14.10)]*. The safety profile for subjects with HS treated with HUMIRA weekly was consistent with the known safety profile of HUMIRA.

Flare of HS, defined as ≥25% increase from baseline in abscesses and inflammatory nodule counts and with a minimum of 2 additional lesions, was documented in 22 (22%) of the 100 subjects who were withdrawn from HUMIRA treatment following the primary efficacy timepoint in two studies.

Uveitis Clinical Studies

HUMIRA has been studied in 464 adult patients with uveitis (UV) in placebo-controlled and open-label extension studies and in 90 pediatric patients with uveitis (Study PUV-I) *[see Clinical Studies (14.11, 14.12)]* . The safety profile for patients with UV treated with HUMIRA was similar to the safety profile seen in patients with RA.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample

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collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other adalimumab products may be misleading.

There are two assays that have been used to measure anti-adalimumab antibodies. With the ELISA, antibodies to adalimumab could be detected only when serum adalimumab concentrations were < 2 mcg/mL. The ECL assay can detect anti-adalimumab antibody titers independent of adalimumab concentrations in the serum samples. The incidence of anti-adalimumab antibody (AAA) development in patients treated with HUMIRA are presented in Table 2.

Table 2: Anti-Adalimumab Antibody Development Determined by ELISA and ECL Assay in Patients Treated with HUMIRA

Indications		**Study Duration**	**Anti-Adalimumab Antibody Incidence by ELISA (n/N)**		**Anti-Adalimumab Antibody Incidence by ECL Assay (n/N)**
			In all patients who received adalimumab	In patients with serum adalimumab concentrations < 2 mcg/mL	
Rheumatoid Arthritis[a]		6 to 12 months	5% (58/1062)	NR	NA
Juvenile Idiopathic Arthritis (JIA)	4 to 17 years of age[b]	48 weeks	16% (27/171)	NR	NA
	2 to 4 years of age or ≥ 4 years of age and weighing < 15 kg	24 weeks	7% (1/15)[c]	NR	NA
Psoriatic Arthritis[d]		48 weeks[e]	13% (24/178)	NR	NA
Ankylosing Spondylitis		24 weeks	9% (16/185)	NR	NA
Adult Crohn's Disease		56 weeks	3% (7/269)	8% (7/86)	NA
Pediatric Crohn's Disease		52 weeks	3% (6/182)	10% (6/58)	NA
Adult Ulcerative Colitis		52 weeks	5% (19/360)	21% (19/92)	NA
Pediatric Ulcerative Colitis		52 weeks	3% (3/100)	13% (3/23)	33% (33/100)[i]
Plaque Psoriasis[f]		Up to 52 weeks[g]	8% (77/920)	21% (77/372)	NA
Hidradenitis Suppurativa		36 weeks	7% (30/461)	28% (58/207)[h]	61% (272/445)[j]
Non-infectious Uveitis		52 weeks	5% (12/249)	21% (12/57)	40% (99/249)[k]

n: number of patients with anti-adalimumab antibody; NR: not reported; NA: Not applicable (not performed)

[a] In patients receiving concomitant methotrexate (MTX), the incidence of anti-adalimumab antibody was 1% compared to 12% with HUMIRA monotherapy

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[b] In patients receiving concomitant MTX, the incidence of anti-adalimumab antibody was 6% compared to 26% with HUMIRA monotherapy
[c] This patient received concomitant MTX
[d] In patients receiving concomitant MTX, the incidence of antibody development was 7% compared to 1% in RA
[e] Subjects enrolled after completing 2 previous studies of 24 weeks or 12 weeks of treatments.
[f] In plaque psoriasis patients who were on HUMIRA monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal
[g] One 12-week Phase 2 study and one 52-week Phase 3 study
[h] Among subjects in the 2 Phase 3 studies who stopped HUMIRA treatment for up to 24 weeks and in whom adalimumab serum levels subsequently declined to <2 mcg/mL (approximately 22% of total subjects studied)
[i] No apparent association between antibody development and safety was observed. The association of antibody development and efficacy outcome was not assessed due to limited number of subjects in each treatment group stratified by anti-adalimumab antibody titer.
[j] No apparent association between antibody development and safety was observed
[k] No correlation of antibody development to safety or efficacy outcomes was observed

Rheumatoid Arthritis and Psoriatic Arthritis: Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab using the ELISA during the 6- to 12-month period. No apparent correlation of antibody development to adverse reactions was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of HUMIRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HUMIRA exposure.

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)

Nervous system disorders: Demyelinating disorders (e.g., optic neuritis, Guillain-Barré syndrome), cerebrovascular accident

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Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis, pulmonary embolism

Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), alopecia, lichenoid skin reaction

Vascular disorders: Systemic vasculitis, deep vein thrombosis

7 DRUG INTERACTIONS

7.1 Methotrexate

HUMIRA has been studied in rheumatoid arthritis (RA) patients taking concomitant methotrexate (MTX). Although MTX reduced the apparent adalimumab clearance, the data do not suggest the need for dose adjustment of either HUMIRA or MTX *[see Clinical Pharmacology (12.3)]*.

7.2 Biological Products

In clinical studies in patients with RA, an increased risk of serious infections has been observed with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of HUMIRA with abatacept or anakinra is not recommended in patients with RA *[see Warnings and Precautions (5.7, 5.11)]*. A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF blocker. There is insufficient information regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, CD, UC, Ps, HS and UV. Concomitant administration of HUMIRA with other biologic DMARDS (e.g., anakinra and abatacept) or other TNF blockers is not recommended based upon the possible increased risk for infections and other potential pharmacological interactions.

7.3 Live Vaccines

Avoid the use of live vaccines with HUMIRA *[see Warnings and Precautions (5.10)]*.

7.4 Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased concentrations of cytokines (e.g., TNFα, IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HUMIRA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available studies with use of adalimumab during pregnancy do not reliably establish an association between adalimumab and major birth defects. Clinical data are available from the Organization of Teratology Information Specialists (OTIS)/MotherToBaby HUMIRA Pregnancy Registry in pregnant women with rheumatoid arthritis (RA) or Crohn's disease (CD). Registry results showed a rate of 10% for major birth defects with first trimester use of adalimumab in pregnant women with RA or CD and a rate of 7.5% for major birth defects in the disease-matched comparison cohort. The lack of pattern of major birth defects is reassuring and differences between exposure groups may have impacted the occurrence of birth defects *(see Data)*.

Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in-utero* exposed infant *(see Clinical Considerations)*. In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo/fetal risk

Published data suggest that the risk of adverse pregnancy outcomes in women with RA or inflammatory bowel disease (IBD) is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Fetal/Neonatal Adverse Reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester *(see Data)*. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to HUMIRA *in utero [see Use in Specific Populations (8.4)]*.

Data

Human Data

A prospective cohort pregnancy exposure registry conducted by OTIS/MotherToBaby in the U.S. and Canada between 2004 and 2016 compared the risk of major birth defects in live-born

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infants of 221 women (69 RA, 152 CD) treated with adalimumab during the first trimester and 106 women (74 RA, 32 CD) not treated with adalimumab.

The proportion of major birth defects among live-born infants in the adalimumab-treated and untreated cohorts was 10% (8.7% RA, 10.5% CD) and 7.5% (6.8% RA, 9.4% CD), respectively. The lack of pattern of major birth defects is reassuring and differences between exposure groups may have impacted the occurrence of birth defects. This study cannot reliably establish whether there is an association between adalimumab and major birth defects because of methodological limitations of the registry, including small sample size, the voluntary nature of the study, and the non-randomized design.

In an independent clinical study conducted in ten pregnant women with IBD treated with HUMIRA, adalimumab concentrations were measured in maternal serum as well as in cord blood (n=10) and infant serum (n=8) on the day of birth. The last dose of HUMIRA was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 µg/mL in cord blood, 4.28-17.7 µg/mL in infant serum, and 0-16.1 µg/mL in maternal serum. In all but one case, the cord blood concentration of adalimumab was higher than the maternal serum concentration, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum concentrations at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed *in utero* for at least 3 months from birth.

Animal Data

In an embryo-fetal perinatal development study, pregnant cynomolgus monkeys received adalimumab from gestation days 20 to 97 at doses that produced exposures up to 373 times that achieved with the MRHD without methotrexate (on an AUC basis with maternal IV doses up to 100 mg/kg/week). Adalimumab did not elicit harm to the fetuses or malformations.

8.2 Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum concentration. Published data suggest that the systemic exposure to a breastfed infant is expected to be low because adalimumab is a large molecule and is degraded in the gastrointestinal tract. However, the effects of local exposure in the gastrointestinal tract are unknown. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMIRA and any potential adverse effects on the breastfed child from HUMIRA or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of HUMIRA have been established for:

- reducing signs and symptoms of moderately to severely active polyarticular JIA in pediatric patients 2 years of age and older.
- the treatment of moderately to severely active Crohn's disease in pediatric patients 6 years of age and older.

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- the treatment of moderately to severely active ulcerative colitis in pediatric patients 5 years of age and older.
- the treatment of moderate to severe hidradenitis suppurativa in patients 12 years of age and older.
- the treatment of non-infectious intermediate, posterior, and panuveitis in pediatric patients 2 years of age and older.

Due to its inhibition of TNFα, HUMIRA administered during pregnancy could affect immune response in the *in utero*-exposed newborn and infant. Data from eight infants exposed to HUMIRA *in utero* suggest adalimumab crosses the placenta *[see Use in Specific Populations (8.1)]*. The clinical significance of elevated adalimumab concentrations in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

Post-marketing cases of lymphoma, including hepatosplenic T-cell lymphoma and other malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including HUMIRA *[see Warnings and Precautions (5.2)]*.

Juvenile Idiopathic Arthritis

In Study JIA-I, HUMIRA was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age *[see Clinical Studies (14.2)]*. In Study JIA-II, the safety profile for patients 2 to <4 years of age was similar to the safety profile for patients 4 to 17 years of age with polyarticular JIA *[see Adverse Reactions (6.1)]*. HUMIRA has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

The safety of HUMIRA in patients in the polyarticular JIA trials was generally similar to that observed in adults with certain exceptions *[see Adverse Reactions (6.1)]*.

The safety and effectiveness of HUMIRA have not been established in pediatric patients with JIA less than 2 years of age.

Pediatric Crohn's Disease

The safety and effectiveness of HUMIRA for the treatment of moderately to severely active Crohn's disease have been established in pediatric patients 6 years of age and older. Use of HUMIRA for this indication is supported by evidence from adequate and well-controlled studies in adults with additional data from a randomized, double-blind, 52-week clinical study of two dose concentrations of HUMIRA in 192 pediatric patients (6 years to 17 years of age) *[see Adverse Reactions (6.1), Clinical Pharmacology (12.2, 12.3), Clinical Studies (14.6)]*. The adverse reaction profile in patients 6 years to 17 years of age was similar to adults.

The safety and effectiveness of HUMIRA have not been established in pediatric patients with Crohn's disease less than 6 years of age.

Pediatric Ulcerative Colitis

The safety and effectiveness of HUMIRA for the treatment of moderately to severely active ulcerative colitis have been established in pediatric patients 5 years of age and older. Use of HUMIRA for this indication is supported by evidence from adequate and well-controlled studies in adults with additional data from a randomized, double-blind, 52-week clinical study of two

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dose concentrations of HUMIRA in 93 pediatric patients (5 years to 17 years of age) *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.8)]*. The adverse reaction profile in patients 5 years to 17 years of age was similar to adults.

The effectiveness of HUMIRA has not been established in patients who have lost response or were intolerant to TNF blockers.

The safety and effectiveness of HUMIRA have not been established in pediatric patients with ulcerative colitis less than 5 years of age.

Pediatric Uveitis

The safety and effectiveness of HUMIRA for the treatment of non-infectious uveitis have been established in pediatric patients 2 years of age and older. The use of HUMIRA is supported by evidence from adequate and well-controlled studies of HUMIRA in adults and a 2:1 randomized, controlled clinical study in 90 pediatric patients *[see Clinical Studies (14.12)]*. The safety and effectiveness of HUMIRA have not been established in pediatric patients with uveitis less than 2 years of age.

Hidradenitis Suppurativa

Use of HUMIRA in pediatric patients 12 years of age and older for HS is supported by evidence from adequate and well-controlled studies of HUMIRA in adult HS patients. Additional population pharmacokinetic modeling and simulation predicted that weight-based dosing of HUMIRA in pediatric patients 12 years of age and older can provide generally similar exposure to adult HS patients. The course of HS is sufficiently similar in adult and adolescent patients to allow extrapolation of data from adult to adolescent patients. The recommended dosage in pediatric patients 12 years of age or older is based on body weight *[see Dosage and Administration (2.6), Clinical Pharmacology (12.3), and Clinical Studies (14.10)]*.

The safety and effectiveness of HUMIRA have not been established in patients less than 12 years of age with HS.

8.5 Geriatric Use

A total of 519 RA patients 65 years of age and older, including 107 patients 75 years of age and older, received HUMIRA in clinical studies RA-I through IV. No overall difference in effectiveness was observed between these patients and younger patients. The frequency of serious infection and malignancy among HUMIRA treated patients 65 years of age and older was higher than for those less than 65 years of age. Consider the benefits and risks of HUMIRA in patients 65 years of age and older. In patients treated with HUMIRA, closely monitor for the development of infection or malignancy *[see Warnings and Precautions (5.1, 5.2)]*.

10 OVERDOSAGE

Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

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11 DESCRIPTION

Adalimumab is a tumor necrosis factor blocker. Adalimumab is a recombinant human IgG1 monoclonal antibody created using phage display technology resulting in an antibody with human derived heavy and light chain variable regions and human IgG1:k constant regions. Adalimumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary (CHO)) expression system and is purified by a process that includes specific viral inactivation and removal steps. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons.

HUMIRA (adalimumab) injection is supplied as a sterile, preservative-free solution for subcutaneous administration. The drug product is supplied as either a single-dose, prefilled pen (HUMIRA Pen), as a single-dose, 1 mL prefilled glass syringe, or as a single-dose institutional use vial. Enclosed within the pen is a single-dose, 1 mL prefilled glass syringe. The solution of HUMIRA is clear and colorless, with a pH of about 5.2.

Each 80 mg/0.8 mL prefilled syringe or prefilled pen delivers 0.8 mL (80 mg) of drug product. Each 0.8 mL of HUMIRA contains adalimumab (80 mg), mannitol (33.6 mg), polysorbate 80 (0.8 mg), and Water for Injection, USP.

Each 40 mg/0.4 mL prefilled syringe or prefilled pen delivers 0.4 mL (40 mg) of drug product. Each 0.4 mL of HUMIRA contains adalimumab (40 mg), mannitol (16.8 mg), polysorbate 80 (0.4 mg), and Water for Injection, USP.

Each 40 mg/0.8 mL prefilled syringe, prefilled pen, or single-dose institutional use vial delivers 0.8 mL (40 mg) of drug product. Each 0.8 mL of HUMIRA contains adalimumab (40 mg), citric acid monohydrate (1.04 mg), dibasic sodium phosphate dihydrate (1.22 mg), mannitol (9.6 mg), monobasic sodium phosphate dihydrate (0.69 mg), polysorbate 80 (0.8 mg), sodium chloride (4.93 mg), sodium citrate (0.24 mg) and Water for Injection, USP. Sodium hydroxide is added as necessary to adjust pH.

Each 20 mg/0.2 mL prefilled syringe delivers 0.2 mL (20 mg) of drug product. Each 0.2 mL of HUMIRA contains adalimumab (20 mg), mannitol (8.4 mg), polysorbate 80 (0.2 mg), and Water for Injection, USP.

Each 20 mg/0.4 mL prefilled syringe delivers 0.4 mL (20 mg) of drug product. Each 0.4 mL of HUMIRA contains adalimumab (20 mg), citric acid monohydrate (0.52 mg), dibasic sodium phosphate dihydrate (0.61 mg), mannitol (4.8 mg), monobasic sodium phosphate dihydrate (0.34 mg), polysorbate 80 (0.4 mg), sodium chloride (2.47 mg), sodium citrate (0.12 mg) and Water for Injection, USP. Sodium hydroxide is added as necessary to adjust pH.

Each 10 mg/0.1 mL prefilled syringe delivers 0.1 mL (10 mg) of drug product. Each 0.1 mL of HUMIRA contains adalimumab (10 mg), mannitol (4.2 mg), polysorbate 80 (0.1 mg), and Water for Injection, USP.

Each 10 mg/0.2 mL prefilled syringe delivers 0.2 mL (10 mg) of drug product. Each 0.2 mL of HUMIRA contains adalimumab (10 mg), citric acid monohydrate (0.26 mg), dibasic sodium phosphate dihydrate (0.31 mg), mannitol (2.4 mg), monobasic sodium phosphate dihydrate (0.17 mg), polysorbate 80 (0.2 mg), sodium chloride (1.23 mg), sodium citrate (0.06 mg) and Water for Injection, USP. Sodium hydroxide is added as necessary to adjust pH.

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12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells *in vitro* in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated concentrations of TNF are found in the synovial fluid of patients with RA, JIA, PsA, and AS and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased concentrations of TNF are also found in psoriasis plaques. In Ps, treatment with HUMIRA may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which HUMIRA exerts its clinical effects is unknown.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the concentrations of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of 1-2 X 10^{-10}M).

12.2 Pharmacodynamics

After treatment with HUMIRA, a decrease in concentrations of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines (IL-6) was observed compared to baseline in patients with rheumatoid arthritis. A decrease in CRP concentrations was also observed in patients with Crohn's disease, ulcerative colitis and hidradenitis suppurativa. Serum concentrations of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after HUMIRA administration.

For pediatric patients 5 years to 17 years with ulcerative colitis, the recommended dosage of HUMIRA is based on modeled dose/exposure-efficacy relationships and pharmacokinetic data. There are no anticipated clinically relevant differences in efficacy between the studied higher dosage administered in the clinical trial (Weeks 0 to 52 in Study PUC-I) *[see Clinical Studies (14.8)]* and the recommended dosage *[see Dosage and Administration (2.4)]*.

12.3 Pharmacokinetics

The pharmacokinetics of adalimumab were linear over the dose range of 0.5 to 10 mg/kg following administration of a single intravenous dose (HUMIRA is not approved for intravenous use). Following 20, 40, and 80 mg every other week and every week subcutaneous administration, adalimumab mean serum trough concentrations at steady state increased approximately proportionally with dose in RA patients. The mean terminal half-life was approximately 2 weeks, ranging from 10 to 20 days across studies. Healthy subjects and patients with RA displayed similar adalimumab pharmacokinetics.

Adalimumab exposure in patients treated with 80 mg every other week is estimated to be comparable with that in patients treated with 40 mg every week.

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Absorption

The average absolute bioavailability of adalimumab following a single 40 mg subcutaneous dose was 64%. The mean time to reach the maximum concentration was 5.5 days (131 ± 56 hours) and the maximum serum concentration was 4.7 ± 1.6 mcg/mL in healthy subjects following a single 40 mg subcutaneous administration of HUMIRA.

Distribution

The distribution volume (V_{ss}) ranged from 4.7 to 6.0 L following intravenous administration of doses ranging from 0.25 to 10 mg/kg in RA patients.

Elimination

The single dose pharmacokinetics of adalimumab in RA patients were determined in several studies with intravenous doses ranging from 0.25 to 10 mg/kg. The systemic clearance of adalimumab is approximately 12 mL/hr. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time in RA patients.

Patient Population

Rheumatoid Arthritis and Ankylosing Spondylitis: In patients receiving 40 mg HUMIRA every other week, adalimumab mean steady-state trough concentrations were approximately 5 mcg/mL and 8 to 9 mcg/mL, without and with MTX concomitant treatment, respectively. Adalimumab concentrations in the synovial fluid from five rheumatoid arthritis patients ranged from 31 to 96% of those in serum. The pharmacokinetics of adalimumab in patients with AS were similar to those in patients with RA.

Psoriatic Arthritis: In patients receiving 40 mg every other week, adalimumab mean steady-state trough concentrations were 6 to 10 mcg/mL and 8.5 to 12 mcg/mL, without and with MTX concomitant treatment, respectively.

Plaque Psoriasis: Adalimumab mean steady-state trough concentration was approximately 5 to 6 mcg/mL during HUMIRA 40 mg every other week treatment.

Adult Uveitis: Adalimumab mean steady concentration was approximately 8 to 10 mcg/mL during HUMIRA 40 mg every other week treatment.

Adult Hidradenitis Suppurativa: Adalimumab trough concentrations were approximately 7 to 8 mcg/mL at Week 2 and Week 4, respectively, after receiving 160 mg on Week 0 followed by 80 mg on Week 2. Mean steady-state trough concentrations at Week 12 through Week 36 were approximately 7 to 11 mcg/mL during HUMIRA 40 mg every week treatment.

Adult Crohn's Disease: Adalimumab mean trough concentrations were approximately 12 mcg/mL at Week 2 and Week 4 after receiving 160 mg on Week 0 followed by 80 mg on Week 2. Mean steady-state trough concentrations were 7 mcg/mL at Week 24 and Week 56 during HUMIRA 40 mg every other week treatment.

Adult Ulcerative Colitis: Adalimumab mean trough concentrations were approximately 12 mcg/mL at Week 2 and Week 4 after receiving 160 mg on Week 0 followed by 80 mg on Week 2. Mean steady-state trough concentrations were approximately 8 mcg/mL and 15 mcg/mL at Week 52 after receiving a dose of HUMIRA 40 mg every other week and 40 mg every week, respectively.

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Anti-Drug Antibody Effects on Pharmacokinetics

Rheumatoid Arthritis: A trend toward higher apparent clearance of adalimumab in the presence of anti-adalimumab antibodies was identified.

Pediatric Ulcerative Colitis: Antibodies to adalimumab by ECL assay were associated with reduced serum adalimumab concentrations in pediatric patients with moderately to severely active ulcerative colitis.

Hidradenitis Suppurativa: In subjects with moderate to severe HS, antibodies to adalimumab were associated with reduced serum adalimumab concentrations. In general, the extent of reduction in serum adalimumab concentrations is greater with increasing titers of antibodies to adalimumab.

Specific Populations

Geriatric Patients: A lower clearance with increasing age was observed in patients with RA aged 40 to >75 years.

Pediatric Patients:

Juvenile Idiopathic Arthritis:

- *4 years to 17 years of age:* The adalimumab mean steady-state trough concentrations were 6.8 mcg/mL and 10.9 mcg/mL in patients weighing <30 kg receiving 20 mg HUMIRA subcutaneously every other week as monotherapy or with concomitant MTX, respectively. The adalimumab mean steady-state trough concentrations were 6.6 mcg/mL and 8.1 mcg/mL in patients weighing ≥30 kg receiving 40 mg HUMIRA subcutaneously every other week as monotherapy or with MTX concomitant treatment, respectively.
- *2 years to <4 years of age or 4 years of age and older weighing <15 kg:* The adalimumab mean steady-state trough adalimumab concentrations were 6.0 mcg/mL and 7.9 mcg/mL in patients receiving HUMIRA subcutaneously every other week as monotherapy or with MTX concomitant treatment, respectively.

Pediatric Hidradenitis Suppurativa: Adalimumab concentrations in adolescent patients with HS receiving the recommended dosage regimens are predicted to be similar to those observed in adult subjects with HS based on population pharmacokinetic modeling and simulation.

Pediatric Crohn's Disease: Adalimumab mean ± SD concentrations were 15.7±6.5 mcg/mL at Week 4 following 160 mg at Week 0 and 80 mg at Week 2, and 10.5±6.0 mcg/mL at Week 52 following 40 mg every other week dosing in patients weighing ≥ 40 kg. Adalimumab mean ± SD concentrations were 10.6±6.1 mcg/mL at Week 4 following dosing 80 mg at Week 0 and 40 mg at Week 2, and 6.9±3.6 mcg/mL at Week 52 following 20 mg every other week dosing in patients weighing < 40 kg.

Pediatric Ulcerative Colitis: The adalimumab mean steady-state trough concentration was 5.0±3.3 mcg/mL at Week 52 following subcutaneous administration of 0.6 mg/kg (maximum of 40 mg) every other week in pediatric UC patients 5 years to 17 years of age. In patients who received 0.6 mg/kg (maximum of 40 mg) every week, the mean steady-state trough concentration was 15.7±5.6 mcg/mL at Week 52 in pediatric UC patients 5 years to 17 years of age.

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Male and Female Patients: No gender-related pharmacokinetic differences were observed after correction for a patient's body weight. Healthy subjects and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics.

Patients with Renal or Hepatic Impairment: No pharmacokinetic data are available in patients with hepatic or renal impairment.

Rheumatoid factor or CRP concentrations: Minor increases in apparent clearance were predicted in RA patients receiving doses lower than the recommended dose and in RA patients with high rheumatoid factor or CRP concentrations. These increases are not likely to be clinically important.

Drug Interaction Studies:

Methotrexate: MTX reduced adalimumab apparent clearance after single and multiple dosing by 29% and 44% respectively, in patients with RA *[see Drug Interactions (7.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

14 CLINICAL STUDIES

14.1 Rheumatoid Arthritis

The efficacy and safety of HUMIRA were assessed in five randomized, double-blind studies in patients ≥18 years of age with active rheumatoid arthritis (RA) diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 6 swollen and 9 tender joints. HUMIRA was administered subcutaneously in combination with methotrexate (MTX) (12.5 to 25 mg, Studies RA-I, RA-III and RA-V) or as monotherapy (Studies RA-II and RA-V) or with other disease-modifying anti-rheumatic drugs (DMARDs) (Study RA-IV).

Study RA-I evaluated 271 patients who had failed therapy with at least one but no more than four DMARDs and had inadequate response to MTX. Doses of 20, 40 or 80 mg of HUMIRA or placebo were given every other week for 24 weeks.

Study RA-II evaluated 544 patients who had failed therapy with at least one DMARD. Doses of placebo, 20 or 40 mg of HUMIRA were given as monotherapy every other week or weekly for 26 weeks.

Study RA-III evaluated 619 patients who had an inadequate response to MTX. Patients received placebo, 40 mg of HUMIRA every other week with placebo injections on alternate weeks, or 20 mg of HUMIRA weekly for up to 52 weeks. Study RA-III had an additional primary endpoint at 52 weeks of inhibition of disease progression (as detected by X-ray results). Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of HUMIRA was administered every other week for up to 5 years.

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Study RA-IV assessed safety in 636 patients who were either DMARD-naive or were permitted to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. Patients were randomized to 40 mg of HUMIRA or placebo every other week for 24 weeks.

Study RA-V evaluated 799 patients with moderately to severely active RA of less than 3 years duration who were ≥18 years old and MTX naïve. Patients were randomized to receive either MTX (optimized to 20 mg/week by week 8), HUMIRA 40 mg every other week or HUMIRA/MTX combination therapy for 104 weeks. Patients were evaluated for signs and symptoms, and for radiographic progression of joint damage. The median disease duration among patients enrolled in the study was 5 months. The median MTX dose achieved was 20 mg.

Clinical Response

The percent of HUMIRA treated patients achieving ACR 20, 50 and 70 responses in Studies RA-II and III are shown in Table 3.

Table 3. ACR Responses in Studies RA-II and RA-III (Percent of Patients)

	Study RA-II Monotherapy (26 weeks)			**Study RA-III Methotrexate Combination (24 and 52 weeks)**	
Response	Placebo	HUMIRA	HUMIRA	Placebo/MTX	HUMIRA/MTX
		40 mg every	40 mg weekly		40 mg every
		other week			other week
	N=110	N=113	N=103	N=200	N=207
ACR20					
Month 6	19%	46%*	53%*	30%	63%*
Month 12	NA	NA	NA	24%	59%*
ACR50					
Month 6	8%	22%*	35%*	10%	39%*
Month 12	NA	NA	NA	10%	42%*
ACR70					
Month 6	2%	12%*	18%*	3%	21%*
Month 12	NA	NA	NA	5%	23%*
* $p<0.01$, HUMIRA *vs.* placebo					

The results of Study RA-I were similar to Study RA-III; patients receiving HUMIRA 40 mg every other week in Study RA-I also achieved ACR 20, 50 and 70 response rates of 65%, 52% and 24%, respectively, compared to placebo responses of 13%, 7% and 3% respectively, at 6 months ($p<0.01$).

The results of the components of the ACR response criteria for Studies RA-II and RA-III are shown in Table 4. ACR response rates and improvement in all components of ACR response were maintained to week 104. Over the 2 years in Study RA-III, 20% of HUMIRA patients receiving 40 mg every other week achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period. ACR responses were maintained in similar

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proportions of patients for up to 5 years with continuous HUMIRA treatment in the open-label portion of Study RA-III.

Table 4. Components of ACR Response in Studies RA-II and RA-III

	Study RA-II				Study RA-III			
Parameter (median)	**Placebo N=110**		**HUMIRA[a] N=113**		**Placebo/MTX N=200**		**HUMIRA[a]/MTX N=207**	
	Baseline	**Wk 26**	**Baseline**	**Wk 26**	**Baseline**	**Wk 24**	**Baseline**	**Wk 24**
Number of tender joints (0-68)	35	26	31	16*	26	15	24	8*
Number of swollen joints (0-66)	19	16	18	10*	17	11	18	5*
Physician global assessment[b]	7.0	6.1	6.6	3.7*	6.3	3.5	6.5	2.0*
Patient global assessment[b]	7.5	6.3	7.5	4.5*	5.4	3.9	5.2	2.0*
Pain[b]	7.3	6.1	7.3	4.1*	6.0	3.8	5.8	2.1*
Disability index (HAQ)[c]	2.0	1.9	1.9	1.5*	1.5	1.3	1.5	0.8*
CRP (mg/dL)	3.9	4.3	4.6	1.8*	1.0	0.9	1.0	0.4*

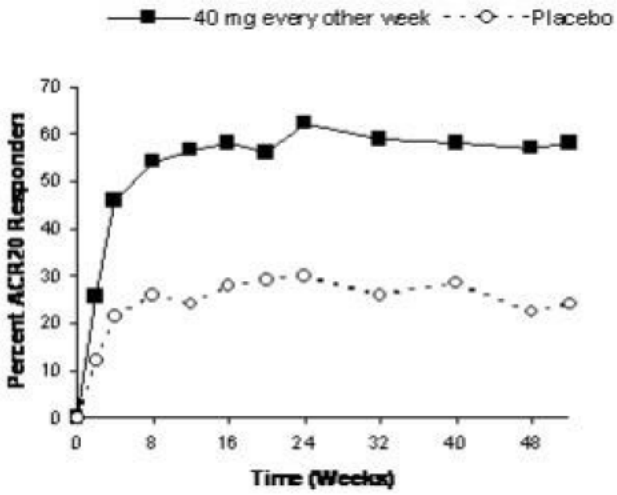
[a] 40 mg HUMIRA administered every other week
[b] Visual analogue scale; 0 = best, 10 = worst
[c] Disability Index of the Health Assessment Questionnaire; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity
* $p<0.001$, HUMIRA *vs.* placebo, based on mean change from baseline

The time course of ACR 20 response for Study RA-III is shown in Figure 1.

In Study RA-III, 85% of patients with ACR 20 responses at week 24 maintained the response at 52 weeks. The time course of ACR 20 response for Study RA-I and Study RA-II were similar.

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Figure 1. Study RA-III ACR 20 Responses over 52 Weeks



In Study RA-IV, 53% of patients treated with HUMIRA 40 mg every other week plus standard of care had an ACR 20 response at week 24 compared to 35% on placebo plus standard of care ($p<0.001$). No unique adverse reactions related to the combination of HUMIRA (adalimumab) and other DMARDs were observed.

In Study RA-V with MTX naïve patients with recent onset RA, the combination treatment with HUMIRA plus MTX led to greater percentages of patients achieving ACR responses than either MTX monotherapy or HUMIRA monotherapy at Week 52 and responses were sustained at Week 104 (see Table 5).

Table 5. ACR Response in Study RA-V (Percent of Patients)

Response	MTX[b] N=257	HUMIRA[c] N=274	HUMIRA/MTX N=268
ACR20			
Week 52	63%	54%	73%
Week 104	56%	49%	69%
ACR50			
Week 52	46%	41%	62%
Week 104	43%	37%	59%
ACR70			
Week 52	27%	26%	46%
Week 104	28%	28%	47%
Major Clinical Response [a]	28%	25%	49%

[a] Major clinical response is defined as achieving an ACR70 response for a continuous six month period
[b] $p<0.05$, HUMIRA/MTX *vs.* MTX for ACR 20
$p<0.001$, HUMIRA/MTX *vs.* MTX for ACR 50 and 70, and Major Clinical Response
[c] $p<0.001$, HUMIRA/MTX *vs.* HUMIRA

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At Week 52, all individual components of the ACR response criteria for Study RA-V improved in the HUMIRA/MTX group and improvements were maintained to Week 104.

Radiographic Response

In Study RA-III, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score, at month 12 compared to baseline. At baseline, the median TSS was approximately 55 in the placebo and 40 mg every other week groups. The results are shown in Table 6. HUMIRA/MTX treated patients demonstrated less radiographic progression than patients receiving MTX alone at 52 weeks.

Table 6. Radiographic Mean Changes Over 12 Months in Study RA-III

	Placebo/MTX	HUMIRA/MTX 40 mg every other week	Placebo/MTX-HUMIRA/MTX (95% Confidence Interval*)	P-value**
Total Sharp score	2.7	0.1	2.6 (1.4, 3.8)	<0.001
Erosion score	1.6	0.0	1.6 (0.9, 2.2)	<0.001
JSN score	1.0	0.1	0.9 (0.3, 1.4)	0.002

*95% confidence intervals for the differences in change scores between MTX and HUMIRA.
**Based on rank analysis

In the open-label extension of Study RA-III, 77% of the original patients treated with any dose of HUMIRA were evaluated radiographically at 2 years. Patients maintained inhibition of structural damage, as measured by the TSS. Fifty-four percent had no progression of structural damage as defined by a change in the TSS of zero or less. Fifty-five percent (55%) of patients originally treated with 40 mg HUMIRA every other week have been evaluated radiographically at 5 years. Patients had continued inhibition of structural damage with 50% showing no progression of structural damage defined by a change in the TSS of zero or less.

In Study RA-V, structural joint damage was assessed as in Study RA-III. Greater inhibition of radiographic progression, as assessed by changes in TSS, erosion score and JSN was observed in the HUMIRA/MTX combination group as compared to either the MTX or HUMIRA monotherapy group at Week 52 as well as at Week 104 (see Table 7).

Table 7. Radiographic Mean Change* in Study RA-V

		MTX[a] N=257	**HUMIRA[a,b] N=274**	**HUMIRA/MTX N=268**
52 Weeks	Total Sharp score	5.7 (4.2, 7.3)	3.0 (1.7, 4.3)	1.3 (0.5, 2.1)
	Erosion score	3.7 (2.7, 4.8)	1.7 (1.0, 2.4)	0.8 (0.4, 1.2)
	JSN score	2.0 (1.2, 2.8)	1.3 (0.5, 2.1)	0.5 (0.0, 1.0)
104 Weeks	Total Sharp score	10.4 (7.7, 13.2)	5.5 (3.6, 7.4)	1.9 (0.9, 2.9)
	Erosion score	6.4 (4.6, 8.2)	3.0 (2.0, 4.0)	1.0 (0.4, 1.6)
	JSN score	4.1 (2.7, 5.4)	2.6 (1.5, 3.7)	0.9 (0.3, 1.5)

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* mean (95% confidence interval)
[a] p<0.001, HUMIRA/MTX *vs.* MTX at 52 and 104 weeks and for HUMIRA/MTX *vs.* HUMIRA at 104 weeks
[b] p<0.01, for HUMIRA/MTX *vs.* HUMIRA at 52 weeks

Physical Function Response

In studies RA-I through IV, HUMIRA showed significantly greater improvement than placebo in the disability index of Health Assessment Questionnaire (HAQ-DI) from baseline to the end of study, and significantly greater improvement than placebo in the health-outcomes as assessed by The Short Form Health Survey (SF 36). Improvement was seen in both the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

In Study RA-III, the mean (95% CI) improvement in HAQ-DI from baseline at week 52 was 0.60 (0.55, 0.65) for the HUMIRA patients and 0.25 (0.17, 0.33) for placebo/MTX (p<0.001) patients. Sixty-three percent of HUMIRA-treated patients achieved a 0.5 or greater improvement in HAQ-DI at week 52 in the double-blind portion of the study. Eighty-two percent of these patients maintained that improvement through week 104 and a similar proportion of patients maintained this response through week 260 (5 years) of open-label treatment. Mean improvement in the SF-36 was maintained through the end of measurement at week 156 (3 years).

In Study RA-V, the HAQ-DI and the physical component of the SF-36 showed greater improvement (p<0.001) for the HUMIRA/MTX combination therapy group versus either the MTX monotherapy or the HUMIRA monotherapy group at Week 52, which was maintained through Week 104.

14.2 Juvenile Idiopathic Arthritis

The safety and efficacy of HUMIRA was assessed in two studies (Studies JIA-I and JIA-II) in patients with active polyarticular juvenile idiopathic arthritis (JIA).

Study JIA-I

The safety and efficacy of HUMIRA were assessed in a multicenter, randomized, withdrawal, double-blind, parallel-group study in 171 patients who were 4 to 17 years of age with polyarticular JIA. In the study, the patients were stratified into two groups: MTX-treated or non-MTX-treated. All patients had to show signs of active moderate or severe disease despite previous treatment with NSAIDs, analgesics, corticosteroids, or DMARDS. Patients who received prior treatment with any biologic DMARDS were excluded from the study.

The study included four phases: an open-label lead in phase (OL-LI; 16 weeks), a double-blind randomized withdrawal phase (DB; 32 weeks), an open-label extension phase (OLE-BSA; up to 136 weeks), and an open-label fixed dose phase (OLE-FD; 16 weeks). In the first three phases of the study, HUMIRA was administered based on body surface area at a dose of 24 mg/m^2 up to a maximum total body dose of 40 mg subcutaneously (SC) every other week. In the OLE-FD phase, the patients were treated with 20 mg of HUMIRA SC every other week if their weight was less than 30 kg and with 40 mg of HUMIRA SC every other week if their weight was 30 kg or greater. Patients remained on stable doses of NSAIDs and or prednisone (≤0.2 mg/kg/day or 10 mg/day maximum).

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Patients demonstrating a Pediatric ACR 30 response at the end of OL-LI phase were randomized into the double blind (DB) phase of the study and received either HUMIRA or placebo every other week for 32 weeks or until disease flare. Disease flare was defined as a worsening of ≥30% from baseline in ≥3 of 6 Pediatric ACR core criteria, ≥2 active joints, and improvement of >30% in no more than 1 of the 6 criteria. After 32 weeks or at the time of disease flare during the DB phase, patients were treated in the open-label extension phase based on the BSA regimen (OLE-BSA), before converting to a fixed dose regimen based on body weight (OLE-FD phase).

Study JIA-I Clinical Response

At the end of the 16-week OL-LI phase, 94% of the patients in the MTX stratum and 74% of the patients in the non-MTX stratum were Pediatric ACR 30 responders. In the DB phase significantly fewer patients who received HUMIRA experienced disease flare compared to placebo, both without MTX (43% *vs.* 71%) and with MTX (37% *vs.* 65%). More patients treated with HUMIRA continued to show pediatric ACR 30/50/70 responses at Week 48 compared to patients treated with placebo. Pediatric ACR responses were maintained for up to two years in the OLE phase in patients who received HUMIRA throughout the study.

Study JIA-II

HUMIRA was assessed in an open-label, multicenter study in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with moderately to severely active polyarticular JIA. Most patients (97%) received at least 24 weeks of HUMIRA treatment dosed 24 mg/m^2 up to a maximum of 20 mg every other week as a single SC injection up to a maximum of 120 weeks duration. During the study, most patients used concomitant MTX, with fewer reporting use of corticosteroids or NSAIDs. The primary objective of the study was evaluation of safety *[see Adverse Reactions (6.1)]*.

14.3 Psoriatic Arthritis

The safety and efficacy of HUMIRA was assessed in two randomized, double-blind, placebo controlled studies in 413 patients with psoriatic arthritis (PsA). Upon completion of both studies, 383 patients enrolled in an open-label extension study, in which 40 mg HUMIRA was administered every other week.

Study PsA-I enrolled 313 adult patients with moderately to severely active PsA (>3 swollen and >3 tender joints) who had an inadequate response to NSAID therapy in one of the following forms: (1) distal interphalangeal (DIP) involvement (N=23); (2) polyarticular arthritis (absence of rheumatoid nodules and presence of plaque psoriasis) (N=210); (3) arthritis mutilans (N=1); (4) asymmetric PsA (N=77); or (5) AS-like (N=2). Patients on MTX therapy (158 of 313 patients) at enrollment (stable dose of ≤30 mg/week for >1 month) could continue MTX at the same dose. Doses of HUMIRA 40 mg or placebo every other week were administered during the 24-week double-blind period of the study.

Compared to placebo, treatment with HUMIRA resulted in improvements in the measures of disease activity (see Tables 8 and 9). Among patients with PsA who received HUMIRA, the clinical responses were apparent in some patients at the time of the first visit (two weeks) and were maintained up to 88 weeks in the ongoing open-label study. Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with

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the arthritis mutilans and ankylosing spondylitis-like subtypes. Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

Patients with psoriatic involvement of at least three percent body surface area (BSA) were evaluated for Psoriatic Area and Severity Index (PASI) responses. At 24 weeks, the proportions of patients achieving a 75% or 90% improvement in the PASI were 59% and 42% respectively, in the HUMIRA group (N=69), compared to 1% and 0% respectively, in the placebo group (N=69) ($p<0.001$). PASI responses were apparent in some patients at the time of the first visit (two weeks). Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

Table 8. ACR Response in Study PsA-I (Percent of Patients)

	Placebo N=162	HUMIRA* N=151
ACR20		
Week 12	14%	58%
Week 24	15%	57%
ACR50		
Week 12	4%	36%
Week 24	6%	39%
ACR70		
Week 12	1%	20%
Week 24	1%	23%

* $p<0.001$ for all comparisons between HUMIRA and placebo

Table 9. Components of Disease Activity in Study PsA-I

	Placebo N=162		HUMIRA* N=151	
Parameter: median	Baseline	24 weeks	Baseline	24 weeks
Number of tender joints[a]	23.0	17.0	20.0	5.0
Number of swollen joints[b]	11.0	9.0	11.0	3.0
Physician global assessment[c]	53.0	49.0	55.0	16.0
Patient global assessment[c]	49.5	49.0	48.0	20.0
Pain[c]	49.0	49.0	54.0	20.0
Disability index (HAQ)[d]	1.0	0.9	1.0	0.4
CRP (mg/dL)[e]	0.8	0.7	0.8	0.2

* $p<0.001$ for HUMIRA *vs.* placebo comparisons based on median changes

[a] Scale 0-78

[b] Scale 0-76

[c] Visual analog scale; 0=best, 100=worst

[d] Disability Index of the Health Assessment Questionnaire; 0=best, 3=worst; measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.

[e] Normal range: 0-0.287 mg/dL

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