ステラーラ点滴静注 130 mg
ステラーラ皮下注 45 mg シリンジ
に関する資料

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1.5 起原又は発見の経緯及び開発の経緯 3

略号一覧表

略号又は略称	名称及び内容
ATC	anatomical therapeutic chemical（解剖治療化学）
IL	interleukin（インターロイキン）
TNF	tumor necrosis factor（腫瘍壊死因子）

1.5　起原又は発見の経緯及び開発の経緯

ウステキヌマブ（以下，本剤）は，ヒトインターロイキン（IL）-12 及び IL-23 を構成する p40 サブユニットタンパク質と高い親和性及び特異性で結合するヒト型免疫グロブリン G1κ モノクローナル抗体である。本剤は，解剖治療化学（ATC）分類法に基づき，IL 阻害薬に分類される（ATC 分類コード：L04AC05）。

本剤の点滴静注製剤は「中等症から重症の活動期クローン病の導入療法（既存治療で効果不十分な場合に限る）」，皮下注製剤は「既存治療で効果不十分な尋常性乾癬，関節症性乾癬」及び「中等症から重症の活動期クローン病の維持療法（既存治療で効果不十分な場合に限る）」として本邦で承認されている。

潰瘍性大腸炎は大腸の粘膜に影響を及ぼす原因不明の慢性炎症性疾患である。潰瘍性大腸炎に対する根治的な内科治療は確立されておらず，現状では，重症度，罹患範囲等に合わせた薬剤が選択されており，活動期には寛解導入療法が行われ，その後に寛解維持を目的とした維持療法が行われている。近年，抗腫瘍壊死因子（TNF）薬，$\alpha_4\beta_7$インテグリン拮抗薬及びヤヌスキナーゼ阻害剤等が使用可能となり，潰瘍性大腸炎に対する治療選択肢は増えたが，既承認の薬剤による寛解導入療法で効果が得られない又は効果が得られても後に消失する場合がある。さらに，既承認薬には，免疫抑制に関連する安全性リスク，悪性腫瘍や重篤な感染症等のリスクが挙げられており，治療を継続できない患者が存在する。これらのことから，既承認薬では効果不十分な患者や，安全性上の理由でその治療が適さないと考えられる患者に対しては依然アンメット・ニーズが存在する。

潰瘍性大腸炎に対する本剤の開発では，潰瘍性大腸炎及びクローン病の病態生理学的類似性，使用される薬剤の類似性，並びにクローン病の試験で得られた本剤の有効性の結果に基づき，クローン病患者を対象とした第 III 相試験と同様の用法・用量を用いて，中等症から重症の活動期潰瘍性大腸炎患者を対象とした第 III 相国際共同試験 CNTO1275UCO3001 試験（以下，UCO3001 試験）を実施した。UCO3001 試験は寛解導入試験及び寛解維持試験からなり，日本はいずれの試験にも参加している。UCO3001 試験の結果から，本剤静脈内投与による寛解導入療法，それに続く本剤皮下投与による寛解維持療法によって，一貫して統計学的に有意かつ臨床的に意味のあるベネフィットが示され，また良好な安全性プロファイルが示された。日本人集団と全体集団を比較した結果，有効性，安全性及び薬物動態のいずれにおいても類似した傾向が認められた。これらの結果を受けて，本剤の点滴静注製剤は「中等症から重症の潰瘍性大腸炎の寛解導入療法（既存治療で効果不十分な場合に限る）」及び皮下注製剤は「中等症から重症の潰瘍性大腸炎の維持療法（既存治療で効果不十分な場合に限る）」の効能・効果の追加を目的とした医薬品製造販売承認事項一部変更承認申請を行うこととした。

起源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「新医薬品の製造販売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）項の記述をもとに，当該内容を主に第 2 部（5）に記載した（表 1.5-1）。また，本剤の開発経緯について，臨床試験の一覧を表 1.5-2 に示す。なお，本申請のために新たに実施した品質試験及び非臨床試験はない。

表 1.5-1 CTD 1.5 項の内容の記載場所

CTD 1.5 項の内容	CTD 第 2 部の記載場所
起原又は発見の経緯	2.5.1　製品開発の根拠
潰瘍性大腸炎の病態	2.5.1.2.1　潰瘍性大腸炎
潰瘍性大腸炎の治療	2.5.1.2.2　潰瘍性大腸炎の治療の現状
開発の経緯	2.5.1.3　臨床開発経緯
非臨床試験の概略	2.4　非臨床試験の概括評価
申請効能・効果に対する本剤の有用性	2.5.6　ベネフィットとリスクに関する結論

表 1.5-2 臨床試験の開発の経緯

相	実施地域	対象	試験番号等	実施時期
III	国際共同	中等症から重症の活動期潰瘍性大腸炎患者	CNTO1275UCO3001 寛解導入試験（評価資料）	2015 年 8 月～2017 年 12 月
	国際共同	中等症から重症の活動期潰瘍性大腸炎患者	CNTO1275UCO3001 寛解維持試験（評価資料）	2015 年 8 月～実施中*
	国際共同	中等症から重症の活動期クローン病患者	CNTO1275CRD3001（参考資料）	2011 年 6 月～2013 年 7 月
	国際共同	中等症から重症の活動期クローン病患者	CNTO1275CRD3002（参考資料）	2011 年 6 月～2014 年 10 月
	国際共同	中等症から重症の活動期クローン病患者	CNTO1275CRD3003（参考資料）	2011 年 9 月～実施中**

*本申請では，44 週目までのデータを元に本剤の有用性を評価した。なお，本剤の寛解維持療法の用法・用量を支持するデータとして，44 週目から 96 週目までのデータも追加で提示した【2.7.3.7.2，2.7.4.7】。

**本申請では，安全性の併合解析には 44 週目までのデータを用い，44 週から 96 週目までのデータも追加で提示した【2.7.4.2.1.10】。

1.6 外国における使用状況等に関する資料

米国及び欧州において，2018 年 12 月に潰瘍性大腸炎の適応について承認申請を行った。米国では 2019 年 10 月に，欧州では 2019 年 9 月に承認された。

なお，主な既承認情報として，ウステキヌマブは乾癬に対して 2008 年 12 月にカナダで承認された後，2020 年 1 月現在，90 以上の国と地域で承認されている。クローン病に対して 2016 年 9 月に米国で承認された後，2020 年 1 月現在，40 以上の国と地域で承認されている。米国及び欧州におけるウステキヌマブの承認状況を表 1.6-1 及び表 1.6-2 に示す。また，外国の添付文書として，米国及び欧州の原文および企業中核データシート（CCDS）を添付する。

表 1.6-1 米国におけるウステキヌマブの承認状況

販売名	STELARA
許可年月日	2009 年 9 月 25 日
剤形・含量	STELARA（ウステキヌマブ）は無色から淡黄色の液体であり，少数の半透明または白色の小粒子を含むことがある。 皮下注 ・ 注射液：45 mg/0.5 mL または 90 mg/mL（単回投与用プレフィルドシリンジに充填） ・ 注射液：45 mg/0.5 mL（単回投与用ガラスバイアルに充填） 点滴静注 ・ 注射液：130 mg/26 mL（5 mg/mL）（単回投与用ガラスバイアルに充填）
効能・効果	**乾癬（Ps）** STELARA は，光線療法または全身療法の候補となる中等度から重度の尋常性乾癬の青年期患者（12 歳以上）を対象とした治療薬である。 **乾癬性関節炎（PsA）** STELARA は，活動性乾癬性関節炎成人患者を対象とした治療薬である。STELARA は単独またはメトトレキサート（MTX）との併用でも使用できる。 **クローン病（CD）** STELARA は，中等度から重度の活動期にあるクローン病成人患者を対象とした治療薬である。 **潰瘍性大腸炎（UC）** STELARA は，中等度から重度の活動期にある潰瘍性大腸炎成人患者を対象とした治療薬である。

用法・用量

乾癬（Ps）

成人に対する皮下投与

- 体重が 100 kg 以下の患者における推奨用量は 45 mg であり，これを初回と 4 週間後に投与し，その後は 12 週間ごとに投与する。
- 体重が 100 kg を超える患者における推奨用量は 90 mg であり，これを初回と 4 週間後に投与し，その後は 12 週間ごとに投与する。

体重が 100 kg を超える患者では，45 mg も有効であることが示された。しかし，これらの患者では 90 mg の方がより高い効果が得られた。

青年に対する皮下投与

STELARA を 0 週目，4 週間後に投与し，その後は 12 週間ごとに皮下投与する。

青年（12 歳から 17 歳）に対する STELARA の体重に基づく推奨用量を次の表 1 に示す。

表 1 青年の乾癬患者に対する STELARA の皮下注射推奨用量

投与時の患者の体重	推奨用量
60 kg 未満	0.75 mg/kg
60 kg 以上 100 kg 未満	45 mg
100 kg 以上	90 mg

単回投与バイアルから適当量を差し引いた体重 60 kg 未満の青年期患者の投与推奨用（0.75 mg/kg）を表 2 に示す。

表 2 体重 60 kg 未満の青年期患者の STELARA 45 mg/0.5mL 単回投与バイアルの注入量

投与時の患者の体重（kg）	用量（mg）	注入量（mL）
30	22.5	0.25
31	23.3	0.26
32	24	0.27
33	24.8	0.27
34	25.5	0.28
35	26.3	0.29
36	27	0.3
37	27.8	0.31
38	28.5	0.32
39	29.3	0.32
40	30	0.33
41	30.8	0.34
42	31.5	0.35
43	32.3	0.36
44	33	0.37
45	33.8	0.37
46	34.5	0.38
47	35.3	0.39
48	36	0.4
49	36.8	0.41
50	37.5	0.42
51	38.3	0.42
52	39	0.43
53	39.8	0.44
54	40.5	0.45
55	41.3	0.46
56	42	0.46
57	42.8	0.47

	58 | 43.5 | 0.48 59 | 44.3 | 0.49 **乾癬性関節炎（PsA）** 成人に対する皮下投与 ・ 推奨用量は 45 mg であり，これを初回と 4 週間後に投与し，その後は 12 週間ごとに投与する。 ・ 体重が 100 kg を超える中等度から重度の局面型乾癬患者における推奨用量は 90 mg であり，これを初回と 4 週間後に投与し，その後は 12 週間ごとに投与する。 **クローン病（CD）及び潰瘍性大腸炎（UC）** 成人に対する静脈内投与による導入療法 STELARA の単回点滴静注投与には，表 3 に規定する体重に基づく投与レジメンを用いる 表 3 STELARA 静脈内投与の初回用量 投与時点の患者の体重 | 用量 | 130 mg/26 mL（5 mg/mL）STELARA バイアル数 55 kg 以下 | 260 mg | 2 55 kg 超，85 kg 以下 | 390 mg | 3 85 kg 超 | 520 mg | 4 成人に対する皮下投与による維持療法 維持療法の推奨用量は 90 mg であり，これを初回静脈内投与の 8 週間後に皮下投与し，その後は 8 週間ごとに投与する。
禁忌	STELARA は，ウステキヌマブまたは添加物に対する臨床的に意義のある過敏症を有する患者には投与しないこと。

警告及び使用上の注意	**1. 感染症** STELARA は，感染症のリスクを増大させる可能性があるほか，潜在性感染を再活性化させる恐れがある。STELARA を投与した被験者に，重篤な細菌感染症，マイコバクテリア感染症，真菌感染症およびウイルス感染症が認められている。 臨床試験で報告された入院に至る重篤な感染症，又はその他の臨床的に重要な感染症には以下が含まれる。 ● 乾癬患者：憩室炎，蜂巣炎，肺炎，虫垂炎，胆嚢炎，敗血症，骨髄炎，ウイルス感染症，胃腸炎および尿路感染症があった。 ● 乾癬性関節炎患者：胆嚢炎 ● クローン病患者：肛門膿瘍，胃腸炎，ヘルペス眼感染，肺炎およびリステリア菌性髄膜炎 ● 潰瘍性大腸炎患者：胃腸炎，ヘルペス眼感染，肺炎およびリステリア菌性髄膜炎 臨床的に重要な活動性の感染症がみられる患者では，それが消失するか適切に治療されるまで，STELARA の投与を開始してはならない。慢性感染症または再発性感染症の既往を有する患者では，STELARA の投与を開始する前に，治療の危険性と有益性を勘案すること。 STELARA 治療下で感染症を示唆する徴候または症状が現れた場合には医師の診察を受け，さらに重篤またはその他の臨床的に意義のある感染症が認められた場合は，感染症が消失するか適切に治療されるまで投与の中止を検討することを，患者に指示すること。 **2. 特定の感染症に対する易感染性の理論的発現リスク** 遺伝的に IL-12/IL-23 が欠損している人は，マイコバクテリア（非結核性マイコバクテリア，環境マイコバクテリアなど），サルモネラ菌（非チフス菌株），およびカルメット・ゲラン菌（BCG）のワクチン接種により，特に播種性感染症に罹患しやすい。このような患者では，重篤な感染症が報告されているほか，死亡も報告されている。 STELARA の投与によって IL-12/IL-23 を薬理学的に阻害した患者がこのような感染症に罹患しやすくなるかどうかは不明である。臨床状況によって必要な場合には，組織培養や便培養などの適切な診断検査を検討すること。 **3. 投与前の結核評価** STELARA を投与する前に，結核の感染について患者を評価すること。 活動性結核菌感染を有する患者には本剤を投与してはならない。潜在性結核に対する治療は，本剤の投与を行う前に開始すること。過去に潜在性または活動性結核に罹患していたことがある患者で，十分な治療が行われたかどうか確認できない場合には，本剤の投与を開始する前に抗結核薬による治療を検討すること。本剤を投与した患者に対しては，治療中ならびに治療後に活動性結核の徴候および症状について綿密な観察を行うこと。 **4. 悪性腫瘍** STELARA は免疫抑制剤であり，悪性腫瘍の発生リスクを増大させる可能

	性がある。臨床試験で STELARA を投与した被験者に悪性腫瘍の発生が認められている。げっ歯類のモデルにおいて，IL-12/IL-23p40 の阻害に伴って悪性腫瘍の発生リスクが増大した。 STELARA の安全性は，悪性腫瘍の既往を有する患者および悪性腫瘍を有していることが判明している患者においては検討されていない。 市販後経験では，非黒色腫皮膚癌発現のリスク因子が認められた STELARA 投与患者に多発性皮膚扁平上皮癌の急性発現は報告されていない。STELARA を投与するすべての患者に対しては，非黒色腫皮膚癌の発現について観察を行うこと。60 歳以上の患者，長期の免疫抑制療法の治療歴がある患者および PUVA 治療歴がある患者に対しては，十分に観察を行うこと。 **5. 過敏性反応** STELARA によるアナフィラキシー反応および血管浮腫を含む過敏症反応が市販後に報告されている。アナフィラキシー反応または他の臨床的に意義のある過敏症反応が生じた場合は，適切な治療を開始し，STELARA を中止すること。 **6. 可逆性後白質脳症症候群** 乾癬および乾癬性関節炎の臨床試験において，可逆性後白質脳症症候群（RPLS）の症例が 1 件報告されている。同被験者は，STELARA の投与を約 2 年間の間に 12 回受け，頭痛，発作および錯乱を呈した。それ以上の本剤の投与は行われず，適切な治療により完全に回復した。クローン病又は潰瘍性大腸炎の臨床試験では RPLS の症例は認められていない。 RPLS は神経疾患であり，脱髄や既知の感染性病原体によって引き起こされるものではない。RPLS では，頭痛，発作，錯乱および視覚障害を呈することがある。本疾患との間に関連性が認められているものには，子癇前症，子癇，急性高血圧，細胞毒性薬および免疫抑制療法などがあり，死亡も報告されている。 RPLS が疑われる場合には，適切な治療を行い，STELARA の投与を中止すること。 **7. ワクチン接種** STELARA による治療を開始する前に，現行のワクチン接種ガイドラインで推奨されている年齢に適したワクチン接種をすべて行っておく必要がある。STELARA を投与している患者に生ワクチンを接種してはならない。BCG ワクチンは，STELARA による治療期間中，治療開始前 1 年間，および治療中止後 1 年間は接種してはならない。STELARA を投与している患者の家族に生ワクチンを接種する場合，接種した家族から患者に伝播する恐れがあるため，慎重に行うこと。

	生ワクチン以外のワクチンを STELARA による治療期間中に接種しても，疾患を予防するのに十分な免疫応答を得ることができない可能性がある。 **8. 併用療法** 乾癬の試験では，STELARA を他の免疫抑制剤または光線療法と併用した場合の安全性については評価されていない。遺伝子操作によって IL-12 と IL-23 の両方および IL-12 のみを欠損させたマウスでは，紫外線による皮膚癌の発生が早まったほか，発生頻度も増加した。 **9. 非感染性肺炎** STELARA の承認後の使用において間質性肺炎，好酸球性肺炎，原因不明の器質化肺炎が報告された。臨床症状として，1～3 回目の投与後に咳嗽，呼吸困難，間質浸潤が認められた。重篤な転帰には呼吸不全及び入院の延長があった。これらの事象は，治療の中止後及び特定の場合には，コルチコステロイドの投与により改善した。診断が確定された場合には，STELARA の使用を中止し，適切な治療を開始すること。

表 1.6-2 欧州におけるウステキヌマブの承認状況

販売名	STELARA 130 mg 濃縮静注液 STELARA 45 mg 注射液 STELARA 90 mg 注射液 STELARA 45 mg 注射液プレフィルドシリンジ STELARA 90 mg 注射液プレフィルドシリンジ
許可年月日	2009 年 1 月 16 日
剤形・含量	**STELARA 130 mg 濃縮静注液** 本剤は澄明の無色～淡黄色の液である。 バイアルにウステキヌマブ 130 mg（26 mL）（5 mg/mL）を含む。 **STELARA 45 mg 注射液** **STELARA 90 mg 注射液** **STELARA 45 mg 注射液プレフィルドシリンジ** **STELARA 90 mg 注射液プレフィルドシリンジ** 本剤は，澄明～わずかに乳白色の，無色～淡黄色の液である。 STELARA 45 mg 注射液 バイアルにウステキヌマブ 45 mg（0.5 mL）を含む。 STELARA 90 mg 注射液 バイアルにウステキヌマブ 90 mg（1 mL）を含む。 STELARA 45 mg 注射液プレフィルドシリンジ プレフィルドシリンジにウステキヌマブ 45 mg（0.5 mL）を含む。 STELARA 90 mg 注射液プレフィルドシリンジ プレフィルドシリンジにウステキヌマブ 90 mg（1 mL）を含む。

効能・効果	**STELARA 130 mg 濃縮静注液** **クローン病** 本剤は従来の治療薬又は TNFα 拮抗薬いずれかに対し効果が不十分であった，効果が失われた，忍容性がなかった又は禁忌である中等症から重症の活動性の成人クローン病患者の治療を適応とする治療薬である。 **潰瘍性大腸炎** 本剤は従来の治療薬又は生物学的製剤いずれかに対し効果が不十分であった，効果が失われた，忍容性がなかった又は禁忌である中等症から重症の活動性の成人潰瘍性大腸炎患者の治療を適応とする治療薬である。 **STELARA 45 mg 注射液** **STELARA 90 mg 注射液** **STELARA 45 mg 注射液プレフィルドシリンジ** **STELARA 90 mg 注射液プレフィルドシリンジ** **局面型乾癬** 本剤は，中等度から重度の局面型乾癬でシクロスポリン，メトトレキサート（MTX）又は PUVA（ソラレンと長波長紫外線との併用療法）などを含む他の全身治療が無効，禁忌，又は忍容性がない成人患者を適応とする治療薬である。 **小児の局面型乾癬** 本剤は，中等度から重度の局面型乾癬で他の全身治療又は光線療法が無効，又は忍容性がない 6 歳以上の小児及び青少年患者を適応とする治療薬である。 **乾癬性関節炎（PsA）** 本剤は，単独又は MTX と併用で，活動性乾癬性関節炎で非生物学的疾患修飾性抗リウマチ薬（DMARD）による前治療が無効となった成人患者を適応とする治療薬である。 **クローン病** 本剤は従来の治療薬又は TNFα 拮抗薬いずれかに対し効果が不十分であった，効果が失われた，忍容性がなかった又は禁忌である中等症から重症の活動性の成人クローン病患者を適応とする治療薬である。 **潰瘍性大腸炎** 本剤は従来の治療薬又は生物学的製剤いずれかに対し効果が不十分であった，効果が失われた，忍容性がなかった又は禁忌である中等症から重症の活動性の成人潰瘍性大腸炎患者の治療を適応とする治療薬である。
用法・用量	**STELARA 130 mg 濃縮静注液** 本剤はクローン病の診断及び治療の経験を有する医師の指導及び監督下で使用すること。本剤の使用は導入療法としての静脈内投与に限られる。 **用量** **クローン病／潰瘍性大腸炎** 本剤による治療は体重に基づいた用量を用いて単回静脈内投与から開始すること。表 1 に記載したように，注入投与液には本剤のバイアル数に応じた投与量が含まれる。 表 1 本剤の初回静脈投与量

投与時の患者の体重	推奨用量 [a]	本剤のバイアル数
≤ 55 kg	260 mg	2
> 55 kg～≤ 85 kg	390 mg	3

	> 85 kg	520 mg	4

[a]約 6 mg/kg

初回皮下投与は静脈内投与の 8 週後に行うこと。

高齢者への投与（65 歳以上）
高齢者に対し，用量を調節する必要はない。

腎機能障害及び肝機能障害を有する患者への投与
これらの患者に対する本剤の検討は行っていないため，推奨用量は決定していない。

小児への投与
18 歳未満の小児クローン病患者／小児潰瘍性大腸炎患者の治療における本剤の安全性及び有効性は確立されていない。利用可能なデータはない。

投与方法
本剤は静脈内投与用である。本剤は 1 時間以上かけて投与すること。

STELARA 45 mg 注射液
STELARA 90 mg 注射液
STELARA 45 mg 注射液プレフィルドシリンジ
STELARA 90 mg 注射液プレフィルドシリンジ
本剤は本剤が適応となる疾患の診断及び治療の経験を有する医師の指導及び監督下で使用すること。

用量
局面型乾癬
本剤は初回用量 45 mg で皮下投与を開始し，次に 4 週間後に 45 mg を投与し，以後は 12 週間毎に投与する。

最長 28 週の治療期間で反応が得られない患者については，投与の中止を検討すること。

体重が 100 kg を超える患者
体重が 100 kg を超える患者については，90 mg で皮下投与を開始し，次に 4 週間後に 90 mg を投与し，以後は 12 週間毎に投与する。これらの患者では 45 mg でも有効性が認められているが，90 mg の方が有効性は高かった。

乾癬性関節炎（PsA）
本剤は初回用量 45 mg で皮下投与を開始し，次に 4 週間後に 45 mg を投与し，以後は 12 週間毎に投与する。ただし，体重が 100 kg を超える患者には 90 mg を投与することができる。

最長 28 週の治療期間で反応が得られない患者については，投与の中止を検討すること。

高齢者への投与（65 歳以上）
高齢者に対し，用量を調節する必要はない。

腎機能障害及び肝機能障害を有する患者への投与
これらの患者に対する本剤の検討は行っていないため，推奨用量は決定していない。

小児への投与

6 歳未満の小児乾癬患者又は 18 歳未満の小児乾癬性関節炎患者における本剤の安全性及び有効性は確立されていない。

小児の局面型乾癬（6 歳以上）

体重に基づいた本剤の推奨用量を下記に示す（表 1 及び表 2）。本剤は，0 週目及び 4 週目に投与し，以後は 12 週間毎に投与する。

表 1 小児乾癬患者に対する推奨用量

投与時の体重	推奨用量
< 60 kg	0.75 mg/kg
≥ 60～≤ 100 kg	45 mg
> 100 kg	90 mg

60 kg 未満の患者に対する投与量（mL）を算出するために，次の式を用いる：*体重*（kg）×*0.0083*（mL/kg）（表 2 参照）。算出された投与量は，0.01 mL の単位に四捨五入し，1 mL 目盛り付きシリンジを用いて投与する。45 mg 全量を投与する必要のない小児患者用に 45 mg バイアルもある。

表 2 60 kg 未満の乾癬小児患者に対する投与量

投与時の体重（kg）	用量（mg）	投与量（mL）
15	11.3	0.12
16	12.0	0.13
17	12.8	0.14
18	13.5	0.15
19	14.3	0.16
20	15.0	0.17
21	15.8	0.17
22	16.5	0.18
23	17.3	0.19
24	18.0	0.20
25	18.8	0.21
26	19.5	0.22
27	20.3	0.22
28	21.0	0.23
29	21.8	0.24
30	22.5	0.25
31	23.3	0.26
32	24.0	0.27
33	24.8	0.27
34	25.5	0.28
35	26.3	0.29
36	27.0	0.30
37	27.8	0.31
38	28.5	0.32
39	29.3	0.32
40	30.0	0.33
41	30.8	0.34
42	31.5	0.35
43	32.3	0.36
44	33.0	0.37

45	33.8	0.37
46	34.5	0.38
47	35.3	0.39
48	36.0	0.40
49	36.8	0.41
50	37.5	0.42
51	38.3	0.42
52	39.0	0.43
53	39.8	0.44
54	40.5	0.45
55	41.3	0.46
56	42.0	0.46
57	42.8	0.47
58	43.5	0.48
59	44.3	0.49

最長 28 週の治療期間で反応が得られない患者については，投与の中止を検討すること。

クローン病／潰瘍性大腸炎
治療レジメンにおける本剤の初回投与は静脈内投与とする。

STELARA 90 mg の初回皮下投与は静脈内投与の 8 週後に行うこと。これ以降の投与は 12 週毎が推奨される。

初回皮下投与から 8 週間後に十分な効果を示さなかった患者は，この時点で 2 回目の皮下投与を受けることができる。

12 週毎の投与で効果を失った患者は，投与頻度を 8 週毎に増加させることでベネフィットを得られる可能性がある。

それ以降は臨床判断に従って 8 週毎又は 12 週毎に投与することができる。

導入療法における静脈内投与後 16 週目までに又は維持療法における 8 週毎投与への切り替え後 16 週間，治療効果が認められない患者については，投与の中止を検討すること。

本剤投与中も，免疫調節剤やコルチコステロイドは継続することができる。本剤投与により効果が認められた患者では，標準治療に従ってコルチコステロイドを減量又は中止することができる。

クローン病において本剤の投与を中断した場合，8 週毎の皮下投与から投与を再開しても安全かつ効果がある。

高齢者への投与（65 歳以上）
高齢者に対し，用量を調節する必要はない。

腎機能障害及び肝機能障害を有する患者への投与
これらの患者に対する本剤の検討は行っていないため，推奨用量は決定していない。

小児への投与

	18 歳未満の小児クローン病患者／小児潰瘍性大腸炎患者の治療における本剤の安全性及び有効性は確立されていない。利用可能なデータはない。 **投与方法** STELARA 45 mg 及び 90 mg バイアル又はプレフィルドシリンジは皮下注射用である。可能であれば，注射部位として，乾癬部分の皮膚は避ける必要がある。 皮下注射の方法について適切に訓練を行った後，医師が適切と判断した場合は，患者又はその介護者が本剤を注射することが可能である。医師は患者の経過観察を適切に行うこと。添付文書に記載の指示に従い，本剤の処方量を注射するよう患者又はその介護者に指導すること。投与に関する包括的な指示は添付文書に記載している。
禁忌	**STELARA 130 mg 濃縮静注液** **STELARA 45 mg 注射液** **STELARA 90 mg 注射液** **STELARA 45 mg 注射液プレフィルドシリンジ** **STELARA 90 mg 注射液プレフィルドシリンジ** 本剤の有効成分又添加物に対し過敏症の既往歴のある患者。臨床的に重要な活動性感染症を有する患者（活動性結核など）
警告及び使用上の注意	**STELARA 130 mg 濃縮静注液** **追跡可能性** 生物学的製剤の追跡可能性を強化するために，投与した製剤の商品名とバッチ番号を明記すること。 **感染症** ウステキヌマブの投与により感染症のリスクが増大し，潜在性感染が再活性化されるおそれがある。臨床試験では，本剤を投与した患者に重篤な細菌性，真菌性，ウイルス性感染症が報告されている。 慢性感染症の患者，又は再発性の感染症の既往がある患者には，慎重に投与すること。 本剤の投与を開始する前に，結核の評価を行うこと。活動性結核の患者には本剤を投与しないこと。潜在性結核感染の治療は，本剤の投与前に開始すること。潜在性又は活動性結核の既往があり，十分な治療コースの実施が確認できない患者については，本剤の投与を開始する前に抗結核薬による治療を検討すること。本剤を投与する患者については，治療中及び治療後の活動性結核の徴候及び症状について，十分に観察を行うこと。 感染症の発症を示唆する徴候又は症状が現れた場合は，医師の診察を受けるよう患者を指導すること。患者が重篤な感染症を発症した場合は，患者の状態を十分に観察し，感染症が治癒するまで本剤を投与しないこと。 **悪性腫瘍** ウステキヌマブなどの免疫抑制剤を投与すると，悪性腫瘍のリスクが増大するおそれがある。臨床試験で本剤を投与し，皮膚及び皮膚以外の悪性腫瘍が報告された症例もある。 悪性腫瘍の既往がある患者，又は本剤の投与中に悪性腫瘍を発症し，治療を継続中の患者を対象とした試験は実施していない。したがって，これらの患者に本剤の投与を検討する場合は，十分注意すること。 すべての患者，特に 60 歳以上の患者，長期の免疫抑制療法の治療歴がある

	患者又は PUVA 治療歴がある患者に対しては，非黒色腫皮膚癌の発現について観察を行うこと。 **全身性及び呼吸器過敏症反応** **全身性過敏症反応** 市販後において重篤な過敏症反応が報告され，いくつかの事例の場合，治療した数日後に発生している。アナフィラキシー反応や血管浮腫が発生している。アナフィラキシー反応又は他の重篤な過敏症反応が生じた場合は，適切な治療を開始し，本剤の投与を中止すること。 **呼吸器過敏症反応** ウステキヌマブの承認後の使用において，アレルギー性肺胞炎及び好酸球性肺炎が報告された。臨床症状として，1～3 回目の投与後に咳嗽，呼吸困難及び間質浸潤が認められた。重篤な転帰には呼吸不全及び入院の延長があった。これらの事象は，ウステキヌマブの中止後に改善したほか，特定の場合には，コルチコステロイドの投与により改善したものもあった。投与が中止され，診断が確定された場合には，ウステキヌマブの使用を中止し，適切な治療を開始すること。 **ワクチン接種** 生ウイルスワクチン又は生細菌ワクチン（Bacillus of Calmette and Guerin（BCG）など）を本剤と同時に投与しないこと。生ウイルスワクチン又は生細菌ワクチンを最近接種した患者を対象とした特定の試験は実施していない。本剤投与中の患者への生ワクチンの被接種者からの二次伝播に関するデータはない。生ウイルスワクチン又は生細菌ワクチンを接種する前は，本剤の投与を最終投与から 15 週間以上中断し，ワクチン接種から 2 週間以上後に投与を再開すること。 本剤を投与中の患者に，不活化ワクチン又は非生ワクチンを併用投与してもよい。 本剤を長期投与しても，肺炎球菌多糖体ワクチン又は破傷風ワクチンに対する体液性免疫反応は抑制されない。 **免疫抑制剤との併用** 乾癬に関する試験では，免疫抑制剤（生物学的製剤を含む）又は光線療法と併用した場合の本剤の安全性及び有効性については検討を行っていない。乾癬性関節炎に関する試験では，MTX と併用しても，本剤の安全性にも有効性にも影響を及ぼさないようであった。クローン病及び潰瘍性大腸炎に関する試験では，免疫抑制剤やコルチコステロイドと併用しても，本剤の安全性にも有効性にも影響を及ぼさないようであった。他の免疫抑制剤と本剤との併用を検討する場合，又は他の免疫抑制剤（生物学的製剤）から本剤に変更する場合は十分に注意すること。 **免疫療法** アレルゲン免疫療法を受けた患者における本剤の使用については評価されていない。本剤のアレルゲン免疫療法に対する影響は不明である。 **重篤な皮膚疾患** 乾癬患者において，ウステキヌマブ投与後に剥脱性皮膚炎が報告されている。局面型乾癬患者は，基礎疾患の自然経過の一部として，剥脱性皮膚炎とは臨床的に区別できない症状を伴う乾癬性紅皮症を発現することがある。医師は，患者の乾癬の観察の一環として，乾癬性紅皮症又は剥脱性皮膚炎の症状に注意を払うこと。これらの症状が生じた場合は，適切な治療を開始すること。薬物反応が疑われた場合は，本剤を中止すること。

	特別な患者集団への投与 *高齢者への投与（65 歳以上）* 年齢 65 歳以上の患者と若年患者における本剤の有効性又は安全性については，既承認の効能・効果における臨床試験では全体的に差は認められなかったが，65 歳以上の患者がそれよりも若い患者と異なる反応を示すかどうかを決定するには患者数が不足している。感染症の発症率は一般的に高齢者の方が高いため，高齢者に本剤を投与する場合は注意すること。 **ナトリウムの含量** STELARA は 1 投与量につき 1 mmol 未満のナトリウム（23 mg）を含有している（有効成分にはナトリウムを含有していない）が，STELARA は注射用に塩化ナトリウム 9 mg/mL （0.9%）溶液に希釈されているため，ナトリウム制限の食事療法を実施している患者に対しては配慮が必要である。 **STELARA 45 mg 注射液** **STELARA 90 mg 注射液** **STELARA 45 mg 注射液プレフィルドシリンジ** **STELARA 90 mg 注射液プレフィルドシリンジ** **追跡可能性** 生物学的製剤の追跡可能性を強化するために，投与した製剤の商品名とバッチ番号を明記すること。 **感染症** ウステキヌマブの投与により感染症のリスクが増大し，潜在性感染が再活性化されるおそれがある。臨床試験では，本剤を投与した患者に重篤な細菌性，真菌性，ウイルス性感染症が報告されている。 慢性感染症の患者，又は再発性の感染症の既往がある患者には，慎重に投与すること。 本剤の投与を開始する前に，結核の評価を行うこと。活動性結核の患者には本剤を投与しないこと。潜在性結核感染の治療は，本剤の投与前に開始すること。潜在性又は活動性結核の既往があり，十分な治療コースの実施が確認できない患者については，本剤の投与を開始する前に抗結核薬による治療を検討すること。本剤を投与する患者については，治療中及び治療後の活動性結核の徴候及び症状について，十分に観察を行うこと。 感染症の発症を示唆する徴候又は症状が現れた場合は，医師の診察を受けるよう患者を指導すること。患者が重篤な感染症を発症した場合は，患者の状態を十分に観察し，感染症が治癒するまで本剤を投与しないこと。 **悪性腫瘍** ウステキヌマブなどの免疫抑制剤を投与すると，悪性腫瘍のリスクが増大するおそれがある。臨床試験で本剤を投与し，皮膚及び皮膚以外の悪性腫瘍が報告された症例もある。 悪性腫瘍の既往がある患者，又は本剤の投与中に悪性腫瘍を発症し，治療を継続中の患者を対象とした試験は実施していない。したがって，これらの患者に本剤の投与を検討する場合は，十分注意すること。 すべての患者，特に 60 歳以上の患者，長期の免疫抑制療法の治療歴がある患者又は PUVA 治療歴がある患者に対しては，非黒色腫皮膚癌の発現について観察を行うこと。

全身性及び呼吸器過敏症反応
全身性過敏症反応
市販後において重篤な過敏症反応が報告され，いくつかの事例の場合，治療した数日後に発生している。アナフィラキシー反応や血管浮腫が発生している。アナフィラキシー反応又は他の重篤な過敏症反応が生じた場合は，適切な治療を開始し，本剤の投与を中止すること。

呼吸器過敏症反応
ウステキヌマブの承認後の使用において，アレルギー性肺胞炎及び好酸球性肺炎が報告された。臨床症状として，1～3 回目の投与後に咳嗽，呼吸困難及び間質浸潤が認められた。重篤な転帰には呼吸不全及び入院の延長があった。これらの事象は，ウステキヌマブの中止後に改善したほか，特定の場合には，コルチコステロイドの投与により改善したものもあった。投与が中止され，診断が確定された場合には，ウステキヌマブの使用を中止し，適切な治療を開始すること。

ラテックス感受性
STELARA プレフィルドシリンジの針カバーは乾燥天然ゴム（ラテックス類縁物質）を用いて使用されていることから，ラテックスに過敏な者はアレルギー反応を引き起こす可能性がある。

ワクチン接種
生ウイルスワクチン又は生細菌ワクチン（Bacillus of Calmette and Guerin（BCG）など）を本剤と同時に投与しないこと。生ウイルスワクチン又は生細菌ワクチンを最近接種した患者を対象とした特定の試験は実施していない。本剤投与中の患者への生ワクチンの被接種者からの二次伝播に関するデータはない。生ウイルスワクチン又は生細菌ワクチンを接種する前は，本剤の投与を最終投与から 15 週間以上中断し，ワクチン接種から 2 週間以上後に投与を再開すること。

本剤を投与中の患者に，不活化ワクチン又は非生ワクチンを併用投与してもよい。

本剤を長期投与しても，肺炎球菌多糖体ワクチン又は破傷風ワクチンに対する体液性免疫反応は抑制されない。

免疫抑制剤との併用
乾癬に関する試験では，免疫抑制剤（生物学的製剤を含む）又は光線療法と併用した場合の本剤の安全性及び有効性については検討を行っていない。乾癬性関節炎に関する試験では，MTX と併用しても，本剤の安全性にも有効性にも影響を及ぼさないようであった。クローン病及び潰瘍性大腸炎に関する試験では，免疫抑制剤やコルチコステロイドと併用しても，本剤の安全性にも有効性にも影響を及ぼさないようであった。他の免疫抑制剤と本剤との併用を検討する場合，又は他の免疫抑制剤（生物学的製剤）から本剤に変更する場合は十分に注意すること。

免疫療法
アレルゲン免疫療法を受けた患者における本剤の使用については評価されていない。本剤のアレルゲン免疫療法に対する影響は不明である。

重篤な皮膚疾患
乾癬患者において，ウステキヌマブ投与後に剥脱性皮膚炎が報告されている。局面型乾癬患者は，基礎疾患の自然経過の一部として，剥脱性皮膚炎とは臨床的に区別できない症状を伴う乾癬性紅皮症を発現することがある。医師は，患者の乾癬の観察の一環として，乾癬性紅皮症又は剥脱性皮膚炎の症

	状に注意を払うこと。これらの症状が生じた場合は，適切な治療を開始すること。薬物反応が疑われた場合は，本剤を中止すること。 **特別な患者集団への投与** ***高齢者への投与（65 歳以上）*** 年齢 65 歳以上の患者と若年患者における本剤の有効性又は安全性については，既承認の効能・効果における臨床試験では全体的に差は認められなかったが，65 歳以上の患者がそれよりも若い患者と異なる反応を示すかどうかを決定するには患者数が不足している。感染症の発症率は一般的に高齢者の方が高いため，高齢者に本剤を投与する場合は注意すること。

Janssen Research & Development, LLC

COMPANY CORE DATA SHEET

STELARA®

以下非公表のため COMPANY CORE DATA SHEET 2～77 頁を省略

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use STELARA® safely and effectively. See full prescribing information for STELARA®.

STELARA® (ustekinumab) injection, for subcutaneous or intravenous use
Initial U.S. Approval: 2009

----------RECENT MAJOR CHANGES----------

Indications and Usage, Ulcerative Colitis (1.4)	10/2019
Dosage and Administration (2.3)	10/2019
Dosage and Administration (2.6)	11/2019
Warnings and Precautions (5.1)	11/2019

----------INDICATIONS AND USAGE----------

STELARA® is a human interleukin-12 and -23 antagonist indicated for the treatment of:

Adult patients with:

- *moderate to severe plaque psoriasis (Ps)* who are candidates for phototherapy or systemic therapy. (1.1)
- *active psoriatic arthritis (PsA)*, alone or in combination with methotrexate. (1.2)
- *moderately to severely active Crohn's disease (CD)*. (1.3)
- *moderately to severely active ulcerative colitis.* (1.4)

Adolescent patients (12 years or older) with:

- *moderate to severe plaque psoriasis*, who are candidates for phototherapy or systemic therapy. (1.1)

----------DOSAGE AND ADMINISTRATION----------

Psoriasis Adult Subcutaneous Recommended Dosage (2.1):

Weight Range (kilogram)	Dosage Regimen
less than or equal to 100 kg	45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks
greater than 100 kg	90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks

Psoriasis Adolescent (12 years and older) Subcutaneous Recommended Dosage (2.1): Weight based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter.

Weight Range (kilogram)	Dosage Regimen
less than 60 kg	0.75 mg/kg
60 kg to 100 kg	45 mg
greater than 100 kg	90 mg

Psoriatic Arthritis Adult Subcutaneous Recommended Dosage (2.2):

- The recommended dosage is 45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks.
- For patients with co-existent moderate-to-severe plaque psoriasis weighing greater than 100 kg, the recommended dosage is 90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks.

Crohn's Disease and Ulcerative Colitis Initial Adult Intravenous Recommended Dosage (2.3): A single intravenous infusion using weight-based dosing:

Weight Range (kilogram)	Recommended Dosage
up to 55 kg	260 mg (2 vials)
greater than 55 kg to 85 kg	390 mg (3 vials)
greater than 85 kg	520 mg (4 vials)

Crohn's Disease and Ulcerative Colitis Maintenance Adult Subcutaneous Recommended Dosage (2.3): A subcutaneous 90 mg dose 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

----------DOSAGE FORMS AND STRENGTHS----------

Subcutaneous Injection (3)

- Injection: 45 mg/0.5 mL or 90 mg/mL in a single-dose prefilled syringe
- Injection: 45 mg/0.5 mL in a single-dose vial

Intravenous Infusion (3)

- Injection: 130 mg/26 mL (5 mg/mL) solution in a single-dose vial (3)

----------CONTRAINDICATIONS----------

Clinically significant hypersensitivity to ustekinumab or to any of the excipients. (4)

----------WARNINGS AND PRECAUTIONS----------

- Infections: Serious infections have occurred. Do not start STELARA® during any clinically important active infection. If a serious infection or clinically significant infection develops, consider discontinuing STELARA® until the infection resolves. (5.1)
- Theoretical Risk for Particular Infections: Serious infections from mycobacteria, salmonella and Bacillus Calmette-Guerin (BCG) vaccinations have been reported in patients genetically deficient in IL-12/IL-23. Diagnostic tests for these infections should be considered as dictated by clinical circumstances. (5.2)
- Tuberculosis (TB): Evaluate patients for TB prior to initiating treatment with STELARA®. Initiate treatment of latent TB before administering STELARA®. (5.3)
- Malignancies: STELARA® may increase risk of malignancy. The safety of STELARA® in patients with a history of or a known malignancy has not been evaluated. (5.4)
- Hypersensitivity Reactions: Anaphylaxis or other clinically significant hypersensitivity reactions may occur. (5.5)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): One case was reported. If suspected, treat promptly and discontinue STELARA®. (5.6)
- Noninfectious Pneumonia: Cases of interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia have been reported during post-approval use of STELARA®. If diagnosis is confirmed, discontinue STELARA® and institute appropriate treatment. (5.9)

----------ADVERSE REACTIONS----------

Most common adverse reactions are:

- Psoriasis (≥3%): nasopharyngitis, upper respiratory tract infection, headache, and fatigue. (6.1)
- Crohn's Disease, induction (≥3%): vomiting. (6.1)
- Crohn's Disease, maintenance (≥3%): nasopharyngitis, injection site erythema, vulvovaginal candidiasis/mycotic infection, bronchitis, pruritus, urinary tract infection, and sinusitis. (6.1)
- Ulcerative colitis, induction (≥3%): nasopharyngitis (6.1)
- Ulcerative colitis, maintenance (≥3%): nasopharyngitis, headache, abdominal pain, influenza, fever, diarrhea, sinusitis, fatigue, and nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2019

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- 1.4 Ulcerative Colitis

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- 2.2 Psoriatic Arthritis
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- 2.5 Instructions for Administration of STELARA® Prefilled Syringes Equipped with Needle Safety Guard
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Psoriasis (Ps)

STELARA® is indicated for the treatment of patients 12 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

1.2 Psoriatic Arthritis (PsA)

STELARA® is indicated for the treatment of adult patients with active psoriatic arthritis. STELARA® can be used alone or in combination with methotrexate (MTX).

1.3 Crohn's Disease (CD)

STELARA® is indicated for the treatment of adult patients with moderately to severely active Crohn's disease.

1.4 Ulcerative Colitis

STELARA® is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis.

2 DOSAGE AND ADMINISTRATION

2.1 Psoriasis

Subcutaneous Adult Dosage Regimen

- For patients weighing 100 kg or less, the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- For patients weighing more than 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

In subjects weighing more than 100 kg, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy in these subjects *[see Clinical Studies (14)]*.

Subcutaneous Adolescent Dosage Regimen

Administer STELARA® subcutaneously at Weeks 0 and 4, then every 12 weeks thereafter.

The recommended dose of STELARA® for adolescents (12-17 years old) based on body weight is shown below (Table 1).

Table 1: Recommended Dose of STELARA® for Subcutaneous Injection in Adolescent Patients with Psoriasis

Body Weight of Patient at the Time of Dosing	Recommended Dose
less than 60 kg	0.75 mg/kg
60 kg to 100 kg	45 mg
more than 100 kg	90 mg

For adolescent patients weighing less than 60 kg, the administration volume for the recommended dose (0.75 mg/kg) is shown in Table 2; withdraw the appropriate volume from the single-dose vial.

Table 2: Injection volumes of STELARA® 45 mg/0.5 mL single-dose vials for adolescent psoriasis patients less than 60 kg

Body Weight (kg) at the time of dosing	Dose (mg)	Volume of injection (mL)
30	22.5	0.25
31	23.3	0.26
32	24	0.27
33	24.8	0.27
34	25.5	0.28
35	26.3	0.29
36	27	0.3
37	27.8	0.31
38	28.5	0.32
39	29.3	0.32
40	30	0.33
41	30.8	0.34
42	31.5	0.35
43	32.3	0.36
44	33	0.37
45	33.8	0.37
46	34.5	0.38
47	35.3	0.39
48	36	0.4
49	36.8	0.41
50	37.5	0.42
51	38.3	0.42
52	39	0.43
53	39.8	0.44
54	40.5	0.45
55	41.3	0.46
56	42	0.46
57	42.8	0.47
58	43.5	0.48
59	44.3	0.49

2.2 Psoriatic Arthritis

Subcutaneous Adult Dosage Regimen

- The recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- For patients with co-existent moderate-to-severe plaque psoriasis weighing more than 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

2.3 Crohn's Disease and Ulcerative Colitis

Intravenous Induction Adult Dosage Regimen

A single intravenous infusion dose of STELARA® using the weight-based dosage regimen specified in Table 3 *[see Instructions for dilution of STELARA® 130 mg vial for intravenous infusion (2.6)]*.

Table 3: Initial Intravenous Dosage of STELARA®

Body Weight of Patient at the time of dosing	Dose	Number of 130 mg/26 mL (5 mg/mL) STELARA® vials
55 kg or less	260 mg	2
more than 55 kg to 85 kg	390 mg	3
more than 85 kg	520 mg	4

Subcutaneous Maintenance Adult Dosage Regimen

The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

2.4 General Considerations for Administration

- STELARA® is intended for use under the guidance and supervision of a physician. STELARA® should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician. The appropriate dose should be determined by a healthcare provider using the patient's current weight at the time of dosing. In adolescent patients, it is recommended that STELARA® be administered by a healthcare provider. If a physician determines that it is appropriate, a patient may self-inject or a caregiver may inject STELARA® after proper training in subcutaneous injection technique. Patients should be instructed to follow the directions provided in the Medication Guide *[see Medication Guide]*.
- The needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex). The needle cover should not be handled by persons sensitive to latex.
- It is recommended that each injection be administered at a different anatomic location (such as upper arms, gluteal regions, thighs, or any quadrant of abdomen) than the previous injection, and not into areas where the skin is tender, bruised, erythematous, or indurated.

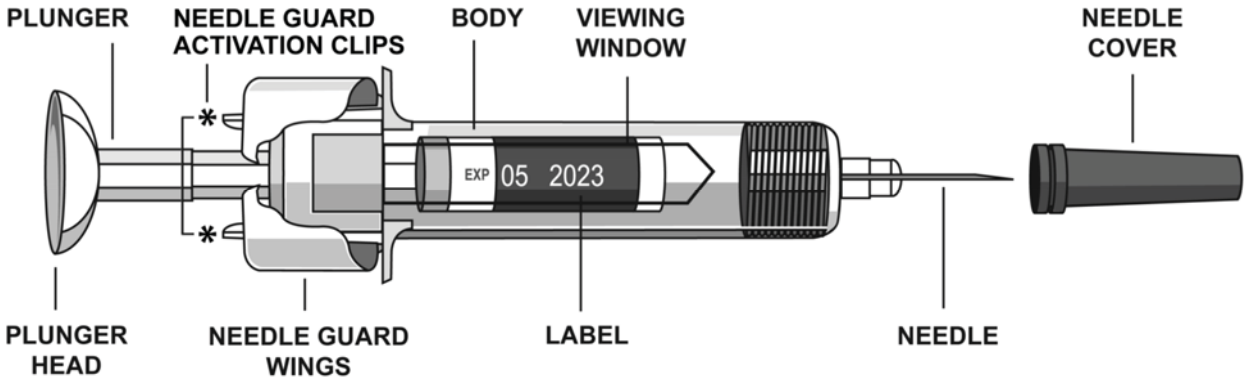
When using the single-dose vial, a 1 mL syringe with a 27 gauge, ½ inch needle is recommended.

- Prior to administration, visually inspect STELARA® for particulate matter and discoloration. STELARA® is a colorless to light yellow solution and may contain a few small translucent or white particles. Do not use STELARA® if it is discolored or cloudy, or if other particulate matter is present. STELARA® does not contain preservatives; therefore, discard any unused product remaining in the vial and/or syringe.

2.5 Instructions for Administration of STELARA® Prefilled Syringes Equipped with Needle Safety Guard

Refer to the diagram below for the provided instructions.

To prevent premature activation of the needle safety guard, do not touch the NEEDLE GUARD ACTIVATION CLIPS at any time during use.



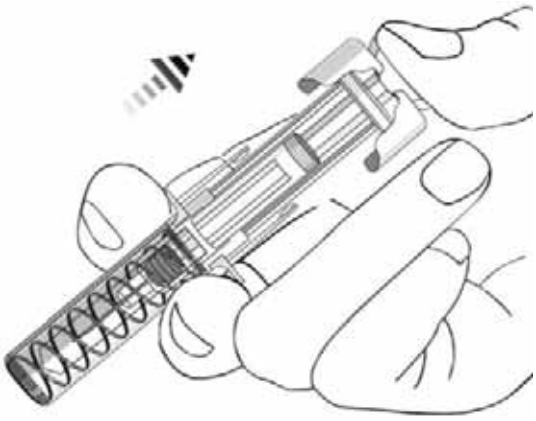
- Hold the BODY and remove the NEEDLE COVER. **Do not hold the PLUNGER or PLUNGER HEAD while removing the NEEDLE COVER or the PLUNGER may move. Do not use the prefilled syringe if it is dropped without the NEEDLE COVER in place**.

- Inject STELARA® subcutaneously as recommended *[see Dosage and Administration (2.1, 2.2, 2.3)]*.

- Inject all of the medication by pushing in the PLUNGER until the PLUNGER HEAD is completely between the needle guard wings. **Injection of the entire prefilled syringe contents is necessary to activate the needle guard**.



- After injection, maintain the pressure on the PLUNGER HEAD and remove the needle from the skin. Slowly take your thumb off the PLUNGER HEAD to allow the empty syringe to move up until the entire needle is covered by the needle guard, as shown by the illustration below:



- Used syringes should be placed in a puncture-resistant container.

2.6 Preparation and Administration of STELARA® 130 mg/26 mL (5 mg/mL) Vial for Intravenous Infusion (Crohn's Disease and Ulcerative Colitis)

STELARA® solution for intravenous infusion must be diluted, prepared and infused by a healthcare professional using aseptic technique.

1. Calculate the dose and the number of STELARA® vials needed based on patient weight (Table 3). Each 26 mL vial of STELARA® contains 130 mg of ustekinumab.

2. Withdraw, and then discard a volume of the 0.9% Sodium Chloride Injection, USP from the 250 mL infusion bag equal to the volume of STELARA® to be added (discard 26 mL sodium chloride for each vial of STELARA® needed, for 2 vials- discard 52 mL, for

3 vials- discard 78 mL, 4 vials- discard 104 mL). Alternatively, a 250 mL infusion bag containing 0.45% Sodium Chloride Injection, USP may be used.

3. Withdraw 26 mL of STELARA® from each vial needed and add it to the 250 mL infusion bag. The final volume in the infusion bag should be 250 mL. Gently mix.

4. Visually inspect the diluted solution before infusion. Do not use if visibly opaque particles, discoloration or foreign particles are observed.

5. Infuse the diluted solution over a period of at least one hour. Once diluted, the infusion should be completely administered within eight hours of the dilution in the infusion bag.

6. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.2 micrometer).

7. Do not infuse STELARA® concomitantly in the same intravenous line with other agents.

8. STELARA® does not contain preservatives. Each vial is for single use only. Discard any remaining solution. Dispose any unused medicinal product in accordance with local requirements.

Storage

If necessary, the diluted infusion solution may be kept at room temperature up to 25°C (77°F) for up to 7 hours. Storage time at room temperature begins once the diluted solution has been prepared. The infusion should be completed within 8 hours after the dilution in the infusion bag (cumulative time after preparation including the storage and the infusion period). Do not freeze. Discard any unused portion of the infusion solution.

3 DOSAGE FORMS AND STRENGTHS

STELARA® (ustekinumab) is a colorless to light yellow solution and may contain a few small translucent or white particles.

Subcutaneous Injection

- Injection: 45 mg/0.5 mL or 90 mg/mL solution in a single-dose prefilled syringe
- Injection: 45 mg/0.5 mL solution in a single-dose vial

Intravenous Infusion

- Injection: 130 mg/26 mL (5 mg/mL) solution in a single-dose vial

4 CONTRAINDICATIONS

STELARA® is contraindicated in patients with clinically significant hypersensitivity to ustekinumab or to any of the excipients *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

STELARA® may increase the risk of infections and reactivation of latent infections. Serious bacterial, mycobacterial, fungal, and viral infections were observed in patients receiving STELARA® *[see Adverse Reactions (6.1, 6.3)]*.

Serious infections requiring hospitalization, or otherwise clinically significant infections, reported in clinical studies included the following:

- *Psoriasis*: diverticulitis, cellulitis, pneumonia, appendicitis, cholecystitis, sepsis, osteomyelitis, viral infections, gastroenteritis and urinary tract infections.
- *Psoriatic arthritis*: cholecystitis.
- *Crohn's disease*: anal abscess, gastroenteritis, ophthalmic herpes zoster, pneumonia, and listeria meningitis.
- *Ulcerative colitis*: gastroenteritis, ophthalmic herpes zoster, pneumonia, and listeriosis.

Treatment with STELARA® should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. Consider the risks and benefits of treatment prior to initiating use of STELARA® in patients with a chronic infection or a history of recurrent infection.

Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur while on treatment with STELARA® and consider discontinuing STELARA® for serious or clinically significant infections until the infection resolves or is adequately treated.

5.2 Theoretical Risk for Vulnerability to Particular Infections

Individuals genetically deficient in IL-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria (including nontuberculous, environmental mycobacteria), salmonella (including nontyphi strains), and Bacillus Calmette-Guerin (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients.

It is not known whether patients with pharmacologic blockade of IL-12/IL-23 from treatment with STELARA® may be susceptible to these types of infections. Appropriate diagnostic testing should be considered, e.g., tissue culture, stool culture, as dictated by clinical circumstances.

5.3 Pre-treatment Evaluation for Tuberculosis

Evaluate patients for tuberculosis infection prior to initiating treatment with STELARA®.

Do not administer STELARA® to patients with active tuberculosis infection. Initiate treatment of latent tuberculosis prior to administering STELARA®. Consider anti-tuberculosis therapy prior to initiation of STELARA® in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Closely monitor patients receiving STELARA® for signs and symptoms of active tuberculosis during and after treatment.

5.4 Malignancies

STELARA® is an immunosuppressant and may increase the risk of malignancy. Malignancies were reported among subjects who received STELARA® in clinical studies *[see Adverse Reactions (6.1)]*. In rodent models, inhibition of IL-12/IL-23p40 increased the risk of malignancy *[see Nonclinical Toxicology (13)]*.

The safety of STELARA® has not been evaluated in patients who have a history of malignancy or who have a known malignancy.

There have been post-marketing reports of the rapid appearance of multiple cutaneous squamous cell carcinomas in patients receiving STELARA® who had pre-existing risk factors for developing non-melanoma skin cancer. All patients receiving STELARA® should be monitored for the appearance of non-melanoma skin cancer. Patients greater than 60 years of age, those with a medical history of prolonged immunosuppressant therapy and those with a history of PUVA treatment should be followed closely *[see Adverse Reactions (6.1)]*.

5.5 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with STELARA® *[see Adverse Reactions (6.1, 6.3)]*. If an anaphylactic or other clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue STELARA®.

5.6 Reversible Posterior Leukoencephalopathy Syndrome

One case of reversible posterior leukoencephalopathy syndrome (RPLS) was observed in clinical studies of psoriasis and psoriatic arthritis. The subject, who had received 12 doses of STELARA® over approximately two years, presented with headache, seizures and confusion. No additional STELARA® injections were administered and the subject fully recovered with appropriate treatment. No cases of RPLS were observed in clinical studies of Crohn's disease or ulcerative colitis.

RPLS is a neurological disorder, which is not caused by demyelination or a known infectious agent. RPLS can present with headache, seizures, confusion and visual disturbances. Conditions with which it has been associated include preeclampsia, eclampsia, acute hypertension, cytotoxic agents and immunosuppressive therapy. Fatal outcomes have been reported.

If RPLS is suspected, administer appropriate treatment and discontinue STELARA®.

5.7 Immunizations

Prior to initiating therapy with STELARA®, patients should receive all age-appropriate immunizations as recommended by current immunization guidelines. Patients being treated with STELARA® should not receive live vaccines. BCG vaccines should not be given during treatment with STELARA® or for one year prior to initiating treatment or one year following discontinuation of treatment. Caution is advised when administering live vaccines to household contacts of patients receiving STELARA® because of the potential risk for shedding from the household contact and transmission to patient.

Non-live vaccinations received during a course of STELARA® may not elicit an immune response sufficient to prevent disease.

5.8 Concomitant Therapies

In clinical studies of psoriasis the safety of STELARA® in combination with other immunosuppressive agents or phototherapy was not evaluated. Ultraviolet-induced skin cancers developed earlier and more frequently in mice genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone *[see Nonclinical Toxicology (13.1)]*.

5.9 Noninfectious Pneumonia

Cases of interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia have been reported during post-approval use of STELARA®. Clinical presentations included cough, dyspnea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalization. Patients improved with discontinuation of therapy and in certain cases administration of corticosteroids. If diagnosis is confirmed, discontinue STELARA® and institute appropriate treatment *[see Postmarketing Experience (6.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the label:

- Infections *[see Warnings and Precautions (5.1)]*
- Malignancies *[see Warnings and Precautions (5.4)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*
- Reversible Posterior Leukoencephalopathy Syndrome *[see Warnings and Precautions (5.6)]*

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.

Adult Subjects with Plaque Psoriasis

The safety data reflect exposure to STELARA® in 3117 adult psoriasis subjects, including 2414 exposed for at least 6 months, 1855 exposed for at least one year, 1653 exposed for at least two years, 1569 exposed for at least three years, 1482 exposed for at least four years and 838 exposed for at least five years.

Table 4 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the STELARA® groups than the placebo group during the placebo-controlled period of Ps STUDY 1 and Ps STUDY 2 *[see Clinical Studies (14)]*.

Table 4: Adverse Reactions Reported by ≥1% of Subjects through Week 12 in Ps STUDY 1 and Ps STUDY 2

		STELARA®	
	Placebo	**45 mg**	**90 mg**
Subjects treated	**665**	**664**	**666**
Nasopharyngitis	51 (8%)	56 (8%)	49 (7%)
Upper respiratory tract infection	30 (5%)	36 (5%)	28 (4%)
Headache	23 (3%)	33 (5%)	32 (5%)
Fatigue	14 (2%)	18 (3%)	17 (3%)
Diarrhea	12 (2%)	13 (2%)	13 (2%)
Back pain	8 (1%)	9 (1%)	14 (2%)
Dizziness	8 (1%)	8 (1%)	14 (2%)
Pharyngolaryngeal pain	7 (1%)	9 (1%)	12 (2%)
Pruritus	9 (1%)	10 (2%)	9 (1%)
Injection site erythema	3 (<1%)	6 (1%)	13 (2%)
Myalgia	4 (1%)	7 (1%)	8 (1%)
Depression	3 (<1%)	8 (1%)	4 (1%)

Adverse reactions that occurred at rates less than 1% in the controlled period of Ps STUDIES 1 and 2 through week 12 included: cellulitis, herpes zoster, diverticulitis and certain injection site reactions (pain, swelling, pruritus, induration, hemorrhage, bruising, and irritation).

One case of RPLS occurred during clinical studies *[see Warnings and Precautions (5.6)]*.

Infections

In the placebo-controlled period of clinical studies of psoriasis subjects (average follow-up of 12.6 weeks for placebo-treated subjects and 13.4 weeks for STELARA®-treated subjects), 27% of STELARA®-treated subjects reported infections (1.39 per subject-year of follow-up) compared with 24% of placebo-treated subjects (1.21 per subject-year of follow-up). Serious infections occurred in 0.3% of STELARA®-treated subjects (0.01 per subject-year of follow-up) and in 0.4% of placebo-treated subjects (0.02 per subject-year of follow-up) *[see Warnings and Precautions (5.1)]*.

In the controlled and non-controlled portions of psoriasis clinical studies (median follow-up of 3.2 years), representing 8998 subject-years of exposure, 72.3% of STELARA®-treated subjects reported infections (0.87 per subject-years of follow-up). Serious infections were reported in 2.8% of subjects (0.01 per subject-years of follow-up).

Malignancies

In the controlled and non-controlled portions of psoriasis clinical studies (median follow-up of 3.2 years, representing 8998 subject-years of exposure), 1.7% of STELARA®-treated subjects reported malignancies excluding non-melanoma skin cancers (0.60 per hundred subject-years of follow-up). Non-melanoma skin cancer was reported in 1.5% of STELARA®-treated subjects (0.52 per hundred subject-years of follow-up) *[see Warnings and Precautions (5.4)]*. The most frequently observed malignancies other than non-melanoma skin cancer during the clinical studies were: prostate, melanoma, colorectal and breast. Malignancies other than non-melanoma skin cancer in STELARA®-treated patients during the controlled and uncontrolled portions of 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]

Adolescent Subjects with Plaque Psoriasis

The safety of STELARA® was assessed in a study of 110 subjects 12 to 17 years of age with moderate to severe plaque psoriasis. The safety profile in these subjects through Week 60 was similar to the safety profile from studies in adults with plaque psoriasis.

Psoriatic Arthritis

The safety of STELARA® was assessed in 927 patients in two randomized, double-blind, placebo-controlled studies in adult patients with active psoriatic arthritis (PsA). The overall safety profile of STELARA® in patients with PsA was consistent with the safety profile seen in adult psoriasis clinical studies. A higher incidence of arthralgia, nausea, and dental infections was observed in STELARA®-treated patients when compared with placebo-treated patients (3% vs. 1% for arthralgia and 3% vs. 1% for nausea; 1% vs. 0.6% for dental infections) in the placebo-controlled portions of the PsA clinical studies.

Crohn's Disease

The safety of STELARA® was assessed in 1407 patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] greater than or equal to 220 and less than or equal to 450) in three randomized, double-blind, placebo-controlled, parallel-group, multicenter studies. These 1407 patients included 40 patients who received a prior investigational intravenous ustekinumab formulation but were not included in the efficacy analyses. In Studies CD-1 and CD-2 there were 470 patients who received STELARA® 6 mg/kg as a weight-based single intravenous induction dose and 466 who received placebo *[see Dosage and Administration (2.3)]*. Patients who were responders in either Study CD-1 or CD-2 were randomized to receive a subcutaneous maintenance regimen of either 90 mg STELARA® every 8 weeks, or placebo for 44 weeks in Study CD-3. Patients in these 3 studies may have received other concomitant therapies including aminosalicylates, immunomodulatory agents [azathioprine (AZA), 6-mercaptopurine (6-MP), MTX], oral corticosteroids (prednisone or budesonide), and/or antibiotics for their Crohn's disease *[see Clinical Studies (14.4)]*.

The overall safety profile of STELARA® was consistent with the safety profile seen in the adult psoriasis and psoriatic arthritis clinical studies. Common adverse reactions in Studies CD-1 and CD-2 and in Study CD-3 are listed in Tables 5 and 6, respectively.

Table 5: Common adverse reactions through Week 8 in Studies CD-1 and CD-2 occurring in ≥3% of STELARA®-treated patients and higher than placebo

	Placebo N=466	STELARA® 6 mg/kg single intravenous induction dose N=470
Vomiting	3%	4%

Other less common adverse reactions reported in patients in Studies CD-1 and CD-2 included asthenia (1% vs 0.4%), acne (1% vs 0.4%), and pruritus (2% vs 0.4%).

Table 6: Common adverse reactions through Week 44 in Study CD-3 occurring in ≥3% of STELARA®-treated patients and higher than placebo

	Placebo N=133	STELARA® 90 mg subcutaneous maintenance dose every 8 weeks N=131
Nasopharyngitis	8%	11%
Injection site erythema	0	5%
Vulvovaginal candidiasis/mycotic infection	1%	5%
Bronchitis	3%	5%
Pruritus	2%	4%
Urinary tract infection	2%	4%
Sinusitis	2%	3%

Infections

In patients with Crohn's disease, serious or other clinically significant infections included anal abscess, gastroenteritis, and pneumonia. In addition, listeria meningitis and ophthalmic herpes zoster were reported in one patient each *[see Warnings and Precautions (5.1)]*.

Malignancies

With up to one year of treatment in the Crohn's disease clinical studies, 0.2% of STELARA®-treated patients (0.36 events per hundred patient-years) and 0.2% of placebo-treated patients (0.58 events per hundred patient-years) developed non-melanoma skin cancer. Malignancies other than non-melanoma skin cancers occurred in 0.2% of STELARA®-treated patients (0.27 events per hundred patient-years) and in none of the placebo-treated patients.

Hypersensitivity Reactions Including Anaphylaxis

In CD studies, two patients reported hypersensitivity reactions following STELARA® administration. One patient experienced signs and symptoms consistent with anaphylaxis (tightness of the throat, shortness of breath, and flushing) after a single subcutaneous administration (0.1% of patients receiving subcutaneous STELARA®). In addition, one patient experienced signs and symptoms consistent with or related to a hypersensitivity reaction (chest discomfort, flushing, urticaria, and increased body temperature) after the initial intravenous STELARA® dose (0.08% of patients receiving intravenous STELARA®). These patients were treated with oral antihistamines or corticosteroids and in both cases symptoms resolved within an hour.

Ulcerative Colitis

The safety of STELARA® was evaluated in two randomized, double-blind, placebo-controlled clinical studies (UC-1 [IV induction] and UC-2 [SC maintenance]) in 960 adult patients with moderately to severely active ulcerative colitis *[see Clinical Studies (14.5)]*. The overall safety profile of STELARA® in patients with ulcerative colitis was consistent with the safety profile seen across all approved indications. Adverse reactions reported in at least 3% of STELARA®-treated patients and at a higher rate than placebo were:

- Induction (UC-1): nasopharyngitis (7% vs 4%).
- Maintenance (UC-2): nasopharyngitis (24% vs 20%), headache (10% vs 4%), abdominal pain (7% vs 3%), influenza (6% vs 5%), fever (5% vs. 4%), diarrhea (4% vs 1%), sinusitis (4% vs 1%), fatigue (4% vs 2%), and nausea (3% vs 2%).

Infections

In patients with ulcerative colitis, serious or other clinically significant infections included gastroenteritis and pneumonia. In addition, listeriosis and ophthalmic herpes zoster were reported in one patient each *[see Warnings and Precautions (5.1)]*.

Malignancies

With up to one year of treatment in the ulcerative colitis clinical studies, 0.4% of STELARA®-treated patients (0.48 events per hundred patient-years) and 0.0% of placebo-treated patients (0.00 events per hundred patient-years) developed non-melanoma skin cancer. Malignancies other than non-melanoma skin cancers occurred in 0.5% of STELARA®-treated patients (0.64 events per hundred patient-years) and 0.2% of placebo-treated patients (0.40 events per hundred patient-years).

6.2 Immunogenicity

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

Approximately 6 to 12.4% of subjects treated with STELARA® in psoriasis and psoriatic arthritis clinical studies developed antibodies to ustekinumab, which were generally low-titer. In psoriasis clinical studies, antibodies to ustekinumab were associated with reduced or undetectable serum ustekinumab concentrations and reduced efficacy. In psoriasis studies, the majority of patients who were positive for antibodies to ustekinumab had neutralizing antibodies.

In Crohn's disease and ulcerative colitis clinical studies, 2.9% and 4.6% of patients, respectively, developed antibodies to ustekinumab when treated with STELARA® for approximately one year. No apparent association between the development of antibodies to ustekinumab and the development of injection site reactions was seen.

6.3 Postmarketing Experience

The following adverse reactions have been reported during post-approval of STELARA®. 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 STELARA® exposure.

Immune system disorders: Serious hypersensitivity reactions (including anaphylaxis and angioedema), other hypersensitivity reactions (including rash and urticaria) *[see Warnings and Precautions (5.5)]*.

Infections and infestations: Lower respiratory tract infection (including opportunistic fungal infections and tuberculosis) *[see Warnings and Precautions (5.1)]*.

Respiratory, thoracic and mediastinal disorders: Interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia *[see Warnings and Precautions (5.9)]*.

Skin reactions: Pustular psoriasis, erythrodermic psoriasis.

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines with STELARA® *[see Warnings and Precautions (5.7)]*.

7.2 Concomitant Therapies

In psoriasis studies the safety of STELARA® in combination with immunosuppressive agents or phototherapy has not been evaluated *[see Warnings and Precautions (5.8)]*. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of STELARA®. In Crohn's disease and ulcerative colitis induction studies, immunomodulators (6-MP, AZA, MTX) were used concomitantly in approximately 30% of patients and corticosteroids were used concomitantly in approximately 40% and 50% of Crohn's disease and ulcerative colitis patients, respectively. Use of these concomitant therapies did not appear to influence the overall safety or efficacy of STELARA®.

7.3 CYP450 Substrates

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Thus, STELARA®, an antagonist of IL-12 and IL-23, could normalize the formation of CYP450 enzymes. Upon initiation of STELARA® in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, monitoring for therapeutic effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) should be considered and the individual dose of the drug adjusted as needed *[see Clinical Pharmacology (12.3)]*.

7.4 Allergen Immunotherapy

STELARA® has not been evaluated in patients who have undergone allergy immunotherapy. STELARA® may decrease the protective effect of allergen immunotherapy (decrease tolerance) which may increase the risk of an allergic reaction to a dose of allergen immunotherapy. Therefore, caution should be exercised in patients receiving or who have received allergen immunotherapy, particularly for anaphylaxis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to STELARA® during pregnancy. Patients should be encouraged to enroll by calling 1-877-311-8972.

Risk Summary

Limited data on the use of STELARA® in pregnant women are insufficient to inform a drug associated risk *[see Data]*. In animal reproductive and developmental toxicity studies, no adverse developmental effects were observed after administration of ustekinumab to pregnant monkeys at exposures greater than 100 times the human exposure at the maximum recommended human subcutaneous dose (MRHD).

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

Data

Human Data

Limited data on use of STELARA® in pregnant women from observational studies, published case reports, and postmarketing surveillance are insufficient to inform a drug associated risk.

Animal Data

Ustekinumab was tested in two embryo-fetal development toxicity studies in cynomolgus monkeys. No teratogenic or other adverse developmental effects were observed in fetuses from pregnant monkeys that were administered ustekinumab subcutaneously twice weekly or intravenously weekly during the period of organogenesis. Serum concentrations of ustekinumab in pregnant monkeys were greater than 100 times the serum concentration in patients treated subcutaneously with 90 mg of ustekinumab weekly for 4 weeks.

In a combined embryo-fetal development and pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered subcutaneous doses of ustekinumab twice weekly at exposures greater than 100 times the human subcutaneous exposure from the beginning of organogenesis to Day 33 after delivery. Neonatal deaths occurred in the offspring of one monkey administered ustekinumab at 22.5 mg/kg and one monkey dosed at 45 mg/kg. No ustekinumab-related effects on functional, morphological, or immunological development were observed in the neonates from birth through six months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of ustekinumab in human milk, the effects on the breastfed infant, or the effects on milk production. Ustekinumab was present in the milk of lactating monkeys administered ustekinumab. Due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk. Maternal IgG is known to be present in human milk. Published data suggest that the systemic exposure to a breastfed infant is expected to be low because ustekinumab is a large molecule and is degraded in the gastrointestinal tract. However, if ustekinumab is transferred into human milk the effects of local exposure in the gastrointestinal tract are unknown.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for STELARA® and any potential adverse effects on the breastfed child from STELARA® or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of STELARA® have been established in pediatric patients 12 to 17 years old with moderate to severe plaque psoriasis. Use of STELARA® in this age group is supported by evidence from a multicenter, randomized, 60-week trial that included a 12-week, double-blind, placebo-controlled, parallel-group portion, in 110 pediatric subjects 12 years and older *[see Adverse Reactions (6.1), Clinical Studies (14.2)]*. The safety and effectiveness of STELARA® for pediatric patients less than 12 years of age with psoriasis have not been established.

The safety and effectiveness of STELARA® have not been established in pediatric patients with psoriatic arthritis, Crohn's disease or ulcerative colitis.

8.5 Geriatric Use

Of the 6709 patients exposed to STELARA®, a total of 340 were 65 years or older (183 patients with psoriasis, 65 patients with psoriatic arthritis, 58 patients with Crohn's disease and 34 patients with ulcerative colitis), and 40 patients were 75 years or older. Although no overall differences in safety or efficacy were observed between older and younger patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

10 OVERDOSAGE

Single doses up to 6 mg/kg intravenously have been administered in clinical studies without dose-limiting toxicity. 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 be instituted immediately.

11 DESCRIPTION

Ustekinumab is a human IgG1κ monoclonal antibody against the p40 subunit of the IL-12 and IL-23 cytokines. Using DNA recombinant technology, ustekinumab is produced in a well characterized recombinant cell line and is purified using standard bio-processing technology. The

manufacturing process contains steps for the clearance of viruses. Ustekinumab is comprised of 1326 amino acids and has an estimated molecular mass that ranges from 148,079 to 149,690 Daltons.

STELARA® (ustekinumab) Injection is a sterile, preservative-free, colorless to light yellow solution and may contain a few small translucent or white particles with pH of 5.7- 6.3.

STELARA® for Subcutaneous Use

Available as 45 mg of ustekinumab in 0.5 mL and 90 mg of ustekinumab in 1 mL, supplied as a sterile solution in a single-dose prefilled syringe with a 27 gauge fixed ½ inch needle and as 45 mg of ustekinumab in 0.5 mL in a single-dose 2 mL Type I glass vial with a coated stopper. The syringe is fitted with a passive needle guard and a needle cover that contains dry natural rubber (a derivative of latex).

Each 0.5 mL prefilled syringe or vial delivers 45 mg ustekinumab, L-histidine and L-histidine monohydrochloride monohydrate (0.5 mg), Polysorbate 80 (0.02 mg), and sucrose (38 mg).

Each 1 mL prefilled syringe delivers 90 mg ustekinumab, L-histidine and L-histidine monohydrochloride monohydrate (1 mg), Polysorbate 80 (0.04 mg), and sucrose (76 mg).

STELARA® for Intravenous Infusion

Available as 130 mg of ustekinumab in 26 mL, supplied as a single-dose 30 mL Type I glass vial with a coated stopper.

Each 26 mL vial delivers 130 mg ustekinumab, EDTA disodium salt dihydrate (0.52 mg), L-histidine (20 mg), L-histidine hydrochloride monohydrate (27 mg), L-methionine (10.4 mg), Polysorbate 80 (10.4 mg) and sucrose (2210 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ustekinumab is a human IgG1κ monoclonal antibody that binds with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines. IL-12 and IL-23 are naturally occurring cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation. In *in vitro* models, ustekinumab was shown to disrupt IL-12 and IL-23 mediated signaling and cytokine cascades by disrupting the interaction of these cytokines with a shared cell-surface receptor chain, IL-12Rβ1. The cytokines IL-12 and IL-23 have been implicated as important contributors to the chronic inflammation that is a hallmark of Crohn's disease and ulcerative colitis. In animal models of colitis, genetic absence or antibody blockade of the p40 subunit of IL-12 and IL-23, the target of ustekinumab, was shown to be protective.

12.2 Pharmacodynamics

Psoriasis

In a small exploratory study, a decrease was observed in the expression of mRNA of its molecular targets IL-12 and IL-23 in lesional skin biopsies measured at baseline and up to two weeks post-treatment in subjects with psoriasis.

Ulcerative Colitis

In both study UC-1 (induction) and study UC-2 (maintenance), a positive relationship was observed between exposure and rates of clinical remission, clinical response, and endoscopic improvement. The response rate approached a plateau at the ustekinumab exposures associated with the recommended dosing regimen for maintenance treatment *[see Clinical Studies (14.5)]*.

12.3 Pharmacokinetics

Absorption

In adult subjects with psoriasis, the median time to reach the maximum serum concentration (T_{max}) was 13.5 days and 7 days, respectively, after a single subcutaneous administration of 45 mg (N=22) and 90 mg (N=24) of ustekinumab. In healthy subjects (N=30), the median T_{max} value (8.5 days) following a single subcutaneous administration of 90 mg of ustekinumab was comparable to that observed in subjects with psoriasis.

Following multiple subcutaneous doses of STELARA® in adult subjects with psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week 28. The mean (±SD) steady-state trough serum ustekinumab concentrations were 0.69 ± 0.69 mcg/mL for patients less than or equal to 100 kg receiving a 45 mg dose and 0.74 ± 0.78 mcg/mL for patients greater than 100 kg receiving a 90 mg dose. There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

Following the recommended intravenous induction dose, mean ±SD peak serum ustekinumab concentration was 125.2 ± 33.6 mcg/mL in patients with Crohn's disease, and 129.1 ± 27.6 mcg/mL in patients with ulcerative colitis. Starting at Week 8, the recommended subcutaneous maintenance dosing of 90 mg ustekinumab was administered every 8 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose. There was no apparent accumulation in ustekinumab concentration over time when given subcutaneously every 8 weeks. Mean ±SD steady-state trough concentration was 2.5 ± 2.1 mcg/mL in patients with Crohn's disease, and 3.3 ± 2.3 mcg/mL in patients with ulcerative colitis for 90 mg ustekinumab administered every 8 weeks.

Distribution

Population pharmacokinetic analyses showed that the volume of distribution of ustekinumab in the central compartment was 2.7 L (95% CI: 2.69, 2.78) in patients with Crohn's disease and 3.0 L (95% CI: 2.96, 3.07) in patients with ulcerative colitis. The total volume of distribution at steady-state was 4.6 L in patients with Crohn's disease and 4.4 L in patients with ulcerative colitis.

Elimination

The mean (±SD) half-life ranged from 14.9 ± 4.6 to 45.6 ± 80.2 days across all psoriasis studies following subcutaneous administration. Population pharmacokinetic analyses showed that the clearance of ustekinumab was 0.19 L/day (95% CI: 0.185, 0.197) in patients with Crohn's disease

and 0.19 L/day (95% CI: 0.179, 0.192) in patients with ulcerative colitis with an estimated median terminal half-life of approximately 19 days for both IBD (Crohn's disease and ulcerative colitis) populations.

These results indicate the pharmacokinetics of ustekinumab were similar between patients with Crohn's disease and ulcerative colitis.

Metabolism

The metabolic pathway of ustekinumab has not been characterized. As a human IgG1κ monoclonal antibody, ustekinumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Specific Populations

Weight

When given the same dose, subjects with psoriasis or psoriatic arthritis weighing more than 100 kg had lower median serum ustekinumab concentrations compared with those subjects weighing 100 kg or less. The median trough serum concentrations of ustekinumab in subjects of higher weight (greater than 100 kg) in the 90 mg group were comparable to those in subjects of lower weight (100 kg or less) in the 45 mg group.

Age: Geriatric Population

A population pharmacokinetic analysis (N=106/1937 patients with psoriasis greater than or equal to 65 years old) was performed to evaluate the effect of age on the pharmacokinetics of ustekinumab. There were no apparent changes in pharmacokinetic parameters (clearance and volume of distribution) in subjects older than 65 years old.

Age: Pediatric Population

Following multiple recommended doses of STELARA® in adolescent subjects 12 to 17 years of age with psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week 28. At Week 28, the mean ±SD steady-state trough serum ustekinumab concentration was 0.54 ± 0.43 mcg/mL.

Drug Interaction Studies

The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4). However, the clinical relevance of *in vitro* data has not been established *[see Drug Interactions (7.3)]*.

No *in vivo* drug interaction studies have been conducted with STELARA®.

Population pharmacokinetic analyses indicated that the clearance of ustekinumab was not impacted by concomitant MTX, NSAIDs, and oral corticosteroids, or prior exposure to a TNF blocker in patients with psoriatic arthritis.

In patients with Crohn's disease and ulcerative colitis, population pharmacokinetic analyses did not indicate changes in ustekinumab clearance with concomitant use of corticosteroids or immunomodulators (AZA, 6-MP, or MTX); and serum ustekinumab concentrations were not impacted by concomitant use of these medications.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of STELARA®. Published literature showed that administration of murine IL-12 caused an anti-tumor effect in mice that contained transplanted tumors and IL-12/IL-23p40 knockout mice or mice treated with anti-IL-12/IL-23p40 antibody had decreased host defense to tumors. Mice genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone developed UV-induced skin cancers earlier and more frequently compared to wild-type mice. The relevance of these experimental findings in mouse models for malignancy risk in humans is unknown.

No effects on fertility were observed in male cynomolgus monkeys that were administered ustekinumab at subcutaneous doses up to 45 mg/kg twice weekly (45 times the MRHD on a mg/kg basis) prior to and during the mating period. However, fertility and pregnancy outcomes were not evaluated in mated females.

No effects on fertility were observed in female mice that were administered an analogous IL-12/IL-23p40 antibody by subcutaneous administration at doses up to 50 mg/kg, twice weekly, prior to and during early pregnancy.

13.2 Animal Toxicology and/or Pharmacology

In a 26-week toxicology study, one out of 10 monkeys subcutaneously administered 45 mg/kg ustekinumab twice weekly for 26 weeks had a bacterial infection.

14 CLINICAL STUDIES

14.1 Psoriasis

Two multicenter, randomized, double-blind, placebo-controlled studies (Ps STUDY 1 and Ps STUDY 2) enrolled a total of 1996 subjects 18 years of age and older with plaque psoriasis who had a minimum body surface area involvement of 10%, and Psoriasis Area and Severity Index (PASI) score ≥12, and who were candidates for phototherapy or systemic therapy. Subjects with guttate, erythrodermic, or pustular psoriasis were excluded from the studies.

Ps STUDY 1 enrolled 766 subjects and Ps STUDY 2 enrolled 1230 subjects. The studies had the same design through Week 28. In both studies, subjects were randomized in equal proportion to placebo, 45 mg or 90 mg of STELARA®. Subjects randomized to STELARA® received 45 mg or 90 mg doses, regardless of weight, at Weeks 0, 4, and 16. Subjects randomized to receive placebo at Weeks 0 and 4 crossed over to receive STELARA® (either 45 mg or 90 mg) at Weeks 12 and 16.

In both studies, the endpoints were the proportion of subjects who achieved at least a 75% reduction in PASI score (PASI 75) from baseline to Week 12 and treatment success (cleared or

minimal) on the Physician's Global Assessment (PGA). The PGA is a 6-category scale ranging from 0 (cleared) to 5 (severe) that indicates the physician's overall assessment of psoriasis focusing on plaque thickness/induration, erythema, and scaling.

In both studies, subjects in all treatment groups had a median baseline PASI score ranging from approximately 17 to 18. Baseline PGA score was marked or severe in 44% of subjects in Ps STUDY 1 and 40% of subjects in Ps STUDY 2. Approximately two-thirds of all subjects had received prior phototherapy, 69% had received either prior conventional systemic or biologic therapy for the treatment of psoriasis, with 56% receiving prior conventional systemic therapy and 43% receiving prior biologic therapy. A total of 28% of subjects had a history of psoriatic arthritis.

Clinical Response

The results of Ps STUDY 1 and Ps STUDY 2 are presented in Table 7 below.

Table 7: Clinical Outcomes Ps STUDY 1 and Ps STUDY 2

Week 12	**Ps STUDY 1**			**Ps STUDY 2**		
		STELARA®			**STELARA®**	
	Placebo	**45 mg**	**90 mg**	**Placebo**	**45 mg**	**90 mg**
Subjects randomized	**255**	**255**	**256**	**410**	**409**	**411**
PASI 75 response	8 (3%)	171 (67%)	170 (66%)	15 (4%)	273 (67%)	311 (76%)
PGA of Cleared or Minimal	10 (4%)	151 (59%)	156 (61%)	18 (4%)	277 (68%)	300 (73%)

Examination of age, gender, and race subgroups did not identify differences in response to STELARA® among these subgroups.

In subjects who weighed 100 kg or less, response rates were similar with both the 45 mg and 90 mg doses; however, in subjects who weighed greater than 100 kg, higher response rates were seen with 90 mg dosing compared with 45 mg dosing (Table 8 below).

Table 8: Clinical Outcomes by Weight Ps STUDY 1 and Ps STUDY 2

	Ps STUDY 1			**Ps STUDY 2**		
		STELARA®			**STELARA®**	
	Placebo	**45 mg**	**90 mg**	**Placebo**	**45 mg**	**90 mg**
Subjects randomized	**255**	**255**	**256**	**410**	**409**	**411**
PASI 75 response at Week 12*						
≤100 kg	4%	74%	65%	4%	73%	78%
	6/166	124/168	107/164	12/290	218/297	225/289
>100 kg	2%	54%	68%	3%	49%	71%
	2/89	47/87	63/92	3/120	55/112	86/121
PGA of Cleared or Minimal at Week 12*						
≤100 kg	4%	64%	63%	5%	74%	75%
	7/166	108/168	103/164	14/290	220/297	216/289
>100 kg	3%	49%	58%	3%	51%	69%
	3/89	43/87	53/92	4/120	57/112	84/121

* Patients were dosed with study medication at Weeks 0 and 4.

Subjects in Ps STUDY 1 who were PASI 75 responders at both Weeks 28 and 40 were re-randomized at Week 40 to either continued dosing of STELARA® (STELARA® at Week 40) or to withdrawal of therapy (placebo at Week 40). At Week 52, 89% (144/162) of subjects re-randomized to STELARA® treatment were PASI 75 responders compared with 63% (100/159) of

subjects re-randomized to placebo (treatment withdrawal after Week 28 dose). The median time to loss of PASI 75 response among the subjects randomized to treatment withdrawal was 16 weeks.

14.2 Adolescent Subjects with Plaque Psoriasis

A multicenter, randomized, double blind, placebo-controlled study (Ps STUDY 3) enrolled 110 adolescent subjects 12 to 17 years of age with a minimum BSA involvement of 10%, a PASI score greater than or equal to 12, and a PGA score greater than or equal to 3, who were candidates for phototherapy or systemic therapy and whose disease was inadequately controlled by topical therapy.

Subjects were randomized to receive placebo (n=37), the recommended dose of STELARA® (n=36), or one-half the recommended dose of STELARA® (n=37) by subcutaneous injection at Weeks 0 and 4 followed by dosing every 12 weeks (q12w). The recommended dose of STELARA® was 0.75 mg/kg for subjects weighing less than 60 kg, 45 mg for subjects weighing 60 kg to 100 kg, and 90 mg for subjects weighing greater than 100 kg. At Week 12, subjects who received placebo were crossed over to receive STELARA® at the recommended dose or one-half the recommended dose.

Of the adolescent subjects, approximately 63% had prior exposure to phototherapy or conventional systemic therapy and approximately 11% had prior exposure to biologics.

The endpoints were the proportion of patients who achieved a PGA score of cleared (0) or minimal (1), PASI 75, and PASI 90 at Week 12. Subjects were followed for up to 60 weeks following first administration of study agent.

Clinical Response

The efficacy results at Week 12 for Ps STUDY 3 are presented in Table 9.

Table 9: Summary of Efficacy Endpoints in the Adolescent Psoriasis Study at Week 12

	Ps STUDY 3	
	Placebo n (%)	**STELARA®* n (%)**
N	**37**	**36**
PGA		
PGA of cleared (0) or minimal (1)	2 (5.4%)	25 (69.4%)
PASI		
PASI 75 responders	4 (10.8%)	29 (80.6%)
PASI 90 responders	2 (5.4%)	22 (61.1%)

* Using the weight-based dosage regimen specified in Table 1 and Table 2.

14.3 Psoriatic Arthritis

The safety and efficacy of STELARA® was assessed in 927 patients (PsA STUDY 1, n=615; PsA STUDY 2, n=312), in two randomized, double-blind, placebo-controlled studies in adult patients 18 years of age and older with active PsA (≥5 swollen joints and ≥5 tender joints) despite non-steroidal anti-inflammatory (NSAID) or disease modifying antirheumatic (DMARD) therapy. Patients in these studies had a diagnosis of PsA for at least 6 months. Patients with each subtype

of PsA were enrolled, including polyarticular arthritis with the absence of rheumatoid nodules (39%), spondylitis with peripheral arthritis (28%), asymmetric peripheral arthritis (21%), distal interphalangeal involvement (12%) and arthritis mutilans (0.5%). Over 70% and 40% of the patients, respectively, had enthesitis and dactylitis at baseline.

Patients were randomized to receive treatment with STELARA® 45 mg, 90 mg, or placebo subcutaneously at Weeks 0 and 4 followed by every 12 weeks (q12w) dosing. Approximately 50% of patients continued on stable doses of MTX (≤25 mg/week). The primary endpoint was the percentage of patients achieving ACR 20 response at Week 24.

In PsA STUDY 1 and PsA STUDY 2, 80% and 86% of the patients, respectively, had been previously treated with DMARDs. In PsA STUDY 1, previous treatment with anti-tumor necrosis factor (TNF)-α agent was not allowed. In PsA STUDY 2, 58% (n=180) of the patients had been previously treated with TNF blocker, of whom over 70% had discontinued their TNF blocker treatment for lack of efficacy or intolerance at any time.

Clinical Response

In both studies, a greater proportion of patients achieved ACR 20, ACR 50 and PASI 75 response in the STELARA® 45 mg and 90 mg groups compared to placebo at Week 24 (see Table 10). ACR 70 responses were also higher in the STELARA® 45 mg and 90 mg groups, although the difference was only numerical (p=NS) in STUDY 2. Responses were similar in patients regardless of prior TNFα exposure.

Table 10: ACR 20, ACR 50, ACR 70 and PASI 75 responses in PsA STUDY 1 and PsA STUDY 2 at Week 24

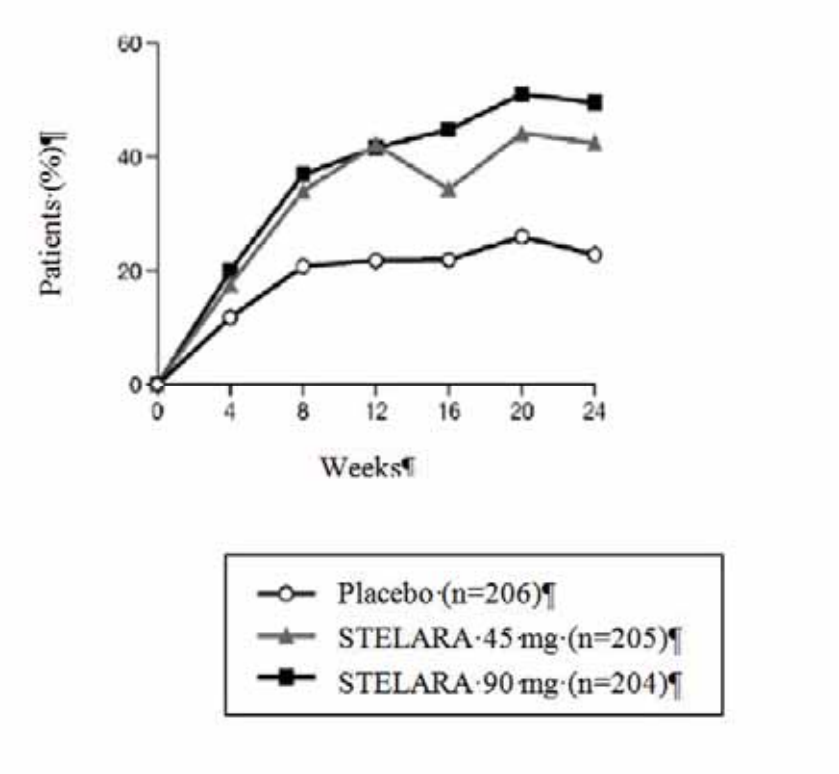
	PsA STUDY 1			**PsA STUDY 2**		
		STELARA®			**STELARA®**	
	Placebo	**45 mg**	**90 mg**	**Placebo**	**45 mg**	**90 mg**
Number of patients randomized	**206**	**205**	**204**	**104**	**103**	**105**
ACR 20 response, N (%)	47 (23%)	87 (42%)	101 (50%)	21 (20%)	45 (44%)	46 (44%)
ACR 50 response, N (%)	18 (9%)	51 (25%)	57 (28%)	7 (7%)	18 (17%)	24 (23%)
ACR 70 response, N (%)	5 (2%)	25 (12%)	29 (14%)	3 (3%)	7 (7%)	9 (9%)
Number of patients with ≥ 3% BSA[a]	**146**	**145**	**149**	**80**	**80**	**81**
PASI 75 response, N (%)	16 (11%)	83 (57%)	93 (62%)	4 (5%)	41 (51%)	45 (56%)

[a] Number of patients with ≥ 3% BSA psoriasis skin involvement at baseline

The percent of patients achieving ACR 20 responses by visit is shown in Figure 1.

Figure 1: Percent of patients achieving ACR 20 response through Week 24

PsA STUDY 1



The results of the components of the ACR response criteria are shown in Table 11.

Table 11: Mean change from baseline in ACR components at Week 24

	PsA STUDY 1		
		STELARA®	
	Placebo (N=206)	45 mg (N=205)	90 mg (N=204)
Number of swollen joints[a]			
Baseline	15	12	13
Mean Change at Week 24	-3	-5	-6
Number of tender joints[b]			
Baseline	25	22	23
Mean Change at Week 24	-4	-8	-9
Patient's assessment of pain[c]			
Baseline	6.1	6.2	6.6
Mean Change at Week 24	-0.5	-2.0	-2.6
Patient global assessment[c]			
Baseline	6.1	6.3	6.4
Mean Change at Week 24	-0.5	-2.0	-2.5
Physician global assessment[c]			
Baseline	5.8	5.7	6.1
Mean Change at Week 24	-1.4	-2.6	-3.1
Disability index (HAQ)[d]			
Baseline	1.2	1.2	1.2

Mean Change at Week 24	-0.1	-0.3	-0.4
CRP (mg/dL)[e]			
Baseline	1.6	1.7	1.8
Mean Change at Week 24	0.01	-0.5	-0.8

[a] Number of swollen joints counted (0-66)

[b] Number of tender joints counted (0-68)

[c] Visual analogue scale; 0= best, 10=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] CRP: (Normal Range 0.0-1.0 mg/dL)

An improvement in enthesitis and dactylitis scores was observed in each STELARA® group compared with placebo at Week 24.

Physical Function

STELARA® treated patients showed improvement in physical function compared to patients treated with placebo as assessed by HAQ-DI at Week 24. In both studies, the proportion of HAQ-DI responders (≥0.3 improvement in HAQ-DI score) was greater in the STELARA® 45 mg and 90 mg groups compared to placebo at Week 24.

14.4 Crohn's Disease

STELARA® was evaluated in three randomized, double-blind, placebo-controlled clinical studies in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of 220 to 450). There were two 8-week intravenous induction studies (CD-1 and CD-2) followed by a 44-week subcutaneous randomized withdrawal maintenance study (CD-3) representing 52 weeks of therapy. Patients in CD-1 had failed or were intolerant to treatment with one or more TNF blockers, while patients in CD-2 had failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a TNF blocker.

Studies CD-1 and CD-2

In studies CD-1 and CD-2, 1409 patients were randomized, of whom 1368 (CD-1, n=741; CD-2, n=627) were included in the final efficacy analysis. Induction of clinical response (defined as a reduction in CDAI score of greater than or equal to 100 points or CDAI score of less than 150) at Week 6 and clinical remission (defined as a CDAI score of less than 150) at Week 8 were evaluated. In both studies, patients were randomized to receive a single intravenous administration of STELARA® at either approximately 6 mg/kg, placebo (see Table 3), or 130 mg (a lower dose than recommended).

In Study CD-1, patients had failed or were intolerant to prior treatment with a TNF blocker: 29% patients had an inadequate initial response (primary non-responders), 69% responded but subsequently lost response (secondary non-responders) and 36% were intolerant to a TNF blocker. Of these patients, 48% failed or were intolerant to one TNF blocker and 52% had failed 2 or 3 prior TNF blockers. At baseline and throughout the study, approximately 46% of the patients were receiving corticosteroids and 31% of the patients were receiving immunomodulators (AZA, 6-MP, MTX). The median baseline CDAI score was 319 in the STELARA® approximately 6 mg/kg group and 313 in the placebo group.

In Study CD-2, patients had failed or were intolerant to prior treatment with corticosteroids (81% of patients), at least one immunomodulator (6-MP, AZA, MTX; 68% of patients), or both (49% of patients). Additionally, 69% never received a TNF blocker and 31% previously received but had not failed a TNF blocker. At baseline, and throughout the study, approximately 39% of the patients were receiving corticosteroids and 35% of the patients were receiving immunomodulators (AZA, 6-MP, MTX). The median baseline CDAI score was 286 in the STELARA® and 290 in the placebo group.

In these induction studies, a greater proportion of patients treated with STELARA® (at the recommended dose of approximately 6 mg/kg dose) achieved clinical response at Week 6 and clinical remission at Week 8 compared to placebo (see Table 12 for clinical response and remission rates). Clinical response and remission were significant as early as Week 3 in STELARA®-treated patients and continued to improve through Week 8.

Table 12: Induction of Clinical Response and Remission in CD-1* and CD-2**

	CD-1 n=741			CD-2 n=627		
	Placebo N=247	STELARA®† N=249	Treatment difference and 95% CI	Placebo N=209	STELARA®† N=209	Treatment difference and 95% CI
Clinical Response (100 point), Week 6	53 (21%)	84 (34%)[a]	12% (4%, 20%)	60 (29%)	116 (56%)[b]	27% (18%, 36%)
Clinical Remission, Week 8	18 (7%)	52 (21%)[b]	14% (8%, 20%)	41 (20%)	84 (40%)[b]	21% (12%, 29%)
Clinical Response (100 point), Week 8	50 (20%)	94 (38%)[b]	18% (10%, 25%)	67 (32%)	121 (58%)[b]	26% (17%, 35%)
70 Point Response, Week 6	75 (30%)	109 (44%)[a]	13% (5%, 22%)	81 (39%)	135 (65%)[b]	26% (17%, 35%)
70 Point Response, Week 3	67 (27%)	101 (41%)[a]	13% (5%, 22%)	66 (32%)	106 (51%)[b]	19% (10%, 28%)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission: 70 point response is defined as reduction in CDAI score by at least 70 points

* Patient population consisted of patients who failed or were intolerant to TNF blocker therapy

** Patient population consisted of patients who failed or were intolerant to corticosteroids or immunomodulators (e.g., 6-MP, AZA, MTX) and previously received but not failed a TNF blocker or were never treated with a TNF blocker.

† Infusion dose of STELARA® using the weight-based dosage regimen specified in Table 3.

[a] $0.001 \leq p < 0.01$

[b] $p < 0.001$

Study CD-3

The maintenance study (CD-3), evaluated 388 patients who achieved clinical response (≥100 point reduction in CDAI score) at Week 8 with either induction dose of STELARA® in studies CD-1 or CD-2. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg STELARA® every 8 weeks or placebo for 44 weeks (see Table 13).

Table 13: Clinical Response and Remission in CD-3 (Week 44; 52 weeks from initiation of the induction dose)

	Placebo* N=131†	90 mg STELARA® every 8 weeks N=128†	Treatment difference and 95% CI
Clinical Remission	47 (36%)	68 (53%)[a]	17% (5%, 29%)

Clinical Response	58 (44%)	76 (59%)[b]	15% (3%, 27%)
Clinical Remission in patients in remission at the start of maintenance therapy**	36/79 (46%)	52/78 (67%)[a]	21% (6%, 36%)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission

* The placebo group consisted of patients who were in response to STELARA® and were randomized to receive placebo at the start of maintenance therapy.

** Patients in remission at the end of maintenance therapy who were in remission at the start of maintenance therapy. This does not account for any other time point during maintenance therapy.

† Patients who achieved clinical response to STELARA® at the end of the induction study.

[a] $p < 0.01$

[b] $0.01 \leq p < 0.05$

At Week 44, 47% of patients who received STELARA® were corticosteroid-free and in clinical remission, compared to 30% of patients in the placebo group.

At Week 0 of Study CD-3, 34/56 (61%) STELARA® treated patients who previously failed or were intolerant to TNF blocker therapies were in clinical remission and 23/56 (41%) of these patients were in clinical remission at Week 44. In the placebo arm, 27/61 (44%) patients were in clinical remission at Week 0 while 16/61 (26%) of these patients were in remission at Week 44.

At Week 0 of Study CD-3, 46/72 (64%) STELARA® treated patients who had previously failed immunomodulator therapy or corticosteroids (but not TNF blockers) were in clinical remission and 45/72 (63%) of these patients were in clinical remission at Week 44. In the placebo arm, 50/70 (71%) of these patients were in clinical remission at Week 0 while 31/70 (44%) were in remission at Week 44. In the subset of these patients who were also naïve to TNF blockers, 34/52 (65%) of STELARA® treated patients were in clinical remission at Week 44 as compared to 25/51 (49%) in the placebo arm.

Patients who were not in clinical response 8 weeks after STELARA® induction were not included in the primary efficacy analyses for Study CD-3; however, these patients were eligible to receive a 90 mg subcutaneous injection of STELARA® upon entry into Study CD-3. Of these patients, 102/219 (47%) achieved clinical response eight weeks later and were followed for the duration of the study.

14.5 Ulcerative Colitis

STELARA® was evaluated in two randomized, double-blind, placebo-controlled clinical studies [UC-1 and UC-2 (NCT02407236)] in adult patients with moderately to severely active ulcerative colitis who had an inadequate response to or failed to tolerate a biologic (i.e., TNF blocker and/or vedolizumab), corticosteroids, and/or 6-MP or AZA therapy. The 8-week intravenous induction study (UC-1) was followed by the 44-week subcutaneous randomized withdrawal maintenance study (UC-2) for a total of 52 weeks of therapy.

Disease assessment was based on the Mayo score, which ranged from 0 to 12 and has four subscores that were each scored from 0 (normal) to 3 (most severe): stool frequency, rectal bleeding, findings on centrally-reviewed endoscopy, and physician global assessment. Moderately to severely active ulcerative colitis was defined at baseline (Week 0) as Mayo score of 6 to 12, including a Mayo endoscopy subscore ≥2. An endoscopy score of 2 was defined by marked erythema, absent vascular pattern, friability, erosions; and a score of 3 was defined by spontaneous

bleeding, ulceration. At baseline, patients had a median Mayo score of 9, with 84% of patients having moderate disease (Mayo score 6-10) and 15% having severe disease (Mayo score 11-12).

Patients in these studies may have received other concomitant therapies including aminosalicylates, immunomodulatory agents (AZA, 6-MP, or MTX), and oral corticosteroids (prednisone).

Study UC-1

In UC-1, 961 patients were randomized at Week 0 to a single intravenous administration of STELARA® of approximately 6 mg/kg, 130 mg (a lower dose than recommended), or placebo. Patients enrolled in UC-1 had to have failed therapy with corticosteroids, immunomodulators or at least one biologic. A total of 51% had failed at least one biologic and 17% had failed both a TNF blocker and an integrin receptor blocker. Of the total population, 46% had failed corticosteroids or immunomodulators but were biologic-naïve and an additional 3% had previously received but had not failed a biologic. At induction baseline and throughout the study, approximately 52% patients were receiving oral corticosteroids, 28% patients were receiving immunomodulators (AZA, 6-MP, or MTX) and 69% patients were receiving aminosalicylates.

The primary endpoint was clinical remission at Week 8. Clinical remission with a definition of: Mayo stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0 (no rectal bleeding), and Mayo endoscopy subscore of 0 or 1 (Mayo endoscopy subscore of 0 defined as normal or inactive disease and Mayo subscore of 1 defined as presence of erythema, decreased vascular pattern and no friability) is provided in Table 14.

The secondary endpoints were clinical response, endoscopic improvement, and histologic-endoscopic mucosal improvement. Clinical response with a definition of (≥ 2 points and ≥ 30% decrease in modified Mayo score, defined as 3-component Mayo score without the Physician's Global Assessment, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1), endoscopic improvement with a definition of Mayo endoscopy subscore of 0 or 1, and histologic-endoscopic mucosal improvement with a definition of combined endoscopic improvement and histologic improvement of the colon tissue [neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue]) are provided in Table 14.

In UC-1, a significantly greater proportion of patients treated with STELARA® (at the recommended dose of approximately 6 mg/kg dose) were in clinical remission and response and achieved endoscopic improvement and histologic-endoscopic mucosal improvement compared to placebo (see Table 14).

Table 14: Proportion of Patients Meeting Efficacy Endpoints at Week 8 in UC-1

Endpoint	**Placebo** N=319		**STELARA®†** N=322		**Treatment difference and 97.5% CI** [a]
	N	**%**	**N**	**%**	
Clinical Remission*	**22**	**7%**	**62**	**19%**	12% (7%, 18%) [b]
Bio-naïve‡	14/151	9%	36/147	24%	

Prior biologic failure	7/161	4%	24/166	14%	
Endoscopic Improvement[§]	**40**	**13%**	**80**	**25%**	12% (6%, 19%) [b]
Bio-naïve[ǂ]	28/151	19%	43/147	29%	
Prior biologic failure	11/161	7%	34/166	20%	
Clinical Response[†]	**99**	**31%**	**186**	**58%**	27% (18%, 35%) [b]
Bio-naïve[ǂ]	55/151	36%	94/147	64%	
Prior biologic failure	42/161	26%	86/166	52%	
Histologic-Endoscopic Mucosal Improvement	**26**	**8%**	**54**	**17%**	9% (3%, 14%) [b]
Bio-naïve[ǂ]	19/151	13%	30/147	20%	
Prior biologic failure	6/161	4%	21/166	13%	

[†]Infusion dose of STELARA® using the weight-based dosage regimen specified in Table 3.

[ǂ]An additional 7 patients on placebo and 9 patients on STELARA® (6 mg/kg) had been exposed to, but had not failed, biologics.

[*] Clinical remission was defined as Mayo stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0, and Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).

[§] Endoscopic improvement was defined as Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).

[†] Clinical response was defined as a decrease from baseline in the modified Mayo score by ≥30% and ≥2 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.

[‡] Histologic-endoscopic mucosal improvement was defined as combined endoscopic improvement (Mayo endoscopy subscore of 0 or 1) and histologic improvement of the colon tissue (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue).

[a] Adjusted treatment difference (97.5% CI)

[b] $p < 0.001$

The relationship of histologic-endoscopic mucosal improvement, as defined in UC-1, at Week 8 to disease progression and long-term outcomes was not evaluated during UC-1.

Rectal Bleeding and Stool Frequency Subscores

Decreases in rectal bleeding and stool frequency subscores were observed as early as Week 2 in STELARA® treated patients.

Study UC-2

The maintenance study (UC-2) evaluated 523 patients who achieved clinical response 8 weeks following the intravenous administration of either induction dose of STELARA® in UC-1. These patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg STELARA® every 8 weeks, or every 12 weeks (a lower dose than recommended), or placebo for 44 weeks.

The primary endpoint was the proportion of patients in clinical remission at Week 44. The secondary endpoints included the proportion of patients maintaining clinical response at Week 44, the proportion of patients with endoscopic improvement at Week 44, the proportion of patients with corticosteroid-free clinical remission at Week 44, and the proportion of patients maintaining clinical remission at Week 44 among patients who achieved clinical remission 8 weeks after induction.

Results of the primary and secondary endpoints at Week 44 in patients treated with STELARA® at the recommended dosage (90 mg every 8 weeks) compared to the placebo are shown in Table 15.

Table 15: Efficacy Endpoints of Maintenance at Week 44 in UC-2 (52 Weeks from Initiation of the Induction Dose)

Endpoint	Placebo* N=175†		90 mg STELARA® every 8 weeks N=176		Treatment difference and 95% CI
	N	%	N	%	
Clinical Remission**	**46**	**26%**	**79**	**45%**	19% (9%, 28%) [a]
Bio-naïve‡	30/84	36%	39/79	49%	
Prior biologic failure	16/88	18%	37/91	41%	
Maintenance of Clinical Response at Week 44†	**84**	**48%**	**130**	**74%**	26% (16%, 36%) [a]
Bio-naïve‡	49/84	58%	62/79	78%	
Prior biologic failure	35/88	40%	64/91	70%	
Endoscopic Improvement§	**47**	**27%**	**83**	**47%**	20% (11%, 30%) [a]
Bio-naïve‡	29/84	35%	42/79	53%	
Prior biologic failure	18/88	20%	38/91	42%	
Corticosteroid-free Clinical Remission‡	**45**	**26%**	**76**	**43%**	17% (8%, 27%) [a]
Bio-naïve‡	30/84	36%	38/79	48%	
Prior biologic failure	15/88	17%	35/91	38%	
Maintenance of Clinical Remission at Week 44 in patients who achieved clinical remission 8 weeks after induction	**18/50**	**36%**	**27/41**	**66%**	31% (12%, 50%) [b]
Bio-naïve‡	12/27	44%	14/20	70%	
Prior biologic failure	6/23	26%	12/18	67%	

‡An additional 3 patients on placebo and 6 patients on STELARA® had been exposed to, but had not failed, biologics.

*The placebo group consisted of patients who were in response to STELARA® and were randomized to receive placebo at the start of maintenance therapy.

**Clinical remission was defined as Mayo stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0, and Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).

† Clinical response was defined as a decrease from baseline in the modified Mayo score by ≥30% and ≥2 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.

§ Endoscopic improvement was defined as Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).

‡ Corticosteroid-free clinical remission was defined as patients in clinical remission and not receiving corticosteroids at Week 44.

[a] p =<0.001

[b] p=0.004

Other Endpoints

Week 16 Responders to Ustekinumab Induction

Patients who were not in clinical response 8 weeks after induction with STELARA® in UC-1 were not included in the primary efficacy analyses for Study UC-2; however, these patients were eligible to receive a 90 mg subcutaneous injection of STELARA® at Week 8. Of these patients, 55/101 (54%) achieved clinical response eight weeks later (Week 16) and received STELARA® 90 mg subcutaneously every 8 weeks during the UC-2 trial. At Week 44, there were 97/157 (62%) patients who maintained clinical response and there were 51/157 (32%) who achieved clinical remission.

Histologic-Endoscopic Mucosal Improvement at Week 44

The proportion of patients achieving histologic-endoscopic mucosal improvement during maintenance treatment in UC-2 was 75/172 (44%) among patients on STELARA® and 40/172 (23%) in patients on placebo at Week 44. The relationship of histologic-endoscopic mucosal improvement, as defined in UC-2, at Week 44 to progression of disease or long-term outcomes was not evaluated in UC-2.

Endoscopic Normalization
Normalization of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0. At Week 8 in UC-1, endoscopic normalization was achieved in 25/322 (8%) of patients treated with STELARA® and 12/319 (4%) of patients in the placebo group. At Week 44 of UC-2, endoscopic normalization was achieved in 51/176 (29%) of patients treated with STELARA® and in 32/175 (18%) of patients in placebo group.

15 REFERENCES

1 Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 6.6.2 Regs Research Data, Nov 2009 Sub (1973-2007) - Linked To County Attributes - Total U.S., 1969-2007 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2010, based on the November 2009 submission.

16 HOW SUPPLIED/STORAGE AND HANDLING

STELARA® (ustekinumab) Injection is a sterile, preservative-free, colorless to light yellow solution and may contain a few small translucent or white particles. It is supplied as individually packaged, single-dose prefilled syringes or single-dose vials.

For Subcutaneous Use

Prefilled Syringes

- 45 mg/0.5 mL (NDC 57894-060-03)
- 90 mg/mL (NDC 57894-061-03)

Each prefilled syringe is equipped with a 27 gauge fixed ½ inch needle, a needle safety guard, and a needle cover that contains dry natural rubber.

Single-dose Vial

- 45 mg/0.5 mL (NDC 57894-060-02)

For Intravenous Infusion

Single-dose Vial

- 130 mg/26 mL (5 mg/mL) (NDC 57894-054-27)

Storage and Stability

STELARA® vials and prefilled syringes must be refrigerated at 2ºC to 8ºC (36ºF to 46ºF). Store STELARA® vials upright. Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Infections

Inform patients that STELARA® may lower the ability of their immune system to fight infections and to contact their healthcare provider immediately if they develop any signs or symptoms of infection *[see Warnings and Precautions (5.1)]*.

Malignancies

Inform patients of the risk of developing malignancies while receiving STELARA® *[see Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions

- Advise patients to seek immediate medical attention if they experience any signs or symptoms of serious hypersensitivity reactions and discontinue STELARA® *[see Warnings and Precautions (5.5)]*.
- Inform patients the needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex *[see Dosage and Administration (2.4)]*

Immunizations

Inform patients that STELARA® can interfere with the usual response to immunizations and that they should avoid live vaccines *[see Warnings and Precautions (5.7)]*.

Pregnancy Registry

Inform patients that there is a pregnancy registry to monitor fetal outcomes of pregnant women exposed to STELARA® *[see Use in Specific Populations (8.1)]*.

Administration

Instruct patients to follow sharps disposal recommendations, as described in the Instructions for Use.

Prefilled Syringe Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, US License No. 1864 at Baxter Pharmaceutical Solutions, Bloomington, IN 47403 and at Cilag AG, Schaffhausen, Switzerland

Vial Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, US License No. 1864 at Cilag AG, Schaffhausen, Switzerland

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MEDICATION GUIDE
STELARA (stel ar' a)
(ustekinumab)
injection, for subcutaneous or intravenous use

What is the most important information I should know about STELARA?

STELARA is a medicine that affects your immune system. STELARA can increase your risk of having serious side effects, including:

Serious infections. STELARA may lower the ability of your immune system to fight infections and may increase your risk of infections. Some people have serious infections while taking STELARA, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses. Some people have to be hospitalized for treatment of their infection.

- Your doctor should check you for TB before starting STELARA.
- If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with STELARA and during treatment with STELARA.
- Your doctor should watch you closely for signs and symptoms of TB while you are being treated with STELARA.

You should not start taking STELARA if you have any kind of infection unless your doctor says it is okay.

Before starting STELARA, tell your doctor if you:

- think you have an infection or have symptoms of an infection such as:
  - fever, sweat, or chills
  - muscle aches
  - cough
  - shortness of breath
  - blood in phlegm
  - weight loss
  - warm, red, or painful skin or sores on your body
  - diarrhea or stomach pain
  - burning when you urinate or urinate more often than normal
  - feel very tired
- are being treated for an infection or have any open cuts.
- get a lot of infections or have infections that keep coming back.
- have TB, or have been in close contact with someone with TB.

After starting STELARA, call your doctor right away if you have any symptoms of an infection (see above). These may be signs of infections such as chest infections, or skin infections or shingles that could have serious complications. STELARA can make you more likely to get infections or make an infection that you have worse. People who have a genetic problem where the body does not make any of the proteins interleukin 12 (IL-12) and interleukin 23 (IL-23) are at a higher risk for certain serious infections. These infections can spread throughout the body and cause death. People who take STELARA may also be more likely to get these infections.

Cancers. STELARA may decrease the activity of your immune system and increase your risk for certain types of cancers. Tell your doctor if you have ever had any type of cancer. Some people who are receiving STELARA and have risk factors for skin cancer have developed certain types of skin cancers. During your treatment with STELARA, tell your doctor if you develop any new skin growths.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS). RPLS is a rare condition that affects the brain and can cause death. The cause of RPLS is not known. If RPLS is found early and treated, most people recover. Tell your doctor right away if you have any new or worsening medical problems including:

- headache
- seizures
- confusion
- vision problems

What is STELARA?

STELARA is a prescription medicine used to treat:

- adults and children 12 years and older with moderate or severe psoriasis who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet light alone or with pills).
- adults 18 years and older with active psoriatic arthritis. STELARA can be used alone or with the medicine methotrexate.
- adults 18 years and older with moderately to severely active Crohn's disease.
- adults 18 years and older with moderately to severely active ulcerative colitis.

It is not known if STELARA is safe and effective in children less than 12 years of age.

Do not take STELARA if you are allergic to ustekinumab or any of the ingredients in STELARA. See the end of this Medication Guide for a complete list of ingredients in STELARA.

Before you receive STELARA, tell your doctor about all of your medical conditions, including if you:

- have any of the conditions or symptoms listed in the section "**What is the most important information I should know about STELARA**?"
- ever had an allergic reaction to STELARA. Ask your doctor if you are not sure.
- are allergic to latex. The needle cover on the prefilled syringe contains latex.
- have recently received or are scheduled to receive an immunization (vaccine). People who take STELARA should not receive live vaccines. Tell your doctor if anyone in your house needs a live vaccine. The viruses used in some types of live vaccines can spread to people with a weakened immune system, and can cause serious problems. **You should not receive the BCG vaccine during the one year before receiving STELARA or one year after you stop receiving STELARA**.
- have any new or changing lesions within psoriasis areas or on normal skin.
- are receiving or have received allergy shots, especially for serious allergic reactions. Allergy shots may not work as well for you during treatment with STELARA. STELARA may also increase your risk of having an allergic reaction to an allergy shot.
- receive or have received phototherapy for your psoriasis.
- are pregnant or plan to become pregnant. It is not known if STELARA can harm your unborn baby. You and your doctor should decide if you will receive STELARA. There is a pregnancy registry for women who are treated with STELARA during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. If you are pregnant or become pregnant while receiving STELARA, talk to your doctor about how you can join this pregnancy registry or you may contact the registry at 1-877-311-8972 to enroll.
- are breastfeeding or plan to breastfeed. It is thought that STELARA passes into your breast milk in small amounts.
- Talk to your doctor about the best way to feed your baby if you receive STELARA.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I use STELARA?

- Use STELARA exactly as your doctor tells you to.
- **The needle cover on the STELARA prefilled syringe contains latex. Do not handle the needle cover if you are sensitive to latex.**
- Adults with Crohn's disease and ulcerative colitis will receive the first dose of STELARA through a vein in the arm (intravenous infusion) in a healthcare facility by a healthcare provider. It takes at least 1 hour to receive the full dose of medicine. You will then receive STELARA as an injection under the skin (subcutaneous injection) 8 weeks after the first dose of STELARA, as described below.
- Adults with psoriasis or psoriatic arthritis and children 12 years and older with psoriasis will receive STELARA as an injection under the skin (subcutaneous injection) as described below.
- **Injecting STELARA under your skin**
  - STELARA is intended for use under the guidance and supervision of your doctor. In children 12 years and older, it is recommended that STELARA be administered by a healthcare provider. If your doctor decides that you or a caregiver may give your injections of STELARA at home, you should receive training on the right way to prepare and inject STELARA. Your doctor will determine the right dose of STELARA for you, the amount for each injection, and how often you should receive it. Do not try to inject STELARA yourself until you or your caregiver have been shown how to inject STELARA by your doctor or nurse.
  - Inject STELARA under the skin (subcutaneous injection) in your upper arms, buttocks, upper legs (thighs) or stomach area (abdomen).
  - Do not give an injection in an area of the skin that is tender, bruised, red or hard.
  - Use a different injection site each time you use STELARA.
  - If you inject more STELARA than prescribed, call your doctor right away.
  - Be sure to keep all of your scheduled follow-up appointments.

Read the detailed Instructions for Use at the end of this Medication Guide for instructions about how to prepare and inject a dose of STELARA, and how to properly throw away (dispose of) used needles and syringes. The syringe, needle and vial must never be re-used. After the rubber stopper is punctured, STELARA can become contaminated by harmful bacteria which could cause an infection if re-used. Therefore, throw away any unused portion of STELARA.

What should I avoid while using STELARA?
You should not receive a live vaccine while taking STELARA. See **"Before you receive STELARA, tell your doctor about all of your medical conditions, including if you:"**

What are the possible side effects of STELARA?

STELARA may cause serious side effects, including:

- See "**What is the most important information I should know about STELARA?**"
- **Serious allergic reactions.** Serious allergic reactions can occur with STELARA. Stop using STELARA and get medical help right away if you have any of the following symptoms of a serious allergic reaction:
  - o feeling faint
  - o swelling of your face, eyelids, tongue, or throat
  - o chest tightness
  - o skin rash
- **Lung inflammation.** Cases of lung inflammation have happened in some people who receive STELARA, and may be serious. These lung problems may need to be treated in a hospital. Tell your doctor right away if you develop shortness of breath or a cough that doesn't go away during treatment with STELARA**.**

Common side effects of STELARA include:

- nasal congestion, sore throat, and runny nose
- upper respiratory infections
- fever
- headache
- tiredness
- itching
- nausea and vomiting
- redness at the injection site
- vaginal yeast infections
- urinary tract infections
- sinus infection
- bronchitis
- diarrhea
- stomach pain

These are not all of the possible side effects of STELARA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Janssen Biotech, Inc. at 1-800 JANSSEN (1-800-526-7736).

How should I store STELARA?

- Store STELARA vials and prefilled syringes in a refrigerator between 36°F to 46°F (2°C to 8°C).
- Store STELARA vials standing up straight.
- Store STELARA in the original carton to protect it from light until time to use it.
- Do not freeze STELARA.
- Do not shake STELARA.

Keep STELARA and all medicines out of the reach of children.

General information about the safe and effective use of STELARA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use STELARA for a condition for which it was not prescribed. Do not give STELARA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your doctor or pharmacist for information about STELARA that was written for health professionals.

What are the ingredients in STELARA?

Active ingredient: ustekinumab

Inactive ingredients: Single-dose prefilled syringe for subcutaneous use contains L-histidine, L-histidine monohydrochloride monohydrate, Polysorbate 80, and sucrose. **Single-dose vial for subcutaneous use** contains L-histidine, L-histidine hydrochloride monohydrate, Polysorbate 80 and sucrose. **Single-dose vial for intravenous infusion** contains EDTA disodium salt dihydrate, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, Polysorbate 80, and sucrose.

Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, US License No. 1864

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For more information, go to *www.stelarainfo.com* or call 1-800-JANSSEN (1-800-526-7736).

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

INSTRUCTIONS FOR USE
STELARA (stel ar' a**)**
(ustekinumab)
injection, for subcutaneous use

Instructions for injecting STELARA from a vial.

Read this Instructions for Use before you start using STELARA. Your doctor or nurse should show you how to prepare, measure your dose, and give your injection of STELARA the right way.

If you cannot give yourself the injection:

- ask your doctor or nurse to help you, or
- ask someone who has been trained by a doctor or nurse to give your injections.

Do not try to inject STELARA yourself until you have been shown how to inject STELARA by your doctor, nurse or health professional.

Important information:

- Before you start, check the carton to make sure that it is the right dose. You will have either 45 mg or 90 mg as prescribed by your doctor.
  - If your dose is 45 mg or less you will receive one 45 mg vial.
  - If your dose is 90 mg, you will receive two 45 mg vials **and you will need to give yourself two injections, one right after the other.**
- Children 12 years of age and older weighing less than 132 pounds require a dose lower than 45 mg.
- Check the expiration date on the vial and carton. If the expiration date has passed, do not use it. If the expiration date has passed, call your doctor or pharmacist, or call 1-800-JANSSEN (1-800-526-7736) for help.
- Check the vial for any particles or discoloration. Your vial should look clear and colorless to light yellow with few white particles.
- Do not use if it is frozen, discolored, cloudy or has large particles. Get a new vial.
- **Do not shake the vial at any time.** Shaking your vial may damage your STELARA medicine. If your vial has been shaken, do not use it. Get a new vial.
- Do not use a STELARA vial more than one time, even if there is medicine left in the vial. After the rubber stopper is punctured, STELARA can become contaminated by harmful bacteria which could cause an infection if re-used. Therefore, throw away any unused STELARA after you give your injection.
- Safely throw away (dispose of) STELARA vials after use.
- Do not re-use syringes or needles. See "**Step 6: Dispose of needles and syringes."**
- To avoid needle-stick injuries, **do not** recap needles.

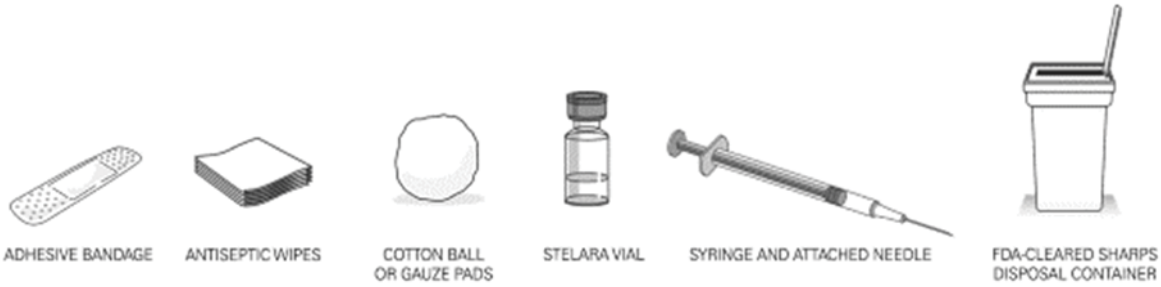
Gather the supplies you will need to prepare STELARA and to give your injection. (See Figure A)

You will need:

- a syringe with the needle attached, you will need a prescription from your healthcare provider to get syringes with the needles attached from your pharmacy.

- antiseptic wipes
- cotton balls or gauze pads
- adhesive bandage
- your prescribed dose of STELARA
- FDA-cleared sharps disposal container. See "**Step 6: Dispose of needles and syringes."**

Figure A



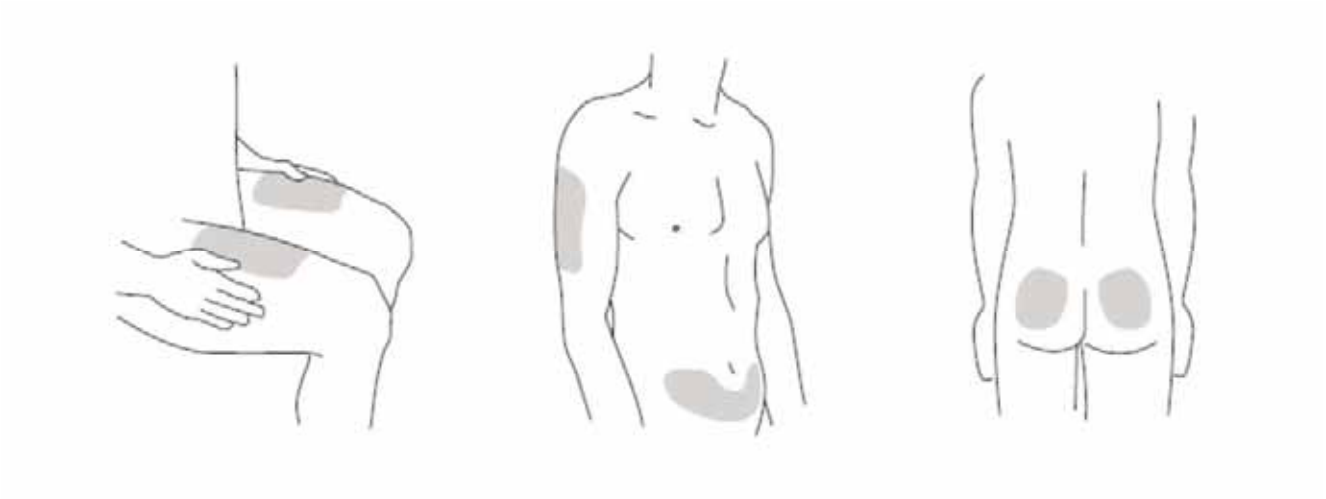
Step 1: Prepare the injection.

- Choose a well-lit, clean, flat work surface.
- Wash your hands well with soap and warm water.

Step 2: Prepare your injection site

- Choose an injection site around your stomach area (abdomen), buttocks, and upper legs (thighs).
  If a caregiver is giving you the injection, the outer area of the upper arms may also be used. **(See Figure B)**
- **Use a different injection site for each injection. Do not** give an injection in an area of the skin that is tender, bruised, red or hard.
- Clean the skin with an antiseptic wipe where you plan to give your injection.
- **Do not** touch this area again before giving the injection. Let your skin dry before injecting.
- **Do not** fan or blow on the clean area.

Figure B



*Areas in gray are recommended injection sites.

Step 3: Prepare the vial.

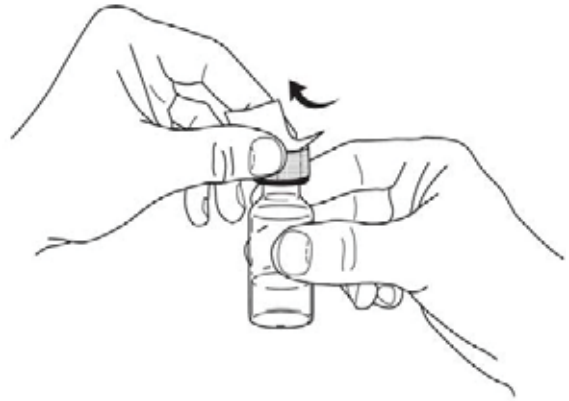
- Remove the cap from the top of the vial. Throw away the cap but do not remove the rubber stopper. **(See Figure C)**

Figure C



- Clean the rubber stopper with an antiseptic swab. **(See Figure D)**

Figure D

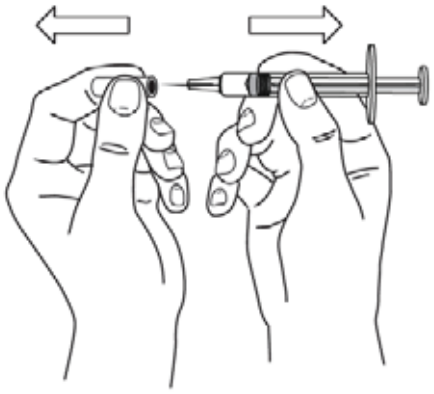


- Do not touch the rubber stopper after you clean it.
- Put the vial on a flat surface.

Step 4: Prepare the needle

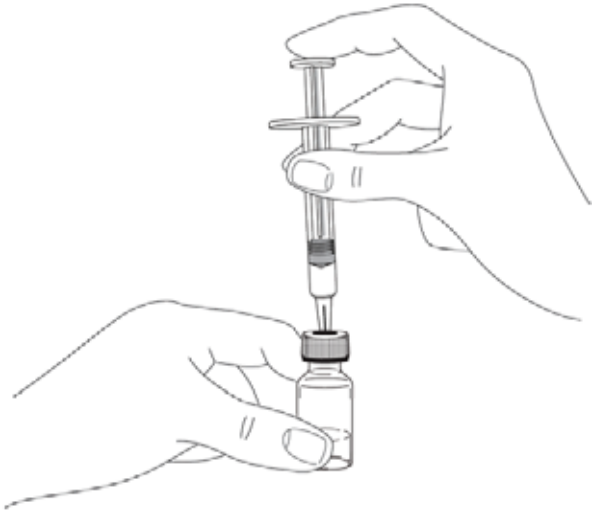
- Pick up the syringe with the needle attached.
- Remove the cap that covers the needle. **(See Figure E)**
- Throw the needle cap away. Do not touch the needle or allow the needle to touch anything.

Figure E



- Carefully pull back on the plunger to the line that matches the dose prescribed by your doctor.
- Hold the vial between your thumb and index (pointer) finger.
- Use your other hand to push the syringe needle through the center of the rubber stopper. **(See Figure F)**

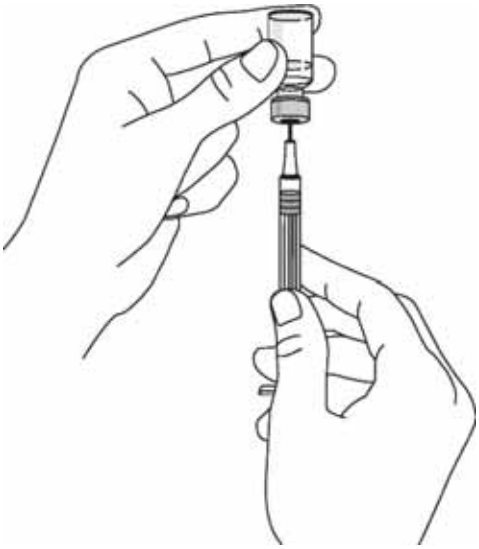
Figure F



- Push down on the plunger until all of the air has gone from the syringe into the vial.
- Turn the vial and the syringe upside down. **(See Figure G)**
- Hold the STELARA vial with one hand.
- It is important that the needle is always in the liquid in order to prevent air bubbles forming in the syringe.

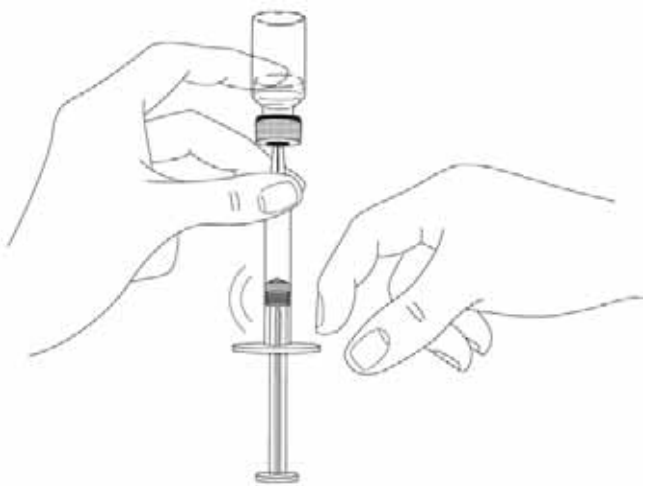
- Pull back on the syringe plunger with your other hand.
- Fill the syringe until the black tip of the plunger lines up with the mark that matches your prescribed dose.

Figure G



- **Do not remove the needle from the vial.** Hold the syringe with the needle pointing up to see if it has any air bubbles inside.
- If there are air bubbles, gently tap the side of the syringe until the air bubbles rise to the top. **(See Figure H)**
- Slowly press the plunger up until all of the air bubbles are out of the syringe (but none of the liquid is out).
- Remove the syringe from the vial. Do not lay the syringe down or allow the needle to touch anything.

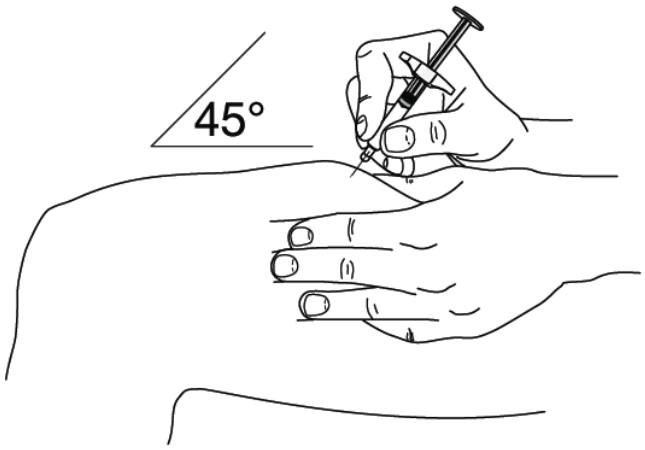
Figure H



Step 5: Inject STELARA

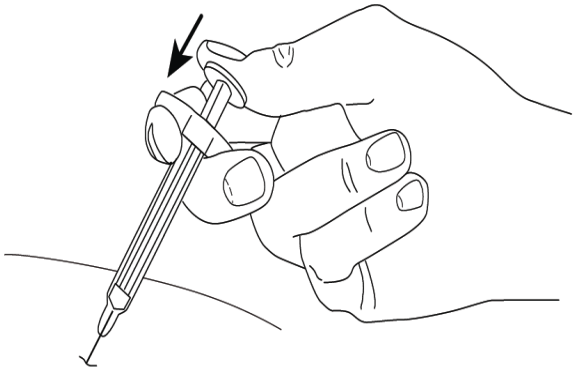
- Hold the barrel of the syringe in one hand, between the thumb and index fingers.
- **Do not** pull back on the plunger at any time.
- Use the other hand to gently pinch the cleaned area of skin. Hold firmly.
- Use a quick, dart-like motion to insert the needle into the pinched skin at about a 45-degree angle. **(See Figure I)**

Figure I



- Push the plunger with your thumb as far as it will go to inject all of the liquid. Push it slowly and evenly, keeping the skin gently pinched.
- When the syringe is empty, pull the needle out of your skin and let go of the skin. **(See Figure J)**

Figure J



- When the needle is pulled out of your skin, there may be a little bleeding at the injection site. This is normal. You can press a cotton ball or gauze pad to the injection site if needed. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

If your dose is 90 mg, you will receive two 45 mg vials and you will need to give yourself a second injection right after the first. Repeat Steps 1-5 using a new syringe. Choose a different site for the second injection.

Step 6: Dispose of the needles and syringes.

- **Do not** re-use a syringe or needle.
- To avoid needle-stick injuries, do not recap a needle.
- Put your needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of heavy-duty plastic
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - upright and stable during use
  - leak-resistant,
  - and properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be local or state laws about how to throw away syringes and needles. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your sharps disposal container.
- Throw away the vial into the container where you put the syringes and needles.

- If you have any questions, talk to your doctor or pharmacist.

Keep STELARA and all medicines out of the reach of children.

Vial Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, US License No. 1864 at Cilag AG, Schaffhausen, Switzerland

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: 11/2019

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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

STELARA 130 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 130 mg ustekinumab in 26 mL (5 mg/mL).

Ustekinumab is a fully human IgG1κ monoclonal antibody to interleukin (IL)-12/23 produced in a murine myeloma cell line using recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

The solution is clear, colourless to light yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Crohn's Disease
STELARA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

Ulcerative colitis
STELARA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies (see section 5.1).

4.2 Posology and method of administration

STELARA concentrate for solution for infusion is intended for use under the guidance and supervision of physicians experienced in the diagnosis and treatment of Crohn's disease or ulcerative colitis. STELARA concentrate for solution for infusion should only be used for the intravenous induction dose.

Posology

Crohn's Disease and Ulcerative Colitis
STELARA treatment is to be initiated with a single intravenous dose based on body weight. The infusion solution is to be composed of the number of vials of STELARA 130 mg as specified in Table 1 (see section 6.6 for preparation).

Table 1 Initial intravenous dosing of STELARA

Body weight of patient at the time of dosing	Recommended dose[a]	Number of 130 mg STELARA Vials
≤ 55 kg	260 mg	2
> 55 kg to ≤ 85 kg	390 mg	3
> 85 kg	520 mg	4

[a] Approximately 6 mg/kg

The first subcutaneous dose should be given at week 8 following the intravenous dose. For the posology of the subsequent subcutaneous dosing regimen, see section 4.2 of the STELARA solution for injection (vial) and solution for injection in pre-filled syringe SmPC.

Elderly (≥ 65 years)
No dose adjustment is needed for elderly patients (see section 4.4).

Renal and hepatic impairment
STELARA has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population
The safety and efficacy of STELARA for the treatment of Crohn's disease or ulcerative colitis in children less than 18 years have not yet been established. No data are available.

Method of administration
STELARA 130 mg is for intravenous use only. It should be administered over at least one hour.
For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

Clinically important, active infection (e.g. active tuberculosis; see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infections
Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. In clinical studies, serious bacterial, fungal, and viral infections have been observed in patients receiving STELARA (see section 4.8).

Caution should be exercised when considering the use of STELARA in patients with a chronic infection or a history of recurrent infection (see section 4.3).

Prior to initiating treatment with STELARA, patients should be evaluated for tuberculosis infection. STELARA must not be given to patients with active tuberculosis (see section 4.3). Treatment of latent tuberculosis infection should be initiated prior to administering STELARA. Anti-tuberculosis therapy should also be considered prior to initiation of STELARA in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving STELARA should be monitored closely for signs and symptoms of active tuberculosis during and after treatment.

Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and STELARA should not be administered until the infection resolves.

Malignancies
Immunosuppressants like ustekinumab have the potential to increase the risk of malignancy. Some patients who received STELARA in clinical studies developed cutaneous and non-cutaneous malignancies (see section 4.8).

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving STELARA. Thus, caution should be exercised when considering the use of STELARA in these patients.

All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of non-melanoma skin cancer (see section 4.8).

Systemic and respiratory hypersensitivity reactions
Systemic
Serious hypersensitivity reactions have been reported in the postmarketing setting, in some cases several days after treatment. Anaphylaxis and angioedema have occurred. If an anaphylactic or other serious hypersensitivity reaction occurs, appropriate therapy should be instituted and administration of STELARA should be discontinued (see section 4.8).

Respiratory
Cases of allergic alveolitis, eosinophilic pneumonia, and non-infectious organising pneumonia have been reported during post-approval use of ustekinumab. Clinical presentations included cough, dyspnoea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalisation. Improvement has been reported after discontinuation of ustekinumab and also, in some cases, administration of corticosteroids. If infection has been excluded and diagnosis is confirmed, discontinue ustekinumab and institute appropriate treatment (see section 4.8).

Vaccinations
It is recommended that live viral or live bacterial vaccines (such as Bacillus of Calmette and Guérin (BCG)) should not be given concurrently with STELARA. Specific studies have not been conducted in patients who had recently received live viral or live bacterial vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving STELARA. Before live viral or live bacterial vaccination, treatment with STELARA should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination. Prescribers should consult the Summary of Product Characteristics for the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.

Patients receiving STELARA may receive concurrent inactivated or non-live vaccinations.

Long term treatment with STELARA does not suppress the humoral immune response to pneumococcal polysaccharide or tetanus vaccines (see section 5.1).

Concomitant immunosuppressive therapy
In psoriasis studies, the safety and efficacy of STELARA in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of STELARA. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of STELARA. Caution should be exercised when considering concomitant use of other immunosuppressants and STELARA or when transitioning from other immunosuppressive biologics (see section 4.5).

Immunotherapy
STELARA has not been evaluated in patients who have undergone allergy immunotherapy. It is not known whether STELARA may affect allergy immunotherapy.

Serious skin conditions
In patients with psoriasis, exfoliative dermatitis has been reported following ustekinumab treatment (see section 4.8). Patients with plaque psoriasis may develop erythrodermic psoriasis, with symptoms that may be clinically indistinguishable from exfoliative dermatitis, as part of the natural course of their disease. As part of the monitoring of the patient's psoriasis, physicians should be alert for symptoms of erythrodermic psoriasis or exfoliative dermatitis. If these symptoms occur, appropriate therapy should be instituted. STELARA should be discontinued if a drug reaction is suspected.

Special populations
Elderly (≥ 65 years)
No overall differences in efficacy or safety in patients age 65 and older who received STELARA were observed compared to younger patients in clinical studies in approved indications, however the number of patients aged 65 and older is not sufficient to determine whether they respond differently from younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Sodium content
STELARA contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'. STELARA is however, diluted in sodium chloride 9 mg/ml (0.9%) solution for infusion. This should be taken into consideration for patients on a controlled sodium diet (see section 6.6).

4.5 Interaction with other medicinal products and other forms of interaction

Live vaccines should not be given concurrently with STELARA (see section 4.4).

No interaction studies have been performed in humans. In the population pharmacokinetic analyses of the phase 3 studies, the effect of the most frequently used concomitant medicinal products in patients with psoriasis (including paracetamol, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, levothyroxine) on pharmacokinetics of ustekinumab was explored. There were no indications of an interaction with these concomitantly administered medicinal products. The basis for this analysis was that at least 100 patients (> 5% of the studied population) were treated concomitantly with these medicinal products for at least 90% of the study period. The pharmacokinetics of ustekinumab was not impacted by concomitant use of MTX, NSAIDs, 6-mercaptopurine, azathioprine and oral corticosteroids in patients with psoriatic arthritis, Crohn's disease or ulcerative colitis, or prior exposure to anti-TNFα agents, in patients with psoriatic arthritis or Crohn's disease or by prior exposure to biologics (i.e. anti-TNFα agents and/or vedolizumab) in patients with ulcerative colitis.

The results of an *in vitro* study do not suggest the need for dose adjustments in patients who are receiving concomitant CYP450 substrates (see section 5.2).

In psoriasis studies, the safety and efficacy of STELARA in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of STELARA. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of STELARA. (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use effective methods of contraception during treatment and for at least 15 weeks after treatment.

Pregnancy
There are no adequate data from the use of ustekinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to

avoid the use of STELARA in pregnancy.

Breast-feeding
It is unknown whether ustekinumab is excreted in human breast milk. Animal studies have shown excretion of ustekinumab at low levels in breast milk. It is not known if ustekinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from ustekinumab, a decision on whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with STELARA must be made taking into account the benefit of breast-feeding to the child and the benefit of STELARA therapy to the woman.

Fertility
The effect of ustekinumab on human fertility has not been evaluated (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions (> 5%) in controlled periods of the adult psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies with ustekinumab were nasopharyngitis and headache. Most were considered to be mild and did not necessitate discontinuation of study treatment. The most serious adverse reaction that has been reported for STELARA is serious hypersensitivity reactions including anaphylaxis (see section 4.4). The overall safety profile was similar for patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

Tabulated list of adverse reactions
The safety data described below reflect exposure in adults to ustekinumab in 14 phase 2 and phase 3 studies in 6,709 patients (4,135 with psoriasis and/or psoriatic arthritis, 1,749 with Crohn's disease and 825 patients with ulcerative colitis). This includes exposure to STELARA in the controlled and non-controlled periods of the clinical studies for at least 6 months or 1 year (4,577 and 3,253 patients respectively with psoriasis, psoriatic arthritis, Crohn's disease or ulcerative colitis) and exposure for at least 4 or 5 years (1,482 and 838 patients with psoriasis respectively).

Table 2 provides a list of adverse reactions from adult psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies as well as adverse reactions reported from post-marketing experience. The adverse reactions are classified by System Organ Class and frequency, using the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 List of adverse reactions

System Organ Class	**Frequency: Adverse reaction**
Infections and infestations	Common: Upper respiratory tract infection, nasopharyngitis, sinusitis Uncommon: Cellulitis, dental infections, herpes zoster, lower respiratory tract infection, viral upper respiratory tract infection, vulvovaginal mycotic infection
Immune system disorders	Uncommon: Hypersensitivity reactions (including rash, urticaria) Rare: Serious hypersensitivity reactions (including anaphylaxis, angioedema)

Psychiatric disorders	Uncommon: Depression
Nervous system disorders	Common: Dizziness, headache Uncommon: Facial palsy
Respiratory, thoracic and mediastinal disorders	Common: Oropharyngeal pain Uncommon: Nasal congestion Rare: Allergic alveolitis, eosinophilic pneumonia Very rare: Organising pneumonia*
Gastrointestinal disorders	Common: Diarrhoea, nausea, vomiting
Skin and subcutaneous tissue disorders	Common: Pruritus Uncommon: Pustular psoriasis, skin exfoliation, acne Rare: Exfoliative dermatitis
Musculoskeletal and connective tissue disorders	Common: Back pain, myalgia, arthralgia
General disorders and administration site conditions	Common: Fatigue, injection site erythema, injection site pain Uncommon: Injection site reactions (including haemorrhage, haematoma, induration, swelling and pruritus), asthenia

* See section 4.4, Systemic and respiratory hypersensitivity reactions.

Description of selected adverse reactions

Infections

In the placebo-controlled studies of patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis, the rates of infection or serious infection were similar between ustekinumab-treated patients and those treated with placebo. In the placebo-controlled period of these clinical studies, the rate of infection was 1.36 per patient-year of follow-up in ustekinumab-treated patients, and 1.34 in placebo-treated patients. Serious infections occurred at the rate of 0.03 per patient-year of follow-up in ustekinumab-treated patients (30 serious infections in 930 patient-years of follow-up) and 0.03 in placebo-treated patients (15 serious infections in 434 patient-years of follow-up) (see section 4.4).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 11,581 patient-years of exposure in 6,709 patients, the median follow up was 1.0 years; 1.1 years for psoriatic disease studies, 0.6 year for Crohn's disease studies and 1.0 years for ulcerative colitis studies. The rate of infection was 0.91 per patient-year of follow-up in ustekinumab-treated patients, and the rate of serious infections was 0.02 per patient-year of follow-up in ustekinumab-treated patients (199 serious infections in 11,581 patient-years of follow-up) and serious infections reported included pneumonia, anal abscess, cellulitis, diverticulitis, gastroenteritis and viral infections.

In clinical studies, patients with latent tuberculosis who were concurrently treated with isoniazid did not develop tuberculosis.

Malignancies

In the placebo-controlled period of the psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.11 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in 929 patient-years of follow-up) compared with 0.23 for placebo-treated patients (1 patient in 434 patient-years of follow-up). The incidence of non-melanoma skin cancer was 0.43 per 100 patient-years of follow-up for ustekinumab-treated patients (4 patients in 929 patient-years of follow-up) compared to 0.46 for placebo-treated patients (2 patients in 433 patient-years of follow-up).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 11,561 patient-years of exposure in 6,709 patients, the

median follow-up was 1.0 years; 1.1 years for psoriatic disease studies, 0.6 year for Crohn's disease studies and 1.0 years for ulcerative colitis studies. Malignancies excluding non-melanoma skin cancers were reported in 62 patients in 11,561 patient-years of follow-up (incidence of 0.54 per 100 patient-years of follow-up for ustekinumab-treated patients). The incidence of malignancies reported in ustekinumab-treated patients was comparable to the incidence expected in the general population (standardised incidence ratio = 0.93 [95% confidence interval: 0.71, 1.20], adjusted for age, gender and race). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, colorectal, melanoma and breast cancers. The incidence of non-melanoma skin cancer was 0.49 per 100 patient-years of follow-up for ustekinumab-treated patients (56 patients in 11,545 patient-years of follow-up). The ratio of patients with basal versus squamous cell skin cancers (3:1) is comparable with the ratio expected in the general population (see section 4.4).

Hypersensitivity and infusion reactions
In Crohn's disease and ulcerative colitis intravenous induction studies, no events of anaphylaxis or other serious infusion reactions were reported following the single intravenous dose. In these studies, 2.2% of 785 placebo treated patients and 1.9% of 790 patients treated with the recommended dose of ustekinumab reported adverse events occurring during or within an hour of the infusion.

Paediatric population
Paediatric patients 6 years and older with plaque psoriasis
The safety of ustekinumab has been studied in two phase 3 studies of paediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks and the second study was in 44 patients from 6 to 11 years of age treated for up to 56 weeks. In general, the adverse events reported in these two studies with safety data up to 1 year were similar to those seen in previous studies in adults with plaque psoriasis.

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

4.9 Overdose

Single doses up to 6 mg/kg have been administered intravenously in clinical studies without dose-limiting toxicity. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC05.

Mechanism of action
Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines participate in immune functions; IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype, IL-23 induces the T helper 17 (Th17) pathway. However, abnormal regulation of IL 12 and IL 23 has

been associated with immune mediated diseases, such as psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.

In patients with Crohn's disease and ulcerative colitis, treatment with ustekinumab resulted in a decrease in inflammatory markers including C-Reactive Protein (CRP) and fecal calprotectin during the induction phase, which were then maintained throughout the maintenance phase.

Immunisation
During the long term extension of Psoriasis Study 2 (PHOENIX 2), adult patients treated with STELARA for at least 3.5 years mounted similar antibody responses to both pneumococcal polysaccharide and tetanus vaccines as a non-systemically treated psoriasis control group. Similar proportions of adult patients developed protective levels of anti-pneumococcal and anti-tetanus antibodies and antibody titers were similar among STELARA-treated and control patients.

Clinical efficacy

Crohn's Disease
The safety and efficacy of ustekinumab was assessed in three randomized, double-blind, placebo-controlled, multicenter studies in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of ≥ 220 and ≤ 450). The clinical development program consisted of two 8-week intravenous induction studies (UNITI-1 and UNITI-2) followed by a 44 week subcutaneous randomized withdrawal maintenance study (IM-UNITI) representing 52 weeks of therapy.

The induction studies included 1409 (UNITI-1, n = 769; UNITI-2 n = 640) patients. The primary endpoint for both induction studies was the proportion of subjects in clinical response (defined as a reduction in CDAI score of ≥ 100 points) at week 6. Efficacy data were collected and analyzed through week 8 for both studies. Concomitant doses of oral corticosteroids, immunomodulators, aminosalicylates and antibiotics were permitted and 75% of patients continued to receive at least one of these medications. In both studies, patients were randomised to receive a single intravenous administration of either the recommended tiered dose of approximately 6 mg/kg (see Table 1, section 4.2), a fixed dose of 130 mg ustekinumab, or placebo at week 0.

Patients in UNITI-1 had failed or were intolerant to prior anti-TNFα therapy. Approximately 48% of the patients had failed 1 prior anti-TNFα therapy and 52% had failed 2 or 3 prior anti-TNFα therapies. In this study, 29.1% of the patients had an inadequate initial response (primary non-responders), 69.4% responded but lost response (secondary non-responders), and 36.4% were intolerant to anti-TNFα therapies.

Patients in UNITI-2 had failed at least one conventional therapy, including corticosteroids or immunomodulators, and were either anti-TNF-α naïve (68.6%) or had previously received but not failed anti-TNFα therapy (31.4%).

In both UNITI-1 and UNITI-2, a significantly greater proportion of patients were in clinical response and remission in the ustekinumab treated group compared to placebo (Table 3). Clinical response and remission were significant as early as week 3 in ustekinumab treated patients and continued to improve through week 8. In these induction studies, efficacy was higher and better sustained in the tiered dose group compared to the 130 mg dose group, and tiered dosing is therefore the recommended intravenous induction dose.

Table 3: Induction of Clinical Response and Remission in UNITI-1 and UNITI 2

	UNITI-1*		UNITI-2**	
	Placebo N = 247	**Recommended dose of ustekinumab N = 249**	**Placebo N = 209**	**Recommended dose of ustekinumab N = 209**
Clinical Remission, week 8	18 (7.3%)	52 (20.9%)[a]	41 (19.6%)	84 (40.2%)[a]
Clinical Response (100 point), week 6	53 (21.5%)	84 (33.7%)[b]	60 (28.7%)	116 (55.5%)[a]
Clinical Response (100 point), week 8	50 (20.2%)	94 (37.8%)[a]	67 (32.1%)	121 (57.9%)[a]
70 Point Response, week 3	67 (27.1%)	101 (40.6%)[b]	66 (31.6%)	106 (50.7%)[a]
70 Point Response, week 6	75 (30.4%)	109 (43.8%)[b]	81 (38.8%)	135 (64.6%)[a]

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission
70 point response is defined as reduction in CDAI score by at least 70 points
* Anti-TNFα failures
** Conventional therapy failures
[a] $p < 0.001$
[b] $p < 0.01$

The maintenance study (IM-UNITI), evaluated 388 patients who achieved 100 point clinical response at week 8 of induction with ustekinumab in studies UNITI-1 and UNITI-2. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks (for recommended maintenance posology, see section 4.2 of the STELARA Solution for injection (vial) and Solution for injection in pre filled syringe SmPC).

Significantly higher proportions of patients maintained clinical remission and response in the ustekinumab treated groups compared to the placebo group at week 44 (see Table 4).

Table 4: Maintenance of Clinical Response and Remission in IM-UNITI (week 44; 52 weeks from initiation of the induction dose)

	Placebo* N = 131†	**90 mg ustekinumab every 8 weeks N = 128†**	**90 mg ustekinumab every 12 weeks N = 129†**
Clinical Remission	36%	53%[a]	49%[b]
Clinical Response	44%	59%[b]	58%[b]
Corticosteroid-Free Clinical Remission	30%	47%[a]	43%[c]
Clinical Remission in patients:			
in remission at the start of maintenance therapy	46% (36/79)	67% (52/78)[a]	56% (44/78)
who entered from study CRD3002‡	44% (31/70)	63% (45/72)[c]	57% (41/72)
who are Anti-TNFα naïve	49% (25/51)	65% (34/52)[c]	57% (30/53)
who entered from study CRD3001§	26% (16/61)	41% (23/56)	39% (22/57)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission
* The placebo group consisted of patients who were in response to ustekinumab and were randomized to receive placebo at the start of maintenance therapy.
† Patients who were in 100 point clinical response to ustekinumab at start of maintenance therapy
‡ Patients who failed conventional therapy but not anti-TNFα therapy
§ Patients who are anti-TNFα refractory/intolerant
[a] $p < 0.01$
[b] $p < 0.05$
[c] nominally significant ($p < 0.05$)

In IM-UNITI, 29 of 129 patients did not maintain response to ustekinumab when treated every 12 weeks and were allowed to dose adjust to receive ustekinumab every 8 weeks. Loss of response

was defined as a CDAI score ≥ 220 points and a ≥ 100 point increase from the CDAI score at baseline. In these patients, clinical remission was achieved in 41.4% of patients 16 weeks after dose adjustment.

Patients who were not in clinical response to ustekinumab induction at week 8 of the UNITI-1 and UNITI-2 induction studies (476 patients) entered into the non-randomized portion of the maintenance study (IM-UNITI) and received a 90 mg subcutaneous injection of ustekinumab at that time. Eight weeks later, 50.5% of the patients achieved clinical response and continued to receive maintenance dosing every 8 weeks; among these patients with continued maintenance dosing, a majority maintained response (68.1%) and achieved remission (50.2%) at week 44, at proportions that were similar to the patients who initially responded to ustekinumab induction.

Of 131 patients who responded to ustekinumab induction, and were randomized to the placebo group at the start of the maintenance study, 51 subsequently lost response and received 90 mg ustekinumab subcutaneously every 8 weeks. The majority of patients who lost response and resumed ustekinumab did so within 24 weeks of the induction infusion. Of these 51 patients, 70.6% achieved clinical response and 39.2% percent achieved clinical remission 16 weeks after receiving the first subcutaneous dose of ustekinumab.

In IM-UNITI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among patients who entered the study extension, clinical remission and response were generally maintained through week 92 for both patients who failed TNF-therapies and those who failed conventional therapies.

No new safety concerns were identified in this study extension with up to 2 years of treatment in patients with Crohn's Disease.

Endoscopy
Endoscopic appearance of the mucosa was evaluated in 252 patients with eligible baseline endoscopic disease activity in a substudy. The primary endpoint was change from baseline in Simplified Endoscopic Disease Severity Score for Crohn's Disease (SES-CD), a composite score across 5 ileo-colonic segments of presence/size of ulcers, proportion of mucosal surface covered by ulcers, proportion of mucosal surface affected by any other lesions and presence/type of narrowing/strictures. At week 8, after a single intravenous induction dose, the change in SES-CD score was greater in the ustekinumab group (n = 155, mean change = -2.8) than in the placebo group (n = 97, mean change = -0.7, p = 0.012).

Fistula Response
In a subgroup of patients with draining fistulas at baseline (8.8%; n = 26), 12/15 (80%) of ustekinumab-treated patients achieved a fistula response over 44 weeks (defined as ≥ 50% reduction from baseline of the induction study in the number of draining fistulas) compared to 5/11 (45.5%) exposed to placebo.

Health-related quality of life
Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ) and SF-36 questionnaires. At week 8, patients receiving ustekinumab showed statistically significantly greater and clinically meaningful improvements on IBDQ total score and SF-36 Mental Component Summary Score in both UNITI-1 and UNITI-2, and SF-36 Physical Component Summary Score in UNITI-2, when compared to placebo. These improvements were generally better maintained in ustekinumab-treated patients in the IM-UNITI study through week 44 when compared to placebo. Improvement in health-related quality of life was generally maintained during the extension through week 92.

Ulcerative colitis
The safety and efficacy of ustekinumab was assessed in two randomized, double-blind, placebo-controlled, multicenter studies in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥ 2). The clinical development program consisted of one intravenous induction study (referred to as UNIFI-I) with treatment of up to 16 weeks followed by a

44 week subcutaneous randomized withdrawal maintenance study (referred to as UNIFI-M) representing at least 52 weeks of therapy.

Efficacy results presented for UNIFI-I and UNIFI-M were based on central review of endoscopies.

UNIFI-I included 961 patients. The primary endpoint for the induction study was the proportion of subjects in clinical remission at week 8. Patients were randomised to receive a single intravenous administration of either the recommended tiered dose of approximately 6 mg/kg (see Table 1, section 4.2), a fixed dose of 130 mg ustekinumab, or placebo at week 0.

Concomitant doses of oral corticosteroids, immunomodulators, and aminosalicylates were permitted and 90% of patients continued to receive at least one of these medications. Enrolled patients had to have failed conventional therapy (corticosteroids or immunomodulators) or at least one biologic (a TNFα antagonist and/or vedolizumab). 49% of patients had failed conventional therapy, but not a biologic (of which 94% where biological-naïve). 51% of patients had failed or were intolerant to a biologic. Approximately 50% of the patients had failed at least 1 prior anti-TNFα therapy (of which 48% were primary non-responders) and 17% had failed at least 1 anti-TNFα therapy and vedolizumab.

In UNIFI-I a significantly greater proportion of patients were in clinical remission in the ustekinumab treated group compared to placebo at week 8 (Table 5). As early as Week 2, the earliest scheduled study visit, and at each visit thereafter, a higher proportion of ustekinumab patients had no rectal bleeding or achieved normal stool frequency as compared with placebo patients. Significant differences in partial Mayo score and symptomatic remission were observed between ustekinumab and placebo as early as Week 2.

Efficacy was higher in the tiered dose group (6 mg/kg) compared to the 130 mg dose group in select endpoints, and tiered dosing is therefore the recommended intravenous induction dose.

Table 5: Summary of Key Efficacy Outcomes in UNIFI-I (Week 8)

	Placebo N = 319	**Recommended dose of ustekinumab£ N = 322**
Clinical Remission*	5%	16%[a]
In patients who failed conventional therapy, but not a biologic	9% (15/158)	19% (29/156)[c]
In patients who failed biological therapy[¥]	1% (2/161)	13% (21/166)[b]
In patients who failed both a TNF and vedolizumab	0% (0/47)	10% (6/58)[c]
Clinical Response[§]	31%	62%[a]
In patients who failed conventional therapy, but not a biologic	35% (56/158)	67% (104/156)[b]
In patients who failed biological therapy[¥]	27% (44/161)	57% (95/166)[b]
In patients who failed both a TNF and vedolizumab	28% (13/47)	52% (30/58)[c]
Mucosal Healing[†]	14%	27%[a]
In patients who failed conventional therapy, but not a biologic	21% (33/158)	33% (52/156)[c]
In patients who failed biological therapy	7% (11/161)	21% (35/166)[b]
Symptomatic Remission[‡]	23%	45%[b]
Combined Symptomatic Remission and Mucosal Healing	8%	21%[b]

£ Infusion dose of ustekinumab using the weight-based dosage regimen specified in *Table 1*.

* Clinical remission is defined as Mayo score ≤2 points, with no individual subscore > 1.

§ Clinical response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.

¥ A TNFα antagonist and/or vedolizumab.

† Mucosal healing is defined as a Mayo endoscopic subscore of 0 or 1.

‡ Symptomatic remission is defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.

□ Combined symptomatic remission and mucosal healing is defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.

a $p < 0.001$

b Nominally significant ($p < 0.001$)

c Nominally significant ($p < 0.05$)

UNIFI-M, evaluated 523 patients who achieved clinical response with single IV administration of ustekinumab in UNIFI-I. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks (for recommended maintenance posology, see section 4.2 of the STELARA Solution for injection (vial) and Solution for injection in pre filled syringe SmPC).

Significantly greater proportions of patients were in clinical remission in both ustekinumab treated groups compared to the placebo group at week 44 (see Table 6).

Table 6: Summary of Key Efficacy Measures in UNIFI-M (week 44; 52 weeks from initiation of the induction dose)

	Placebo* **N** = 175	**90 mg ustekinumab every 8 Weeks** **N** = 176	**90 mg ustekinumab every 12 Weeks** **N** = 172
Clinical Remission**	24%	44% [a]	38% [b]
In patients who failed conventional therapy, but not a biologic	31% (27/87)	48% (41/85) [d]	49% (50/102) [d]
In patients who failed biological therapy[¥]	17% (15/88)	40% (36/91) [c]	23% (16/70) [d]
In patients who failed both a TNF and vedolizumab	15% (4/27)	33% (7/21) [e]	23% (5/22) [e]
Maintenance of Clinical Response through week 44[§]	45%	71% [a]	68% [a]
In patients who failed conventional therapy, but not a biologic	51% (44/87)	78% (66/85) [c]	77% (78/102) [c]
In patients who failed biological therapy[¥]	39% (34/88)	65% (59/91) [c]	56% (39/70) [d]
In patients who failed both a TNF and vedolizumab	41% (11/27)	67% (14/21) [e]	50% (11/22) [e]
Mucosal Healing[†]	29%	51% [a]	44% [b]
Maintenance of Clinical Remission through week 44[£]	38% (17/45)	58% (22/38)	65% (26/40) [c]
Corticosteroid Free Clinical Remission[€]	23%	42% [a]	38% [b]
Durable Remission[I]	35%	57% [c]	48% [d]
Symptomatic Remission[‡]	45%	68% [c]	62% [d]
Combined Symptomatic Remission and Mucosal Healing[□]	28%	48% [c]	41% [d]

* Following response to IV ustekinumab.
** Clinical remission is defined as Mayo score ≤2 points, with no individual subscore > 1.
§ Clinical response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.
¥ A TNFα antagonist and/or vedolizumab.
† Mucosal healing is defined as a Mayo endoscopic sub-score of 0 or 1.
£ Maintenance of clinical remission through Week 44 is defined as patients in clinical remission through Week 44 among patients in clinical remission at maintenance baseline.
€ Corticosteroid-free clinical remission is defined as patients in clinical remission and not receiving corticosteroids at Week 44.
‖ Durable Remission is defined as partial Mayo remission at ≥80% of all visits prior to Week 44 and in partial Mayo remission at last visit (Week 44).
‡ Symptomatic remission is defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.
□ Combined symptomatic remission and mucosal healing is defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
[a] $p < 0.001$
[b] $p < 0.05$
[c] Nominally significant ($p < 0.001$)
[d] Nominally significant ($p < 0.05$)
[e] Not statistically significant

The beneficial effect of ustekinumab on clinical response, mucosal healing and clinical remission was observed in induction and in maintenance both in patients who failed conventional therapy but not a biologic therapy, as well as in those who had failed at least one prior TNFα antagonist therapy including in patients with a primary non-response to TNFα antagonist therapy. A beneficial effect was also observed in induction in patients who failed at least one prior TNFα antagonist therapy and vedolizumab, however the number of patients in this subgroup was too small to draw definitive conclusions about the beneficial effect in this group during maintenance.

Week 16 Responders to Ustekinumab Induction
Ustekinumab treated patients who were not in response at week 8 of UNIFI-I received an administration of 90 mg SC ustekinumab at week 8 (36% of patients). Of those patients, 9% of patients who were initially randomized to the recommended induction dose achieved clinical remission and 58% achieved clinical response at Week 16.

Patients who were not in clinical response to ustekinumab induction at week 8 of the UNFI-I study but were in response at week 16 (157 patients) entered into the non-randomized portion of UNIFI-M and continued to receive maintenance dosing every 8 weeks; among these patients, a majority (62%) maintained response and 30% achieved remission at week 44.

Endoscopic Normalization
Endoscopic normalization was defined as a Mayo endoscopic subscore of 0 and was observed as early as week 8 of UNIFI-I. At week 44 of UNIFI-M, it was achieved in 24% and 29% of patients treated with ustekinumab every 12 or 8 weeks, respectively, as compared to 18% of patients in the placebo group.

Histologic & Histo-Endoscopic Mucosal Healing
Histologic healing (defined as neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue) was assessed at week 8 of UNIFI-I and Week 44 of UNIFI-M. At week 8, after a single intravenous induction dose, significantly greater proportions of patients in the recommended dose group achieved histologic healing (36%) compared with patients in the placebo group (22%). At Week 44 maintenance of this effect was observed with significantly more patients in histologic healing in the every 12 week (54%) and every 8 week (59%) ustekinumab groups as compared to placebo (33%).

A combined endpoint of histo-endoscopic mucosal healing defined as subjects having both mucosal healing and histologic healing was evaluated at week 8 of UNIFI-I and week 44 of UNIFI-M. Patients receiving ustekinumab at the recommended dose showed significant improvements on the histo-

endoscopic mucosal healing endpoint at week 8 in the ustekinumab group (18%) as compared to the placebo group (9%). At week 44, maintenance of this effect was observed with significantly more patients in histo-endoscopic mucosal healing in the every 12 week (39%) and every 8 week (46%) ustekinumab groups compared to placebo (24%).

Health-related quality of life
Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ), SF-36 and EuroQoL-5D (EQ-5D) questionnaires.

At week 8 of UNIFI-I, patients receiving ustekinumab showed significantly greater and clinically meaningful improvements on IBDQ total score, EQ-5D and EQ-5D VAS, and SF-36 Mental Component Summary Score and SF-36 Physical Component Summary Score when compared to placebo. These improvements were maintained in ustekinumab-treated patients in UNIFI-M through week 44.

Patients receiving ustekinumab experienced significantly more improvements in work productivity as assessed by greater reductions in overall work impairment and in activity impairment as assessed by the WPAI-GH questionnaire than patients receiving placebo.

Hospitalizations and ulcerative colits (UC) related surgeries
Through week 8 of UNIFI-I, the proportions of subjects with UC disease related hospitalizations were significantly lower for subjects in the ustekinumab recommended dose group (1.6%, 5/322) compared with subjects in the placebo group (4.4%, 14/319) and no subjects underwent UC disease related surgeries in subjects receiving ustekinumab at the recommended induction dose compared to 0.6% (2/319) subjects in the placebo group.

Through week 44 of UNIFI-M, a significantly lower number of UC-related hospitalizations was observed in subjects in the combined ustekinumab group (2.0%, 7/348) as compared with subjects in the placebo group (5.7%, 10/175). A numerically lower number of subjects in the ustekinumab group (0.6%, 2/348) underwent UC disease related surgeries compared with subjects in the placebo group (1.7%, 3/175) through week 44.

Immunogenicity
Antibodies to ustekinumab may develop during ustekinumab treatment and most are neutralising. The formation of anti-ustekinumab antibodies is associated with increased clearance of ustekinumab in patients with Crohn's disease or ulcerative colitis. No reduced efficacy was observed. There is no apparent correlation between the presence of anti-ustekinumab antibodies and the occurrence of injection site reactions.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with ustekinumab in one or more subsets of the paediatric population in Crohn's Disease and ulcerative colitis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Following the recommended intravenous induction dose, median peak serum ustekinumab concentration, observed 1 hour after the infusion, was 126.1 µg/mL in patients with Crohn's disease and 127.0 µg/mL in patients with ulcerative colitis.

Distribution
Median volume of distribution during the terminal phase (Vz) following a single intravenous administration to patients with psoriasis ranged from 57 to 83 mL/kg.

Biotransformation
The exact metabolic pathway for ustekinumab is unknown.

Elimination
Median systemic clearance (CL) following a single intravenous administration to patients with psoriasis ranged from 1.99 to 2.34 mL/day/kg. Median half-life ($t_{1/2}$) of ustekinumab was approximately 3 weeks in patients with ulcerative colitis, Crohn's disease, psoriasis and/or psoriatic arthritis, ranging from 15 to 32 days across all psoriasis and psoriatic arthritis studies.

Dose linearity
The systemic exposure of ustekinumab (C_{max} and AUC) increased in an approximately dose-proportional manner after a single intravenous administration at doses ranging from 0.09 mg/kg to 4.5 mg/kg.

Special populations
No pharmacokinetic data are available in patients with impaired renal or hepatic function.
No specific studies have been conducted with intravenous ustekinumab in elderly or paediatric patients.

In patients with Crohn's disease and ulcerative colitis, variability in ustekinumab clearance was affected by body weight, serum albumin level, sex, and antibody to ustekinumab status while body weight was the main covariate affecting the volume of distribution. Additionally in Crohn's disease, clearance was affected by C-reactive protein, TNF antagonist failure status and race (Asian versus non-Asian). The impact of these covariates was within ±20% of the typical or reference value of the respective PK parameter, thus dose adjustment is not warranted for these covariates. Concomitant use of immunomodulators did not have a significant impact on ustekinumab disposition.

Regulation of CYP450 enzymes
The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4; see section 4.5).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard (e.g. organ toxicity) for humans based on studies of repeated-dose toxicity and developmental and reproductive toxicity, including safety pharmacology evaluations. In developmental and reproductive toxicity studies in cynomolgus monkeys, neither adverse effects on male fertility indices nor birth defects or developmental toxicity were observed. No adverse effects on female fertility indices were observed using an analogous antibody to IL-12/23 in mice.

Dose levels in animal studies were up to approximately 45-fold higher than the highest equivalent dose intended to be administered to psoriasis patients and resulted in peak serum concentrations in monkeys that were more than 100-fold higher than observed in humans.

Carcinogenicity studies were not performed with ustekinumab due to the lack of appropriate models for an antibody with no cross-reactivity to rodent IL-12/23 p40.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

EDTA disodium salt dihydrate
L-histidine
L-histidine monohydrochloride monohydrate
L-methionine
Polysorbate 80
Sucrose
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. STELARA should only be diluted with sodium chloride 9 mg/mL (0.9%) solution. STELARA should not be administered concomitantly in the same intravenous line with other medicinal products.

6.3 Shelf life

3 years.
Do not freeze.

Chemical and physical in-use stability has been demonstrated for 8 hours at 15-25°C.

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

26 mL solution in a type I glass 30 mL vial closed with a coated butyl rubber stopper. STELARA is available in a 1 vial pack.

6.6 Special precautions for disposal and other handling

The solution in the STELARA vial should not be shaken. The solution should be visually inspected for particulate matter or discoloration prior to administration. The solution is clear, colourless to light yellow. The medicinal product should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present.

Dilution
STELARA concentrate for solution for infusion must be diluted and prepared by a healthcare professional using aseptic technique.

1. Calculate the dose and the number of STELARA vials needed based on patient weight (see section 4.2, Table 1). Each 26 mL vial of STELARA contains 130 mg of ustekinumab. Only use complete vials of STELARA.
2. Withdraw and discard a volume of the sodium chloride 9 mg/mL (0.9%) solution from the 250 mL infusion bag equal to the volume of STELARA to be added. (discard 26 mL sodium chloride for each vial of STELARA needed, for 2 vials-discard 52 mL, for 3 vials- discard 78 mL, for 4 vials- discard 104 mL)
3. Withdraw 26 mL of STELARA from each vial needed and add it to the 250 mL infusion bag. The final volume in the infusion bag should be 250 mL. Gently mix.
4. Visually inspect the diluted solution before administration. Do not use if visibly opaque particles, discoloration or foreign particles are observed.
5. Administer the diluted solution over a period of at least one hour. Once diluted, the infusion should be completed within eight hours of the dilution in the infusion bag.
6. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.2 micrometer).

7. Each vial is for single use only and any unused medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/494/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 January 2009
Date of latest renewal: 19 September 2013

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

STELARA 45 mg solution for injection
STELARA 90 mg solution for injection
STELARA 45 mg solution for injection in pre-filled syringe
STELARA 90 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

STELARA 45 mg solution for injection
Each vial contains 45 mg ustekinumab in 0.5 mL.

STELARA 90 mg solution for injection
Each vial contains 90 mg ustekinumab in 1 mL.

STELARA 45 mg solution for injection in pre-filled syringe
Each pre-filled syringe contains 45 mg ustekinumab in 0.5 mL.

STELARA 90 mg solution for injection in pre-filled syringe
Each pre-filled syringe contains 90 mg ustekinumab in 1 mL.

Ustekinumab is a fully human IgG1κ monoclonal antibody to interleukin (IL)-12/23 produced in a murine myeloma cell line using recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

STELARA 45 mg solution for injection
Solution for injection.

STELARA 90 mg solution for injection
Solution for injection.

STELARA 45 mg solution for injection in pre-filled syringe
Solution for injection.

STELARA 90 mg solution for injection in pre-filled syringe
Solution for injection.

The solution is clear to slightly opalescent, colourless to light yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Plaque psoriasis
STELARA is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A) (see section 5.1).

Paediatric plaque psoriasis
STELARA is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are

intolerant to, other systemic therapies or phototherapies (see section 5.1).

Psoriatic arthritis (PsA)
STELARA, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate (see section 5.1).

Crohn's Disease
STELARA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

Ulcerative colitis
STELARA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies (see section 5.1).

4.2 Posology and method of administration

STELARA is intended for use under the guidance and supervision of physicians experienced in the diagnosis and treatment of conditions for which STELARA is indicated.

Posology

Plaque psoriasis
The recommended posology of STELARA is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter.

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Patients with body weight > 100 kg
For patients with a body weight > 100 kg the initial dose is 90 mg administered subcutaneously, followed by a 90 mg dose 4 weeks later, and then every 12 weeks thereafter. In these patients, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy. (see section 5.1, Table 4)

Psoriatic arthritis (PsA)
The recommended posology of STELARA is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg.

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Elderly (≥ 65 years)
No dose adjustment is needed for elderly patients (see section 4.4).

Renal and hepatic impairment
STELARA has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population
The safety and efficacy of STELARA in children with psoriasis less than 6 years of age or in children with psoriatic arthritis less than 18 years of age have not yet been established.

Paediatric plaque psoriasis (6 years and older)

The recommended dose of STELARA based on body weight is shown below (Tables 1 and 2). STELARA should be administered at Weeks 0 and 4, then every 12 weeks thereafter.

Table 1 Recommended dose of STELARA for paediatric psoriasis

Body weight at the time of dosing	**Recommended Dose**
< 60 kg	0.75 mg/kg
≥ 60-≤ 100 kg	45 mg
> 100 kg	90 mg

To calculate the volume of injection (mL) for patients < 60 kg, use the following formula: body weight (kg) x 0.0083 (mL/kg) or see Table 2. The calculated volume should be rounded to the nearest 0.01 mL and administered using a 1 mL graduated syringe. A 45 mg vial is available for paediatric patients who need to receive less than the full 45 mg dose.

Table 2 Injection volumes of STELARA for paediatric psoriasis patients < 60 kg

Body weight at time of dosing (kg)	**Dose (mg)**	**Volume of injection (mL)**
15	11.3	0.12
16	12.0	0.13
17	12.8	0.14
18	13.5	0.15
19	14.3	0.16
20	15.0	0.17
21	15.8	0.17
22	16.5	0.18
23	17.3	0.19
24	18.0	0.20
25	18.8	0.21
26	19.5	0.22
27	20.3	0.22
28	21.0	0.23
29	21.8	0.24
30	22.5	0.25
31	23.3	0.26
32	24.0	0.27
33	24.8	0.27
34	25.5	0.28
35	26.3	0.29
36	27.0	0.30
37	27.8	0.31
38	28.5	0.32
39	29.3	0.32
40	30.0	0.33
41	30.8	0.34
42	31.5	0.35
43	32.3	0.36
44	33.0	0.37
45	33.8	0.37
46	34.5	0.38
47	35.3	0.39
48	36.0	0.40
49	36.8	0.41
50	37.5	0.42
51	38.3	0.42

52	39.0	0.43
53	39.8	0.44
54	40.5	0.45
55	41.3	0.46
56	42.0	0.46
57	42.8	0.47
58	43.5	0.48
59	44.3	0.49

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Crohn's Disease and Ulcerative Colitis
In the treatment regimen, the first dose of STELARA is administered intravenously. For the posology of the intravenous dosing regimen, see section 4.2 of the STELARA 130 mg Concentrate for solution for infusion SmPC.

The first subcutaneous administration of 90 mg STELARA should take place at week 8 after the intravenous dose. After this, dosing every 12 weeks is recommended.

Patients who have not shown adequate response at 8 weeks after the first subcutaneous dose, may receive a second subcutaneous dose at this time (see section 5.1).

Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks (see section 5.1, section 5.2).

Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment (see section 5.1).

Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit 16 weeks after the IV induction dose or 16 weeks after switching to the 8-weekly maintenance dose.

Immunomodulators and/or corticosteroids may be continued during treatment with STELARA. In patients who have responded to treatment with STELARA, corticosteroids may be reduced or discontinued in accordance with standard of care.

In Crohn's disease, if therapy is interrupted, resumption of treatment with subcutaneous dosing every 8 weeks is safe and effective.

Elderly (≥ 65 years)
No dose adjustment is needed for elderly patients (see section 4.4).

Renal and hepatic impairment
STELARA has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population
The safety and efficacy of STELARA in treatment of Crohn's disease or ulcerative colitis in children less than 18 years have not yet been established. No data are available.

Method of administration
STELARA 45 mg and 90 mg vials or pre-filled syringes are for subcutaneous injection only. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

After proper training in subcutaneous injection technique, patients or their caregivers may inject STELARA if a physician determines that it is appropriate. However, the physician should ensure appropriate follow-up of patients. Patients or their caregivers should be instructed to inject the

prescribed amount of STELARA according to the directions provided in the package leaflet. Comprehensive instructions for administration are given in the package leaflet.

For further instructions on preparation and special precautions for handling, see section 6.6.

4.3 Contraindications

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

Clinically important, active infection (e.g. active tuberculosis; see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infections
Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. In clinical studies, serious bacterial, fungal, and viral infections have been observed in patients receiving STELARA (see section 4.8).

Caution should be exercised when considering the use of STELARA in patients with a chronic infection or a history of recurrent infection (see section 4.3).

Prior to initiating treatment with STELARA, patients should be evaluated for tuberculosis infection. STELARA must not be given to patients with active tuberculosis (see section 4.3). Treatment of latent tuberculosis infection should be initiated prior to administering STELARA. Anti-tuberculosis therapy should also be considered prior to initiation of STELARA in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving STELARA should be monitored closely for signs and symptoms of active tuberculosis during and after treatment.

Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and STELARA should not be administered until the infection resolves.

Malignancies
Immunosuppressants like ustekinumab have the potential to increase the risk of malignancy. Some patients who received STELARA in clinical studies developed cutaneous and non-cutaneous malignancies (see section 4.8).

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving STELARA. Thus, caution should be exercised when considering the use of STELARA in these patients.

All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of non-melanoma skin cancer (see section 4.8).

Systemic and respiratory hypersensitivity reactions
Systemic
Serious hypersensitivity reactions have been reported in the postmarketing setting, in some cases several days after treatment. Anaphylaxis and angioedema have occurred. If an anaphylactic or other serious hypersensitivity reaction occurs, appropriate therapy should be instituted and administration of STELARA should be discontinued (see section 4.8).

Respiratory
Cases of allergic alveolitis, eosinophilic pneumonia, and non-infectious organising pneumonia have been reported during post-approval use of ustekinumab. Clinical presentations included cough, dyspnoea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalisation. Improvement has been reported after discontinuation of ustekinumab and also, in some cases, administration of corticosteroids. If infection has been excluded and diagnosis is confirmed, discontinue ustekinumab and institute appropriate treatment (see section 4.8).

Latex sensitivity
The needle cover on the syringe in the STELARA pre-filled syringe is manufactured from dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Vaccinations
It is recommended that live viral or live bacterial vaccines (such as Bacillus of Calmette and Guérin (BCG)) should not be given concurrently with STELARA. Specific studies have not been conducted in patients who had recently received live viral or live bacterial vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving STELARA. Before live viral or live bacterial vaccination, treatment with STELARA should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination. Prescribers should consult the Summary of Product Characteristics for the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.

Patients receiving STELARA may receive concurrent inactivated or non-live vaccinations.

Long term treatment with STELARA does not suppress the humoral immune response to pneumococcal polysaccharide or tetanus vaccines (see section 5.1).

Concomitant immunosuppressive therapy
In psoriasis studies, the safety and efficacy of STELARA in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of STELARA. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of STELARA. Caution should be exercised when considering concomitant use of other immunosuppressants and STELARA or when transitioning from other immunosuppressive biologics (see section 4.5).

Immunotherapy
STELARA has not been evaluated in patients who have undergone allergy immunotherapy. It is not known whether STELARA may affect allergy immunotherapy.

Serious skin conditions
In patients with psoriasis, exfoliative dermatitis has been reported following ustekinumab treatment (see section 4.8). Patients with plaque psoriasis may develop erythrodermic psoriasis, with symptoms that may be clinically indistinguishable from exfoliative dermatitis, as part of the natural course of their disease. As part of the monitoring of the patient's psoriasis, physicians should be alert for symptoms of erythrodermic psoriasis or exfoliative dermatitis. If these symptoms occur, appropriate therapy should be instituted. STELARA should be discontinued if a drug reaction is suspected.

Special populations
Elderly (≥ 65 years)
No overall differences in efficacy or safety in patients age 65 and older who received STELARA were observed compared to younger patients in clinical studies in approved indications, however the number of patients aged 65 and older is not sufficient to determine whether they respond differently from younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

4.5 Interaction with other medicinal products and other forms of interaction

Live vaccines should not be given concurrently with STELARA (see section 4.4).

No interaction studies have been performed in humans. In the population pharmacokinetic analyses of the phase 3 studies, the effect of the most frequently used concomitant medicinal products in patients with psoriasis (including paracetamol, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, levothyroxine) on pharmacokinetics of ustekinumab was explored. There were no indications of an interaction with these concomitantly administered medicinal products. The basis for this analysis was that at least 100 patients (> 5% of the studied population) were treated concomitantly with these medicinal products for at least 90% of the study period. The pharmacokinetics of ustekinumab was not impacted by concomitant use of MTX, NSAIDs, 6-mercaptopurine, azathioprine and oral corticosteroids in patients with psoriatic arthritis, Crohn's disease or ulcerative colitis, or prior exposure to anti-TNFα agents, in patients with psoriatic arthritis or Crohn's disease or by prior exposure to biologics (i.e. anti-TNFα agents and/or vedolizumab) in patients with ulcerative colitis.

The results of an *in vitro* study do not suggest the need for dose adjustments in patients who are receiving concomitant CYP450 substrates (see section 5.2).

In psoriasis studies, the safety and efficacy of STELARA in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of STELARA. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of STELARA. (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use effective methods of contraception during treatment and for at least 15 weeks after treatment.

Pregnancy
There are no adequate data from the use of ustekinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of STELARA in pregnancy.

Breast-feeding
It is unknown whether ustekinumab is excreted in human breast milk. Animal studies have shown excretion of ustekinumab at low levels in breast milk. It is not known if ustekinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from ustekinumab, a decision on whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with STELARA must be made taking into account the benefit of breast-feeding to the child and the benefit of STELARA therapy to the woman.

Fertility
The effect of ustekinumab on human fertility has not been evaluated (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions (> 5%) in controlled periods of the adult psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies with ustekinumab were nasopharyngitis

and headache. Most were considered to be mild and did not necessitate discontinuation of study treatment. The most serious adverse reaction that has been reported for STELARA is serious hypersensitivity reactions including anaphylaxis (see section 4.4). The overall safety profile was similar for patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

Tabulated list of adverse reactions

The safety data described below reflect exposure in adults to ustekinumab in 14 phase 2 and phase 3 studies in 6,709 patients (4,135 with psoriasis and/or psoriatic arthritis, 1,749 with Crohn's disease and 825 patients with ulcerative colitis). This includes exposure to STELARA in the controlled and non-controlled periods of the clinical studies for at least 6 months or 1 year (4,577 and 3,253 patients respectively with psoriasis, psoriatic arthritis, Crohn's disease or ulcerative colitis) and exposure for at least 4 or 5 years (1,482 and 838 patients with psoriasis respectively).

Table 3 provides a list of adverse reactions from adult psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies as well as adverse reactions reported from post-marketing experience. The adverse reactions are classified by System Organ Class and frequency, using the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3 List of adverse reactions

System Organ Class	**Frequency: Adverse reaction**
Infections and infestations	Common: Upper respiratory tract infection, nasopharyngitis, sinusitis Uncommon: Cellulitis, dental infections, herpes zoster, lower respiratory tract infection, viral upper respiratory tract infection, vulvovaginal mycotic infection
Immune system disorders	Uncommon: Hypersensitivity reactions (including rash, urticaria) Rare: Serious hypersensitivity reactions (including anaphylaxis, angioedema)
Psychiatric disorders	Uncommon: Depression
Nervous system disorders	Common: Dizziness, headache Uncommon: Facial palsy
Respiratory, thoracic and mediastinal disorders	Common: Oropharyngeal pain Uncommon: Nasal congestion Rare: Allergic alveolitis, eosinophilic pneumonia Very rare: Organising pneumonia*
Gastrointestinal disorders	Common: Diarrhoea, nausea, vomiting
Skin and subcutaneous tissue disorders	Common: Pruritus Uncommon: Pustular psoriasis, skin exfoliation, acne Rare: Exfoliative dermatitis
Musculoskeletal and connective tissue disorders	Common: Back pain, myalgia, arthralgia
General disorders and administration site conditions	Common: Fatigue, injection site erythema, injection site pain Uncommon: Injection site reactions (including haemorrhage, haematoma, induration, swelling and pruritus), asthenia

* See section 4.4, Systemic and respiratory hypersensitivity reactions.

Description of selected adverse reactions

Infections

In the placebo-controlled studies of patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis, the rates of infection or serious infection were similar between ustekinumab-treated patients and those treated with placebo. In the placebo-controlled period of these clinical studies, the rate of infection was 1.36 per patient-year of follow-up in ustekinumab-treated patients, and 1.34 in placebo-treated patients. Serious infections occurred at the rate of 0.03 per patient-year of follow-up in ustekinumab-treated patients (30 serious infections in 930 patient-years of follow-up) and 0.03 in placebo-treated patients (15 serious infections in 434 patient-years of follow-up) (see section 4.4).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 11,581 patient-years of exposure in 6,709 patients, the median follow up was 1.0 years; 1.1 years for psoriatic disease studies, 0.6 year for Crohn's disease studies, and 1.0 years for ulcerative colitis studies. The rate of infection was 0.91 per patient-year of follow-up in ustekinumab-treated patients, and the rate of serious infections was 0.02 per patient-year of follow-up in ustekinumab-treated patients (199 serious infections in 11,581 patient-years of follow-up) and serious infections reported included pneumonia, anal abscess, cellulitis, diverticulitis, gastroenteritis and viral infections.

In clinical studies, patients with latent tuberculosis who were concurrently treated with isoniazid did not develop tuberculosis.

Malignancies

In the placebo-controlled period of the psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.11 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in 929 patient-years of follow-up) compared with 0.23 for placebo-treated patients (1 patient in 434 patient-years of follow-up). The incidence of non-melanoma skin cancer was 0.43 per 100 patient-years of follow-up for ustekinumab-treated patients (4 patients in 929 patient-years of follow-up) compared to 0.46 for placebo-treated patients (2 patients in 433 patient-years of follow-up).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 11,561 patient-years of exposure in 6,709 patients, the median follow-up was 1.0 years; 1.1 years for psoriatic disease studies, 0.6 year for Crohn's disease studies and 1.0 years for ulcerative colitis studies. Malignancies excluding non-melanoma skin cancers were reported in 62 patients in 11,561 patient-years of follow-up (incidence of 0.54 per 100 patient-years of follow-up for ustekinumab-treated patients). The incidence of malignancies reported in ustekinumab-treated patients was comparable to the incidence expected in the general population (standardised incidence ratio = 0.93 [95% confidence interval: 0.71, 1.20], adjusted for age, gender and race). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, colorectal, melanoma and breast cancers. The incidence of non-melanoma skin cancer was 0.49 per 100 patient-years of follow-up for ustekinumab-treated patients (56 patients in 11,545 patient-years of follow-up). The ratio of patients with basal versus squamous cell skin cancers (3:1) is comparable with the ratio expected in the general population (see section 4.4).

Hypersensitivity reactions

During the controlled periods of the psoriasis and psoriatic arthritis clinical studies of ustekinumab, rash and urticaria have each been observed in < 1% of patients (see section 4.4).

Paediatric population

Paediatric patients 6 years and older with plaque psoriasis

The safety of ustekinumab has been studied in two phase 3 studies of paediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks and the second study was in 44 patients from 6 to 11 years of age treated for up to 56 weeks. In general, the adverse events reported in these two studies with safety data up to 1 year were similar to those seen in previous studies in adults with plaque psoriasis.

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

4.9 Overdose

Single doses up to 6 mg/kg have been administered intravenously in clinical studies without dose-limiting toxicity. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC05.

Mechanism of action
Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines participate in immune functions; IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype, IL-23 induces the T helper 17 (Th17) pathway. However, abnormal regulation of IL 12 and IL 23 has been associated with immune mediated diseases, such as psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.

In patients with Crohn's disease and ulcerative colitis, treatment with ustekinumab resulted in a decrease in inflammatory markers including C-Reactive Protein (CRP) and fecal calprotectin during the induction phase, which were then maintained throughout the maintenance phase.

Immunisation
During the long term extension of Psoriasis Study 2 (PHOENIX 2), adult patients treated with STELARA for at least 3.5 years mounted similar antibody responses to both pneumococcal polysaccharide and tetanus vaccines as a non-systemically treated psoriasis control group. Similar proportions of adult patients developed protective levels of anti-pneumococcal and anti-tetanus antibodies and antibody titers were similar among STELARA-treated and control patients.

Clinical efficacy

Plaque psoriasis (Adults)
The safety and efficacy of ustekinumab was assessed in 1,996 patients in two randomised, double-blind, placebo-controlled studies in patients with moderate to severe plaque psoriasis and who were candidates for phototherapy or systemic therapy. In addition, a randomised, blinded assessor, active-controlled study compared ustekinumab and etanercept in patients with moderate to severe

plaque psoriasis who had had an inadequate response to, intolerance to, or contraindication to ciclosporin, MTX, or PUVA.

Psoriasis Study 1 (PHOENIX 1) evaluated 766 patients. 53% of these patients were either non-responsive, intolerant, or had a contraindication to other systemic therapy. Patients randomised to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4 and followed by the same dose every 12 weeks. Patients randomised to receive placebo at Weeks 0 and 4 crossed over to receive ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16 followed by dosing every 12 weeks. Patients originally randomised to ustekinumab who achieved Psoriasis Area and Severity Index 75 response (PASI improvement of at least 75% relative to baseline) at both Weeks 28 and 40 were re-randomised to receive ustekinumab every 12 weeks or to placebo (i.e., withdrawal of therapy). Patients who were re-randomised to placebo at week 40 reinitiated ustekinumab at their original dosing regimen when they experienced at least a 50% loss of their PASI improvement obtained at week 40. All patients were followed for up to 76 weeks following first administration of study treatment.

Psoriasis Study 2 (PHOENIX 2) evaluated 1,230 patients. 61% of these patients were either non-responsive, intolerant, or had a contraindication to other systemic therapy. Patients randomised to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4 followed by an additional dose at 16 weeks. Patients randomised to receive placebo at Weeks 0 and 4 crossed over to receive ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16. All patients were followed for up to 52 weeks following first administration of study treatment.

Psoriasis Study 3 (ACCEPT) evaluated 903 patients with moderate to severe psoriasis who inadequately responded to, were intolerant to, or had a contraindication to other systemic therapy and compared the efficacy of ustekinumab to etanercept and evaluated the safety of ustekinumab and etanercept. During the 12-week active-controlled portion of the study, patients were randomised to receive etanercept (50 mg twice a week), ustekinumab 45 mg at Weeks 0 and 4, or ustekinumab 90 mg at Weeks 0 and 4.

Baseline disease characteristics were generally consistent across all treatment groups in Psoriasis Studies 1 and 2 with a median baseline PASI score from 17 to 18, median baseline Body Surface Area (BSA) ≥ 20, and median Dermatology Life Quality Index (DLQI) range from 10 to 12. Approximately one third (Psoriasis Study 1) and one quarter (Psoriasis Study 2) of subjects had Psoriatic Arthritis (PsA). Similar disease severity was also seen in Psoriasis Study 3.

The primary endpoint in these studies was the proportion of patients who achieved PASI 75 response from baseline at week 12 (see Tables 4 and 5).

Table 4 Summary of clinical response in Psoriasis Study 1 (PHOENIX 1) and Psoriasis Study 2 (PHOENIX 2)

	Week 12 2 doses (week 0 and week 4)			Week 28 3 doses (week 0, week 4 and week 16)	
	PBO	45 mg	90 mg	45 mg	90 mg
Psoriasis Study 1					
Number of patients randomised	255	255	256	250	243
PASI 50 response N (%)	26 (10%)	213 (84%)[a]	220 (86%)[a]	228 (91%)	234 (96%)
PASI 75 response N (%)	8 (3%)	171 (67%)[a]	170 (66%)[a]	178 (71%)	191 (79%)
PASI 90 response N (%)	5 (2%)	106 (42%)[a]	94 (37%)[a]	123 (49%)	135 (56%)
PGA[b] of cleared or minimal N (%)	10 (4%)	151 (59%)[a]	156 (61%)[a]	146 (58%)	160 (66%)
Number of patients ≤ 100 kg	166	168	164	164	153
PASI 75 response N (%)	6 (4%)	124 (74%)	107 (65%)	130 (79%)	124 (81%)
Number of patients > 100 kg	89	87	92	86	90
PASI 75 response N (%)	2 (2%)	47 (54%)	63 (68%)	48 (56%)	67 (74%)

Psoriasis Study 2					
Number of patients randomised	410	409	411	397	400
PASI 50 response N (%)	41 (10%)	342 (84%)[a]	367 (89%)[a]	369 (93%)	380 (95%)
PASI 75 response N (%)	15 (4%)	273 (67%)[a]	311 (76%)[a]	276 (70%)	314 (79%)
PASI 90 response N (%)	3 (1%)	173 (42%)[a]	209 (51%)[a]	178 (45%)	217 (54%)
PGA[b] of cleared or minimal N (%)	18 (4%)	277 (68%)[a]	300 (73%)[a]	241 (61%)	279 (70%)
Number of patients ≤ 100 kg	290	297	289	287	280
PASI 75 response N (%)	12 (4%)	218 (73%)	225 (78%)	217 (76%)	226 (81%)
Number of patients > 100 kg	120	112	121	110	119
PASI 75 response N (%)	3 (3%)	55 (49%)	86 (71%)	59 (54%)	88 (74%)

[a] $p < 0.001$ for ustekinumab 45 mg or 90 mg in comparison with placebo (PBO).

[b] PGA = Physician Global Assessment

Table 5 Summary of clinical response at week 12 in Psoriasis Study 3 (ACCEPT)

	Psoriasis Study 3		
	Etanercept 24 doses (50 mg twice a week)	Ustekinumab 2 doses (week 0 and week 4)	
		45 mg	90 mg
Number of patients randomised	347	209	347
PASI 50 response N (%)	286 (82%)	181 (87%)	320 (92%)[a]
PASI 75 response N (%)	197 (57%)	141 (67%)[b]	256 (74%)[a]
PASI 90 response N (%)	80 (23%)	76 (36%)[a]	155 (45%)[a]
PGA of cleared or minimal N (%)	170 (49%)	136 (65%)[a]	245 (71%)[a]
Number of patients ≤ 100 kg	251	151	244
PASI 75 response N (%)	154 (61%)	109 (72%)	189 (77%)
Number of patients > 100 kg	96	58	103
PASI 75 response N (%)	43 (45%)	32 (55%)	67 (65%)

[a] $p < 0.001$ for ustekinumab 45 mg or 90 mg in comparison with etanercept.

[b] $p = 0.012$ for ustekinumab 45 mg in comparison with etanercept.

In Psoriasis Study 1 maintenance of PASI 75 was significantly superior with continuous treatment compared with treatment withdrawal ($p < 0.001$). Similar results were seen with each dose of ustekinumab. At 1 year (week 52), 89% of patients re-randomised to maintenance treatment were PASI 75 responders compared with 63% of patients re-randomised to placebo (treatment withdrawal) ($p < 0.001$). At 18 months (week 76), 84% of patients re-randomised to maintenance treatment were PASI 75 responders compared with 19% of patients re-randomised to placebo (treatment withdrawal). At 3 years (week 148), 82% of patients re-randomised to maintenance treatment were PASI 75 responders. At 5 years (week 244), 80% of patients re-randomised to maintenance treatment were PASI 75 responders.

In patients re-randomised to placebo, and who reinitiated their original ustekinumab treatment regimen after loss of ≥ 50% of PASI improvement 85% regained PASI 75 response within 12 weeks after re-initiating therapy.

In Psoriasis Study 1, at week 2 and week 12, significantly greater improvements from baseline were demonstrated in the DLQI in each ustekinumab treatment group compared with placebo. The improvement was sustained through week 28. Similarly, significant improvements were seen in Psoriasis Study 2 at week 4 and 12, which were sustained through week 24. In Psoriasis Study 1, improvements in nail psoriasis (Nail Psoriasis Severity Index), in the physical and mental component summary scores of the SF-36 and in the Itch Visual Analogue Scale (VAS) were also significant in each ustekinumab treatment group compared with placebo. In Psoriasis Study 2, the Hospital Anxiety and Depression Scale (HADS) and Work Limitations Questionnaire (WLQ) were also significantly improved in each ustekinumab treatment group compared with placebo.

Psoriatic arthritis (PsA) (Adults)
Ustekinumab has been shown to improve signs and symptoms, physical function and health-related quality of life, and reduce the rate of progression of peripheral joint damage in adult patients with active PsA.

The safety and efficacy of ustekinumab was assessed in 927 patients in two randomised, double-blind, placebo-controlled studies in patients with active PsA (≥ 5 swollen joints and ≥ 5 tender joints) despite non-steroidal anti-inflammatory (NSAID) or disease modifying antirheumatic (DMARD) therapy. Patients in these studies had a diagnosis of PsA for at least 6 months. Patients with each subtype of PsA were enrolled, including polyarticular arthritis with no evidence of rheumatoid nodules (39%), spondylitis with peripheral arthritis (28%), asymmetric peripheral arthritis (21%), distal interphalangeal involvement (12%) and arthritis mutilans (0.5%). Over 70% and 40% of the patients in both studies had enthesitis and dactylitis at baseline, respectively. Patients were randomised to receive treatment with ustekinumab 45 mg, 90 mg, or placebo subcutaneously at Weeks 0 and 4 followed by every 12 weeks (q12w) dosing. Approximately 50% of patients continued on stable doses of MTX (≤ 25 mg/week).

In PsA Study 1 (PSUMMIT I) and PsA Study 2 (PSUMMIT II), 80% and 86% of the patients, respectively, had been previously treated with DMARDs. In Study 1 previous treatment with anti-tumour necrosis factor (TNF)α agent was not allowed. In Study 2, the majority of patients (58%, n = 180) had been previously treated with one or more anti-TNFα agent(s), of whom over 70% had discontinued their anti-TNFα treatment for lack of efficacy or intolerance at any time.

Signs and symptoms
Treatment with ustekinumab resulted in significant improvements in the measures of disease activity compared to placebo at week 24. The primary endpoint was the percentage of patients who achieved American College of Rheumatology (ACR) 20 response at week 24. The key efficacy results are shown in Table 6 below.

Table 6 Number of patients who achieved clinical response in Psoriatic arthritis Study 1 (PSUMMIT I) and Study 2 (PSUMMIT II) at week 24

	Psoriatic arthritis Study 1			**Psoriatic arthritis Study 2**		
	PBO	**45 mg**	**90 mg**	**PBO**	**45 mg**	**90 mg**
Number of patients randomised	**206**	**205**	**204**	**104**	**103**	**105**
ACR 20 response, N (%)	47 (23%)	87 (42%)[a]	101 (50%)[a]	21 (20%)	45 (44%)[a]	46 (44%)[a]
ACR 50 response, N (%)	18 (9%)	51 (25%)[a]	57 (28%)[a]	7 (7%)	18 (17%)[b]	24 (23%)[a]
ACR 70 response, N (%)	5 (2%)	25 (12%)[a]	29 (14%)[a]	3 (3%)	7 (7%)[c]	9 (9%)[c]
Number of patients with ≥ 3% BSA[d]	146	145	149	80	80	81
PASI 75 response, N (%)	16 (11%)	83 (57%)[a]	93 (62%)[a]	4 (5%)	41 (51%)[a]	45 (56%)[a]
PASI 90 response, N (%)	4 (3%)	60 (41%)[a]	65 (44%)[a]	3 (4%)	24 (30%)[a]	36 (44%)[a]
Combined PASI 75 and ACR 20 response, N (%)	8 (5%)	40 (28%)[a]	62 (42%)[a]	2 (3%)	24 (30%)[a]	31 (38%)[a]
Number of patients ≤ 100 kg	154	153	154	74	74	73
ACR 20 response, N (%)	39 (25%)	67 (44%)	78 (51%)	17 (23%)	32 (43%)	34 (47%)

Number of patients with ≥ 3% BSA[d]	105	105	111	54	58	57
PASI 75 response, N (%)	14 (13%)	64 (61%)	73 (66%)	4 (7%)	31 (53%)	32 (56%)
Number of patients > 100 kg	52	52	50	30	29	31
ACR 20 response, N (%)	8 (15%)	20 (38%)	23 (46%)	4 (13%)	13 (45%)	12 (39%)
Number of patients with ≥ 3% BSA[d]	41	40	38	26	22	24
PASI 75 response, N (%)	2 (5%)	19 (48%)	20 (53%)	0	10 (45%)	13 (54%)

[a] $p < 0.001$

[b] $p < 0.05$

[c] p = NS

[d] Number of patients with ≥ 3% BSA psoriasis skin involvement at baseline

ACR 20, 50 and 70 responses continued to improve or were maintained through week 52 (PsA Study 1 and 2) and week 100 (PsA Study 1). In PsA Study 1, ACR 20 responses at week 100 were achieved by 57% and 64%, for 45 mg and 90 mg, respectively. In PsA Study 2, ACR 20 responses at week 52 were achieved by 47% and 48%, for 45 mg and 90 mg, respectively.

The proportion of patients achieving a modified PsA response criteria (PsARC) response was also significantly greater in the ustekinumab groups compared to placebo at week 24. PsARC responses were maintained through weeks 52 and 100. A higher proportion of patients treated with ustekinumab who had spondylitis with peripheral arthritis as their primary presentation, demonstrated 50 and 70 percent improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores compared with placebo at week 24.

Responses observed in the ustekinumab treated groups were similar in patients receiving and not receiving concomitant MTX, and were maintained through weeks 52 and 100. Patients previously treated with anti-TNFα agents who received ustekinumab achieved a greater response at week 24 than patients receiving placebo (ACR 20 response at week 24 for 45 mg and 90 mg was 37% and 34%, respectively, compared with placebo 15%; $p < 0.05$), and responses were maintained through week 52.

For patients with enthesitis and/or dactylitis at baseline, in PsA Study 1 significant improvement in enthesitis and dactylitis score was observed in the ustekinumab groups compared with placebo at week 24. In PsA Study 2 significant improvement in enthesitis score and numerical improvement (not statistically significant) in dactylitis score was observed in the ustekinumab 90 mg group compared with placebo at week 24. Improvements in enthesitis score and dactylitis score were maintained through weeks 52 and 100.

Radiographic Response

Structural damage in both hands and feet was expressed as change in total van der Heijde-Sharp score (vdH-S score), modified for PsA by addition of hand distal interphalangeal joints, compared to baseline. A pre-specified integrated analysis combining data from 927 subjects in both PsA Study 1 and 2 was performed. Ustekinumab demonstrated a statistically significant decrease in the rate of progression of structural damage compared to placebo, as measured by change from baseline to week 24 in the total modified vdH-S score (mean ± SD score was 0.97 ± 3.85 in the placebo group compared with 0.40 ± 2.11 and 0.39 ± 2.40 in the ustekinumab 45 mg ($p < 0.05$) and 90 mg ($p < 0.001$) groups, respectively). This effect was driven by PsA Study 1. The effect is considered demonstrated irrespective of concomitant MTX use, and was maintained through Weeks 52 (integrated analysis) and 100 (PsA Study 1).

Physical function and health-related quality of life

Ustekinumab-treated patients showed significant improvement in physical function as assessed by the Disability Index of the Health Assessment Questionnaire (HAQ-DI) at week 24. The proportion of patients achieving a clinically meaningful ≥ 0.3 improvement in HAQ-DI score from baseline was also

significantly greater in the ustekinumab groups when compared with placebo. Improvement in HAQ-DI score from baseline was maintained through Weeks 52 and 100.

There was significant improvement in DLQI scores in the ustekinumab groups as compared with placebo at week 24, which was maintained through weeks 52 and 100. In PsA Study 2 there was a significant improvement in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores in the ustekinumab groups when compared with placebo at week 24. The proportion of patients achieving a clinically significant improvement in fatigue (4 points in FACIT-F) was also significantly greater in the ustekinumab groups compared with placebo. Improvements in FACIT scores were maintained through week 52.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with ustekinumab in one or more subsets of the paediatric population with juvenile idiopathic arthritis (see section 4.2 for information on paediatric use).

Paediatric plaque psoriasis

Ustekinumab has been shown to improve signs and symptoms, and health related quality of life in paediatric patients 6 years and older with plaque psoriasis.

Adolescent patients (12-17 years)

The efficacy of ustekinumab was studied in 110 paediatric patients aged 12 to 17 years with moderate to severe plaque psoriasis in a multicenter, phase 3, randomised, double blind, placebo controlled study (CADMUS). Patients were randomised to receive either placebo (n = 37), or the recommended dose of ustekinumab (see section 4.2; n = 36) or half of the recommended dose of ustekinumab (n = 37) by subcutaneous injection at Weeks 0 and 4 followed by every 12 week (q12w) dosing. At week 12, placebo treated patients crossed over to receive ustekinumab.

Patients with PASI ≥ 12, PGA ≥ 3 and BSA involvement of at least 10%, who were candidates for systemic therapy or phototherapy, were eligible for the study. Approximately 60% of the patients had prior exposure to conventional systemic therapy or phototherapy. Approximately 11% of the patients had prior exposure to biologics.

The primary endpoint was the proportion of patients who achieved a PGA score of cleared (0) or minimal (1) at week 12. Secondary endpoints included PASI 75, PASI 90, change from baseline in Children's Dermatology Life Quality Index (CDLQI), change from baseline in the total scale score of PedsQL (Paediatric Quality of Life Inventory) at week 12. At week 12, subjects treated with ustekinumab showed significantly greater improvement in their psoriasis and health related quality of life compared with placebo (Table 7).

All patients were followed for efficacy for up to 52 weeks following first administration of study agent. The proportion of patients with a PGA score of cleared (0) or minimal (1) and the proportion achieving PASI 75 showed separation between the ustekinumab treated group and placebo at the first post-baseline visit at week 4, reaching a maximum by week 12. Improvements in PGA, PASI, CDLQI and PedsQL were maintained through week 52 (Table 7).

Table 7 Summary of primary and secondary endpoints at week 12 and week 52

Paediatric psoriasis study (CADMUS) (Age 12-17)			
	Week 12		**Week 52**
	Placebo	Recommended dose of Ustekinumab	Recommended dose of Ustekinumab
	N (%)	N (%)	N (%)
Patients randomised	37	36	35
PGA			
PGA of cleared (0) or minimal (1)	2 (5.4%)	25 (69.4%)[a]	20 (57.1%)

PGA of Cleared (0)	1 (2.7%)	17 (47.2%)[a]	13 (37.1%)
PASI			
PASI 75 responders	4 (10.8%)	29 (80.6%)[a]	28 (80.0%)
PASI 90 responders	2 (5.4%)	22 (61.1%)[a]	23 (65.7%)
PASI 100 responders	1 (2.7%)	14 (38.9%)[a]	13 (37.1%)
CDLQI			
CDLQI of 0 or 1[b]	6 (16.2%)	18 (50.0%)[c]	20 (57.1%)
PedsQL			
Change from baseline Mean (SD)[d]	3.35 (10.04)	8.03 (10.44)[e]	7.26 (10.92)

[a] $p < 0.001$

[b] CDLQI: The CDLQI is a dermatology instrument to assess the effect of a skin problem on the health-related quality of life in the paediatric population. CDLQI of 0 or 1 indicates no effect on child's quality of life.

[c] $p = 0.002$

[d] PedsQL: The PedsQL Total Scale Score is a general health-related quality of life measure developed for use in children and adolescent populations. For the placebo group at week 12, N = 36

[e] $p = 0.028$

During the placebo controlled period through week 12, the efficacy of both the recommended and half of the recommended dose groups were generally comparable at the primary endpoint (69.4% and 67.6% respectively) although there was evidence of a dose response for higher level efficacy criteria (e.g. PGA of cleared (0), PASI 90). Beyond week 12, efficacy was generally higher and better sustained in the recommended dose group compared with half of the recommended dosage group in which a modest loss of efficacy was more frequently observed toward the end of each 12 week dosing interval. The safety profiles of the recommended dose and half of the recommended dose were comparable.

Children (6-11 years)
The efficacy of ustekinumab was studied in 44 paediatric patients aged 6 to 11 years with moderate to severe plaque psoriasis in an open label, single-arm, multicenter, phase 3, study (CADMUS Jr.). Patients were treated with the recommended dose of ustekinumab (see section 4.2; n = 44) by subcutaneous injection at weeks 0 and 4 followed by every 12 week (q12w) dosing.

Patients with PASI ≥ 12, PGA ≥ 3 and BSA involvement of at least 10%, who were candidates for systemic therapy or phototherapy, were eligible for the study. Approximately 43% of the patients had prior exposure to conventional systemic therapy or phototherapy. Approximately 5% of the patients had prior exposure to biologics.

The primary endpoint was the proportion of patients who achieved a PGA score of cleared (0) or minimal (1) at week 12. Secondary endpoints included PASI 75, PASI 90, and change from baseline in Children's Dermatology Life Quality Index (CDLQI) at week 12. At week 12, subjects treated with ustekinumab showed clinically meaningful improvements in their psoriasis and health related quality of life (Table 8).

All patients were followed for efficacy for up to 52 weeks following first administration of study agent. The proportion of patients with a PGA score of cleared (0) or minimal (1) at week 12 was 77.3%. Efficacy (defined as PGA 0 or 1) was observed as early as the first post-baseline visit at week 4 and the proportion of subjects who achieved a PGA score of 0 or 1 increased through week 16 and then remained relatively stable through week 52. Improvements in PGA, PASI, and CDLQI were maintained through week 52 (Table 8).

Table 8 Summary of primary and secondary endpoints at week 12 and week 52

Paediatric psoriasis study (CADMUS Jr.) (Age 6-11)		
	Week 12	**Week 52**
	Recommended dose of Ustekinumab	Recommended dose of Ustekinumab

	N (%)	N (%)
Patients enrolled	44	41
PGA		
PGA of cleared (0) or minimal (1)	34 (77.3%)	31 (75.6%)
PGA of cleared (0)	17 (38.6%)	23 (56.1%)
PASI		
PASI 75 responders	37 (84.1%)	36 (87.8%)
PASI 90 responders	28 (63.6%)	29 (70.7%)
PASI 100 responders	15 (34.1%)	22 (53.7%)
CDLQI[a]		
Patients with a CDLQI > 1 at baseline	(N=39)	(N=36)
CDLQI of 0 or 1	24 (61.5%)	21 (58.3%)

[a] CDLQI: The CDLQI is a dermatology instrument to assess the effect of a skin problem on the health-related quality of life in the paediatric population. CDLQI of 0 or 1 indicates no effect on child's quality of life.

Crohn's Disease

The safety and efficacy of ustekinumab was assessed in three randomized, double-blind, placebo-controlled, multicenter studies in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of ≥ 220 and ≤ 450). The clinical development program consisted of two 8-week intravenous induction studies (UNITI-1 and UNITI-2) followed by a 44 week subcutaneous randomized withdrawal maintenance study (IM-UNITI) representing 52 weeks of therapy.

The induction studies included 1409 (UNITI-1, n = 769; UNITI-2 n = 640) patients. The primary endpoint for both induction studies was the proportion of subjects in clinical response (defined as a reduction in CDAI score of ≥ 100 points) at week 6. Efficacy data were collected and analyzed through week 8 for both studies. Concomitant doses of oral corticosteroids, immunomodulators, aminosalicylates and antibiotics were permitted and 75% of patients continued to receive at least one of these medications. In both studies, patients were randomised to receive a single intravenous administration of either the recommended tiered dose of approximately 6 mg/kg (see section 4.2 of the STELARA 130 mg Concentrate for solution for infusion SmPC), a fixed dose of 130 mg ustekinumab, or placebo at week 0.

Patients in UNITI-1 had failed or were intolerant to prior anti-TNFα therapy. Approximately 48% of the patients had failed 1 prior anti-TNFα therapy and 52% had failed 2 or 3 prior anti-TNFα therapies. In this study, 29.1% of the patients had an inadequate initial response (primary non-responders), 69.4% responded but lost response (secondary non-responders), and 36.4% were intolerant to anti-TNFα therapies.

Patients in UNITI-2 had failed at least one conventional therapy, including corticosteroids or immunomodulators, and were either anti-TNF-α naïve (68.6%) or had previously received but not failed anti-TNFα therapy (31.4%).

In both UNITI-1 and UNITI-2, a significantly greater proportion of patients were in clinical response and remission in the ustekinumab treated group compared to placebo (Table 9). Clinical response and remission were significant as early as week 3 in ustekinumab treated patients and continued to improve through week 8. In these induction studies, efficacy was higher and better sustained in the tiered dose group compared to the 130 mg dose group, and tiered dosing is therefore the recommended intravenous induction dose.

Table 9: Induction of Clinical Response and Remission in UNITI-1 and UNITI 2

	UNITI-1*		UNITI-2**	
	Placebo N = 247	**Recommended dose of ustekinumab N = 249**	**Placebo N = 209**	**Recommended dose of ustekinumab N = 209**
Clinical Remission, week 8	18 (7.3%)	52 (20.9%)[a]	41 (19.6%)	84 (40.2%)[a]
Clinical Response (100 point), week 6	53 (21.5%)	84 (33.7%)[b]	60 (28.7%)	116 (55.5%)[a]
Clinical Response (100 point), week 8	50 (20.2%)	94 (37.8%)[a]	67 (32.1%)	121 (57.9%)[a]
70 Point Response, week 3	67 (27.1%)	101 (40.6%)[b]	66 (31.6%)	106 (50.7%)[a]
70 Point Response, week 6	75 (30.4%)	109 (43.8%)[b]	81 (38.8%)	135 (64.6%)[a]

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission

70 point response is defined as reduction in CDAI score by at least 70 points

* Anti-TNFα failures

** Conventional therapy failures

[a] $p < 0.001$

[b] $p < 0.01$

The maintenance study (IM-UNITI), evaluated 388 patients who achieved 100 point clinical response at week 8 of induction with ustekinumab in studies UNITI-1 and UNITI-2. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks (for recommended maintenance posology, see section 4.2).

Significantly higher proportions of patients maintained clinical remission and response in the ustekinumab treated groups compared to the placebo group at week 44 (see Table 10).

Table 10: Maintenance of Clinical Response and Remission in IM-UNITI (week 44; 52 weeks from initiation of the induction dose)

	Placebo* N = 131†	**90 mg ustekinumab every 8 weeks N = 128†**	**90 mg ustekinumab every 12 weeks N = 129†**
Clinical Remission	36%	53%[a]	49%[b]
Clinical Response	44%	59%[b]	58%[b]
Corticosteroid-Free Clinical Remission	30%	47%[a]	43%[c]
Clinical Remission in patients:			
in remission at the start of maintenance therapy	46% (36/79)	67% (52/78)[a]	56% (44/78)
who entered from study CRD3002‡	44% (31/70)	63% (45/72)[c]	57% (41/72)
who are Anti-TNFα naïve	49% (25/51)	65% (34/52)[c]	57% (30/53)
who entered from study CRD3001§	26% (16/61)	41% (23/56)	39% (22/57)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission

* The placebo group consisted of patients who were in response to ustekinumab and were randomized to receive placebo at the start of maintenance therapy.

† Patients who were in 100 point clinical response to ustekinumab at start of maintenance therapy

‡ Patients who failed conventional therapy but not anti-TNFα therapy

§ Patients who are anti-TNFα refractory/intolerant

[a] $p < 0.01$

[b] $p < 0.05$

[c] nominally significant ($p < 0.05$)

In IM-UNITI, 29 of 129 patients did not maintain response to ustekinumab when treated every 12 weeks and were allowed to dose adjust to receive ustekinumab every 8 weeks. Loss of response

was defined as a CDAI score ≥ 220 points and a ≥ 100 point increase from the CDAI score at baseline. In these patients, clinical remission was achieved in 41.4% of patients 16 weeks after dose adjustment.

Patients who were not in clinical response to ustekinumab induction at week 8 of the UNITI-1 and UNITI-2 induction studies (476 patients) entered into the non-randomized portion of the maintenance study (IM-UNITI) and received a 90 mg subcutaneous injection of ustekinumab at that time. Eight weeks later, 50.5% of the patients achieved clinical response and continued to receive maintenance dosing every 8 weeks; among these patients with continued maintenance dosing, a majority maintained response (68.1%) and achieved remission (50.2%) at week 44, at proportions that were similar to the patients who initially responded to ustekinumab induction.

Of 131 patients who responded to ustekinumab induction, and were randomized to the placebo group at the start of the maintenance study, 51 subsequently lost response and received 90 mg ustekinumab subcutaneously every 8 weeks. The majority of patients who lost response and resumed ustekinumab did so within 24 weeks of the induction infusion. Of these 51 patients, 70.6% achieved clinical response and 39.2% percent achieved clinical remission 16 weeks after receiving the first subcutaneous dose of ustekinumab.

In IM-UNITI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among patients who entered the study extension, clinical remission and response were generally maintained through week 92 for both patients who failed TNF-therapies and those who failed conventional therapies.

No new safety concerns were identified in this study extension with up to 2 years of treatment in patients with Crohn's Disease.

Endoscopy
Endoscopic appearance of the mucosa was evaluated in 252 patients with eligible baseline endoscopic disease activity in a substudy. The primary endpoint was change from baseline in Simplified Endoscopic Disease Severity Score for Crohn's Disease (SES-CD), a composite score across 5 ileo-colonic segments of presence/size of ulcers, proportion of mucosal surface covered by ulcers, proportion of mucosal surface affected by any other lesions and presence/type of narrowing/strictures. At week 8, after a single intravenous induction dose, the change in SES-CD score was greater in the ustekinumab group (n = 155, mean change = -2.8) than in the placebo group (n = 97, mean change = -0.7, p = 0.012).

Fistula Response
In a subgroup of patients with draining fistulas at baseline (8.8%; n = 26), 12/15 (80%) of ustekinumab-treated patients achieved a fistula response over 44 weeks (defined as ≥ 50% reduction from baseline of the induction study in the number of draining fistulas) compared to 5/11 (45.5%) exposed to placebo.

Health-related quality of life
Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ) and SF-36 questionnaires. At week 8, patients receiving ustekinumab showed statistically significantly greater and clinically meaningful improvements on IBDQ total score and SF-36 Mental Component Summary Score in both UNITI-1 and UNITI-2, and SF-36 Physical Component Summary Score in UNITI-2, when compared to placebo. These improvements were generally better maintained in ustekinumab-treated patients in the IM-UNITI study through week 44 when compared to placebo. Improvement in health-related quality of life was generally maintained during the extension through week 92.

Ulcerative colitis
The safety and efficacy of ustekinumab was assessed in two randomized, double-blind, placebo-controlled, multicenter studies in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥ 2). The clinical development program consisted of one intravenous induction study (referred to as UNIFI-I) with treatment of up to 16 weeks followed by a

44 week subcutaneous randomized withdrawal maintenance study (referred to as UNIFI-M) representing at least 52 weeks of therapy.

Efficacy results presented for UNIFI-I and UNIFI-M were based on central review of endoscopies.

UNIFI-I included 961 patients. The primary endpoint for the induction study was the proportion of subjects in clinical remission at week 8. Patients were randomised to receive a single intravenous administration of either the recommended tiered dose of approximately 6 mg/kg (see Table 1, section 4.2), a fixed dose of 130 mg ustekinumab, or placebo at week 0.

Concomitant doses of oral corticosteroids, immunomodulators, and aminosalicylates were permitted and 90% of patients continued to receive at least one of these medications. Enrolled patients had to have failed conventional therapy (corticosteroids or immunomodulators) or at least one biologic (a TNFα antagonist and/or vedolizumab). 49% of patients had failed conventional therapy, but not a biologic (of which 94% where biological-naïve). 51% of patients had failed or were intolerant to a biologic. Approximately 50% of the patients had failed at least 1 prior anti-TNFα therapy (of which 48% were primary non-responders) and 17% had failed at least 1 anti-TNFα therapy and vedolizumab.

In UNIFI-I a significantly greater proportion of patients were in clinical remission in the ustekinumab treated group compared to placebo at week 8 (Table 11). As early as Week 2, the earliest scheduled study visit, and at each visit thereafter, a higher proportion of ustekinumab patients had no rectal bleeding or achieved normal stool frequency as compared with placebo patients. Significant differences in partial Mayo score and symptomatic remission were observed between ustekinumab and placebo as early as Week 2.

Efficacy was higher in the tiered dose group (6 mg/kg) compared to the 130 mg dose group in select endpoints, and tiered dosing is therefore the recommended intravenous induction dose.

Table 11: Summary of Key Efficacy Outcomes in UNIFI-I (Week 8)

	Placebo N = 319	**Recommended dose of ustekinumab£ N = 322**
Clinical Remission*	5%	16%[a]
In patients who failed conventional therapy, but not a biologic	9% (15/158)	19% (29/156)[c]
In patients who failed biological therapy¥	1% (2/161)	13% (21/166)[b]
In patients who failed both a TNF and vedolizumab	0% (0/47)	10% (6/58%)[c]
Clinical Response§	31%	62%[a]
In patients who failed conventional therapy, but not a biologic	35% (56/158)	67% (104/156)[b]
In patients who failed biological therapy¥	27% (44/161)	57% (95/166)[b]
In patients who failed both a TNF and vedolizumab	28% (13/47)	52% (30/58)[c]
Mucosal Healing†	14%	27%[a]
In patients who failed conventional therapy, but not a biologic	21% (33/158)	33% (52/156)[c]
In patients who failed biological therapy	7% (11/161)	21% (35/166)[b]
Symptomatic Remission‡	23%	45%[b]
Combined Symptomatic Remission and Mucosal Healing	8%	21%[b]

£ Infusion dose of ustekinumab using the weight-based dosage regimen specified in *Table 1*.

* Clinical remission is defined as Mayo score ≤2 points, with no individual subscore > 1.

§ Clinical response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.

¥ A TNFα antagonist and/or vedolizumab.

† Mucosal healing is defined as a Mayo endoscopic subscore of 0 or 1.

‡ Symptomatic remission is defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.

□ Combined symptomatic remission and mucosal healing is defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.

a $p < 0.001$

b Nominally significant ($p < 0.001$)

c Nominally significant ($p < 0.05$)

UNIFI-M, evaluated 523 patients who achieved clinical response with single IV administration of ustekinumab in UNIFI-I. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks (for recommended maintenance posology, see section 4.2 of the STELARA Solution for injection (vial) and Solution for injection in pre filled syringe SmPC).

Significantly greater proportions of patients were in clinical remission in both ustekinumab treated groups compared to the placebo group at week 44 (see Table 12).

Table 12: Summary of Key Efficacy Measures in UNIFI-M (week 44; 52 weeks from initiation of the induction dose)

	Placebo* **N** = 175	**90 mg ustekinumab every 8 Weeks** **N** = 176	**90 mg ustekinumab every 12 Weeks** **N** = 172
Clinical Remission**	24%	44% [a]	38% [b]
In patients who failed conventional therapy, but not a biologic	31% (27/87)	48% (41/85) [d]	49% (50/102) [d]
In patients who failed biological therapy¥	17% (15/88)	40% (36/91) [c]	23% (16/70) [d]
In patients who failed both a TNF and vedolizumab	15% (4/27)	33% (7/21) [e]	23% (5/22) [e]
Maintenance of Clinical Response through week 44§	45%	71% [a]	68% [a]
In patients who failed conventional therapy, but not a biologic	51% (44/87)	78% (66/85) [c]	77% (78/102) [c]
In patients who failed biological therapy¥	39% (34/88)	65% (59/91) [c]	56% (39/70) [d]
In patients who failed both a TNF and vedolizumab	41% (11/27)	67% (14/21) [e]	50% (11/22) [e]
Mucosal Healing†	29%	51% [a]	44% [b]
Maintenance of Clinical Remission through week 44£	38% (17/45)	58% (22/38)	65% (26/40) [c]
Corticosteroid Free Clinical Remission€	23%	42% [a]	38% [b]
Durable Remission‖	35%	57% [c]	48% [d]
Symptomatic Remission‡	45%	68% [c]	62% [d]
Combined Symptomatic Remission and Mucosal Healing□	28%	48% [c]	41% [d]

* Following response to IV ustekinumab.
** Clinical remission is defined as Mayo score ≤2 points, with no individual subscore > 1.
§ Clinical response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.
¥ A TNFα antagonist and/or vedolizumab.
† Mucosal healing is defined as a Mayo endoscopic sub-score of 0 or 1.
£ Maintenance of clinical remission through Week 44 is defined as patients in clinical remission through Week 44 among patients in clinical remission at maintenance baseline.
€ Corticosteroid-free clinical remission is defined as patients in clinical remission and not receiving corticosteroids at Week 44.
‖ Durable Remission is defined as partial Mayo remission at ≥80% of all visits prior to Week 44 and in partial Mayo remission at last visit (Week 44).
‡ Symptomatic remission is defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.
□ Combined symptomatic remission and mucosal healing is defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
[a] $p < 0.001$
[b] $p < 0.05$
[c] Nominally significant ($p < 0.001$)
[d] Nominally significant ($p < 0.05$)
[e] Not statistically significant

The beneficial effect of ustekinumab on clinical response, mucosal healing and clinical remission was observed in induction and in maintenance both in patients who failed conventional therapy but not a biologic therapy, as well as in those who had failed at least one prior TNFα antagonist therapy including in patients with a primary non-response to TNFα antagonist therapy. A beneficial effect was also observed in induction in patients who failed at least one prior TNFα antagonist therapy and vedolizumab, however the number of patients in this subgroup was too small to draw definitive conclusions about the beneficial effect in this group during maintenance.

Week 16 Responders to Ustekinumab Induction
Ustekinumab treated patients who were not in response at week 8 of UNIFI-I received an administration of 90 mg SC ustekinumab at week 8 (36% of patients). Of those patients, 9% of patients who were initially randomized to the recommended induction dose achieved clinical remission and 58% achieved clinical response at Week 16.

Patients who were not in clinical response to ustekinumab induction at week 8 of the UNFI-I study but were in response at week 16 (157 patients) entered into the non-randomized portion of UNIFI-M and continued to receive maintenance dosing every 8 weeks; among these patients, a majority (62%) maintained response and 30% achieved remission at week 44.

Endoscopic Normalization
Endoscopic normalization was defined as a Mayo endoscopic subscore of 0 and was observed as early as week 8 of UNIFI-I. At week 44 of UNIFI-M, it was achieved in 24% and 29% of patients treated with ustekinumab every 12 or 8 weeks, respectively, as compared to 18% of patients in the placebo group.

Histologic & Histo-Endoscopic Mucosal Healing
Histologic healing (defined as neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue) was assessed at week 8 of UNIFI-I and Week 44 of UNIFI-M. At week 8, after a single intravenous induction dose, significantly greater proportions of patients in the recommended dose group achieved histologic healing (36%) compared with patients in the placebo group (22%). At Week 44 maintenance of this effect was observed with significantly more patients in histologic healing in the every 12 week (54%) and every 8 week (59%) ustekinumab groups as compared to placebo (33%).

A combined endpoint of histo-endoscopic mucosal healing defined as subjects having both mucosal healing and histologic healing was evaluated at week 8 of UNIFI-I and week 44 of UNIFI-M. Patients receiving ustekinumab at the recommended dose showed significant improvements on the histo-

endoscopic mucosal healing endpoint at week 8 in the ustekinumab group (18%) as compared to the placebo group (9%). At week 44, maintenance of this effect was observed with significantly more patients in histo-endoscopic mucosal healing in the every 12 week (39%) and every 8 week (46%) ustekinumab groups as compared to placebo (24%).

Health-related quality of life
Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ), SF-36 and EuroQoL-5D (EQ-5D) questionnaires.

At week 8 of UNIFI-I, patients receiving ustekinumab showed significantly greater and clinically meaningful improvements on IBDQ total score, EQ-5D and EQ-5D VAS, and SF-36 Mental Component Summary Score and SF-36 Physical Component Summary Score when compared to placebo. These improvements were maintained in ustekinumab-treated patients in UNIFI-M through week 44.

Patients receiving ustekinumab experienced significantly more improvements in work productivity as assessed by greater reductions in overall work impairment and in activity impairment as assessed by the WPAI-GH questionnaire than patients receiving placebo.

Hospitalizations and ulcerative colitis (UC) related surgeries
Through week 8 of UNIFI-I, the proportions of subjects with UC disease related hospitalizations were significantly lower for subjects in the ustekinumab recommended dose group (1.6%, 5/322) compared with subjects in the placebo group (4.4%, 14/319) and no subjects underwent UC disease related surgeries in subjects receiving ustekinumab at the recommended induction dose compared to 0.6% (2/319) subjects in the placebo group.

Through week 44 of UNIFI-M, a significantly lower number of UC-related hospitalizations was observed in subjects in the combined ustekinumab group (2.0%, 7/348) as compared with subjects in the placebo group (5.7%, 10/175). A numerically lower number of subjects in the ustekinumab group (0.6%, 2/348) underwent UC disease related surgeries compared with subjects in the placebo group (1.7%, 3/175) through week 44.

Immunogenicity
Antibodies to ustekinumab may develop during ustekinumab treatment and most are neutralising. The formation of anti-ustekinumab antibodies is associated with both increased clearance and reduced efficacy of ustekinumab, except in patients with Crohn's disease or ulcerative colitis where no reduced efficacy was observed. There is no apparent correlation between the presence of anti-ustekinumab antibodies and the occurrence of injection site reactions.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with ustekinumab in one or more subsets of the paediatric population in Crohn's Disease and ulcerative colitis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
The median time to reach the maximum serum concentration (t_{max}) was 8.5 days after a single 90 mg subcutaneous administration in healthy subjects. The median t_{max} values of ustekinumab following a single subcutaneous administration of either 45 mg or 90 mg in patients with psoriasis were comparable to those observed in healthy subjects.

The absolute bioavailability of ustekinumab following a single subcutaneous administration was estimated to be 57.2% in patients with psoriasis.

Distribution
Median volume of distribution during the terminal phase (Vz) following a single intravenous administration to patients with psoriasis ranged from 57 to 83 mL/kg.

Biotransformation
The exact metabolic pathway for ustekinumab is unknown.

Elimination
Median systemic clearance (CL) following a single intravenous administration to patients with psoriasis ranged from 1.99 to 2.34 mL/day/kg. Median half-life ($t_{1/2}$) of ustekinumab was approximately 3 weeks in patients with psoriasis, psoriatic arthritis, Crohn's disease or ulcerative colitis, ranging from 15 to 32 days across all psoriasis and psoriatic arthritis studies. In a population pharmacokinetic analysis, the apparent clearance (CL/F) and apparent volume of distribution (V/F) were 0.465 l/day and 15.7 l, respectively, in patients with psoriasis. The CL/F of ustekinumab was not impacted by gender. Population pharmacokinetic analysis showed that there was a trend towards a higher clearance of ustekinumab in patients who tested positive for antibodies to ustekinumab.

Dose linearity
The systemic exposure of ustekinumab (C_{max} and AUC) increased in an approximately dose-proportional manner after a single intravenous administration at doses ranging from 0.09 mg/kg to 4.5 mg/kg or following a single subcutaneous administration at doses ranging from approximately 24 mg to 240 mg in patients with psoriasis.

Single dose versus multiple doses
Serum concentration-time profiles of ustekinumab were generally predictable after single or multiple subcutaneous dose administrations. In patients with psoriasis, steady-state serum concentrations of ustekinumab were achieved by week 28 after initial subcutaneous doses at Weeks 0 and 4 followed by doses every 12 weeks. The median steady-state trough concentration ranged from 0.21 μg/mL to 0.26 μg/mL (45 mg) and from 0.47 μg/mL to 0.49 μg/mL (90 mg). There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

In patients with Crohn's disease and ulcerative colitis, following an intravenous dose of ~6 mg/kg, starting at week 8, subcutaneous maintenance dosing of 90 mg ustekinumab was administered every 8 or 12 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose. In patients with Crohn's disease, median steady-state trough concentrations ranged from 1.97 μg/mL to 2.24 μg/mL and from 0.61 μg/mL to 0.76 μg/mL for 90 mg ustekinumab every 8 weeks or every 12 weeks respectively. In patients with ulcerative colitis, median steady-state trough concentrations ranged from 2.69 μg/mL to 3.09 μg/mL and from 0.92 μg/mL to 1.19 μg/mL for 90 mg ustekinumab every 8 weeks or every 12 weeks. The steady-state trough ustekinumab levels resulting from 90 mg ustekinumab every 8 weeks were associated with higher clinical remission rates as compared to the steady-state trough levels following 90 mg every 12 weeks.

Impact of weight on pharmacokinetics
In a population pharmacokinetic analysis using data from patients with psoriasis, body weight was found to be the most significant covariate affecting the clearance of ustekinumab. The median CL/F in patients with weight > 100 kg was approximately 55% higher compared to patients with weight ≤ 100 kg. The median V/F in patients with weight > 100 kg was approximately 37% higher as compared to patients with weight ≤ 100 kg. The median trough serum concentrations of ustekinumab in patients with higher weight (> 100 kg) in the 90 mg group were comparable to those in patients with lower weight (≤ 100 kg) in the 45 mg group. Similar results were obtained from a confirmatory population pharmacokinetic analysis using data from patients with psoriatic arthritis.

Dosing frequency adjustment
In patients with Crohn's disease and ulcerative colitis, based on observed data and population PK analyses, randomized subjects who lost response to treatment had lower serum ustekinumab concentrations over time compared with subjects who did not lose response. In Crohn's disease, dose

adjustment from 90 mg every 12 weeks to 90 mg every 8 weeks was associated with an increase in trough serum ustekinumab concentrations and an accompanying increase in efficacy. In ulcerative colitis, population PK model based simulations demonstrated that adjusting dosing from 90 mg every 12 weeks to every 8 weeks would be expected to result in a 3-fold increase in steady-state trough ustekinumab concentrations. Additionally on the basis of clinical trial data in patients with ulcerative colitis, a positive exposure-response relationship was established between trough concentrations, and clinical remission and mucosal healing.

Special populations
No pharmacokinetic data are available in patients with impaired renal or hepatic function.
No specific studies have been conducted in elderly patients.

The pharmacokinetics of ustekinumab were generally comparable between Asian and non-Asian patients with psoriasis and ulcerative colitis.

In patients with Crohn's disease and ulcerative colitis, variability in ustekinumab clearance was affected by body weight, serum albumin level, sex, and antibody to ustekinumab status while body weight was the main covariate affecting the volume of distribution. Additionally in Crohn's disease, clearance was affected by C-reactive protein, TNF antagonist failure status and race (Asian versus non-Asian). The impact of these covariates was within ± 20% of the typical or reference value of the respective PK parameter, thus dose adjustment is not warranted for these covariates. Concomitant use of immunomodulators did not have a significant impact on ustekinumab disposition.

In the population pharmacokinetic analysis, there were no indications of an effect of tobacco or alcohol on the pharmacokinetics of ustekinumab.

Serum ustekinumab concentrations in paediatric psoriasis patients 6 to 17 years of age, treated with the recommended weight-based dose were generally comparable to those in the adult psoriasis population treated with the adult dose. Serum ustekinumab concentrations in paediatric psoriasis patients 12-17 years of age (CADMUS) treated with half of the recommended weight-based dose were generally lower than those in adults.

Regulation of CYP450 enzymes
The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4; see section 4.5).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard (e.g. organ toxicity) for humans based on studies of repeated-dose toxicity and developmental and reproductive toxicity, including safety pharmacology evaluations. In developmental and reproductive toxicity studies in cynomolgus monkeys, neither adverse effects on male fertility indices nor birth defects or developmental toxicity were observed. No adverse effects on female fertility indices were observed using an analogous antibody to IL-12/23 in mice.

Dose levels in animal studies were up to approximately 45-fold higher than the highest equivalent dose intended to be administered to psoriasis patients and resulted in peak serum concentrations in monkeys that were more than 100-fold higher than observed in humans.

Carcinogenicity studies were not performed with ustekinumab due to the lack of appropriate models for an antibody with no cross-reactivity to rodent IL-12/23 p40.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine monohydrochloride monohydrate
Polysorbate 80
Sucrose
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

STELARA 45 mg solution for injection
2 years

STELARA 90 mg solution for injection
2 years

STELARA 45 mg solution for injection in pre-filled syringe
3 years

STELARA 90 mg solution for injection in pre-filled syringe
3 years

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the vial or pre-filled syringe in the outer carton in order to protect from light.

6.5 Nature and contents of container

STELARA 45 mg solution for injection
0.5 mL solution in a type I glass 2 mL vial closed with a coated butyl rubber stopper.

STELARA 90 mg solution for injection
1 mL solution in a type I glass 2 mL vial closed with a coated butyl rubber stopper.

STELARA 45 mg solution for injection in pre-filled syringe
0.5 mL solution in a type I glass 1 mL syringe with a fixed stainless steel needle and a needle cover containing dry natural rubber (a derivative of latex). The syringe is fitted with a passive safety guard.

STELARA 90 mg solution for injection in pre-filled syringe
1 mL solution in a type I glass 1 mL syringe with a fixed stainless steel needle and a needle cover containing dry natural rubber (a derivative of latex). The syringe is fitted with a passive safety guard.

STELARA is available in a 1 vial pack or a pack of 1 pre-filled syringe.

6.6 Special precautions for disposal and other handling

The solution in the STELARA vial or pre-filled syringe should not be shaken. The solution should be visually inspected for particulate matter or discoloration prior to subcutaneous administration. The solution is clear to slightly opalescent, colourless to light yellow and may contain a few small

translucent or white particles of protein. This appearance is not unusual for proteinaceous solutions. The medicinal product should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present. Before administration, STELARA should be allowed to reach room temperature (approximately half an hour). Detailed instructions for use are provided in the package leaflet.

STELARA does not contain preservatives; therefore any unused medicinal product remaining in the vial and the syringe should not be used. STELARA is supplied as a sterile, single-use vial or single-use pre-filled syringe. The syringe, needle and vial must never be re-used. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

When using the single-dose vial, a 1 mL syringe with a 27 gauge, ½ inch (13 mm) needle is recommended.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

STELARA 45 mg solution for injection
EU/1/08/494/001

STELARA 90 mg solution for injection
EU/1/08/494/002

STELARA 45 mg solution for injection in pre-filled syringe
EU/1/08/494/003

STELARA 90 mg solution for injection in pre-filled syringe
EU/1/08/494/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 January 2009
Date of latest renewal: 19 September 2013

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

Name and address of the manufacturers of the biological active substance

Janssen Biologics B.V.
Einsteinweg 101
NL-2333 CB Leiden
The Netherlands

Janssen Sciences Ireland UC
Barnahely
Ringaskiddy
Co. Cork
Ireland

Name and address of the manufacturer responsible for batch release

Janssen Biologics B.V.
Einsteinweg 101
NL-2333 CB Leiden
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

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

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (130 mg)

1. NAME OF THE MEDICINAL PRODUCT

STELARA 130 mg concentrate for solution for infusion
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 130 mg of ustekinumab in 26 mL.

3. LIST OF EXCIPIENTS

Excipients: EDTA disodium salt dihydrate, L-histidine, L-histidine monohydrochloride monohydrate, L-methionine, polysorbate 80, sucrose, water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for Solution for infusion
130 mg/26 mL
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Read the package leaflet before use.
For single use only.
Intravenous use after dilution.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the vial in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/494/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including in Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL TEXT (130 mg)

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

STELARA 130 mg concentrate for solution for infusion
Ustekinumab

2. METHOD OF ADMINISTRATION

For IV use after dilution.
Do not shake.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

130 mg/26 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

VIAL CARTON TEXT (45 mg)

1. NAME OF THE MEDICINAL PRODUCT

STELARA 45 mg solution for injection
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 45 mg of ustekinumab in 0.5 mL.

3. LIST OF EXCIPIENTS

Excipients: Sucrose, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
45 mg/0.5 mL
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Subcutaneous use
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the vial in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/494/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

STELARA 45 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL TEXT (45 mg)

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

STELARA 45 mg solution for injection
ustekinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

45 mg/0.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

VIAL CARTON TEXT (90 mg)

1. NAME OF THE MEDICINAL PRODUCT

STELARA 90 mg solution for injection
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 90 mg of ustekinumab in 1 mL.

3. LIST OF EXCIPIENTS

Excipients: Sucrose, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
90 mg/1 mL
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Subcutaneous use
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the vial in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/494/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

STELARA 90 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL TEXT (90 mg)

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

STELARA 90 mg solution for injection
ustekinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

90 mg/1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON TEXT (45 mg)

1. NAME OF THE MEDICINAL PRODUCT

STELARA 45 mg solution for injection in pre-filled syringe
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 45 mg of ustekinumab in 0.5 mL.

3. LIST OF EXCIPIENTS

Excipients: Sucrose, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injections. The container of this medicinal product contains latex rubber. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
45 mg/0.5 mL
1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Subcutaneous use
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/494/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

STELARA 45 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL TEXT (45 mg)

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

STELARA 45 mg injection
ustekinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

45 mg/0.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON TEXT (90 mg)

1. NAME OF THE MEDICINAL PRODUCT

STELARA 90 mg solution for injection in pre-filled syringe
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 90 mg of ustekinumab in 1 mL.

3. LIST OF EXCIPIENTS

Excipients: Sucrose, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injections. The container of this medicinal product contains latex rubber. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
90 mg/1 mL
1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Subcutaneous use
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/494/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

STELARA 90 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL TEXT (90 mg)

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

STELARA 90 mg injection
ustekinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

90 mg/1 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

STELARA 130 mg concentrate for solution for infusion
Ustekinumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Stelara is and what it is used for
2. What you need to know before you use Stelara
3. How Stelara will be given
4. Possible side effects
5. How to store Stelara
6. Contents of the pack and other information

1. What Stelara is and what it is used for

What Stelara is
Stelara contains the active substance 'ustekinumab', a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Stelara belongs to a group of medicines called 'immunosuppressants'. These medicines work by weakening part of the immune system.

What Stelara is used for
Stelara is used to treat the following inflammatory diseases:
- Moderate to severe Crohn's disease - in adults
- Moderate to severe ulcerative colitis - in adults

Crohn's disease
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

Ulcerative colitis
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

2. What you need to know before you use Stelara

Do not use Stelara:
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks is important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using

Stelara.

Warnings and precautions
Talk to your doctor or pharmacist before using Stelara. Your doctor will check how well you are before treatment. Make sure you tell your doctor about any illness you have before treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Stelara. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Stelara can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Stelara. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Stelara tell your doctor:
- **If you ever had an allergic reaction to Stelara**. Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like Stelara weaken part of the immune system. This may increase the risk of cancer.
- **If you have or have had a recent infection or if you have any abnormal skin openings (fistulae)**.
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis** – such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using these therapies together with Stelara has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.
- **If you are having or have ever had injections to treat allergies** – it is not known if Stelara may affect these.
- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Children and adolescents
Stelara is not recommended for use in children under 18 years of age with Crohn's disease or ulcerative colitis because it has not been studied in this age group.

Other medicines, vaccines and Stelara
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Stelara.

Pregnancy and breast-feeding
- It is preferable to avoid the use of Stelara in pregnancy. The effects of Stelara in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Stelara and for at least 15 weeks after the last Stelara treatment.
- Talk to your doctor if you are pregnant, think you may be pregnant or are planning to have a baby.
- Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use Stelara - do not do both.

Driving and using machines
Stelara has no or negligible influence on the ability to drive and use machines.

Stelara contains sodium
Stelara contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'. However, before Stelara is given to you, it is mixed with a solution that contains sodium. Talk to your doctor if you are on a low salt diet.

3. How Stelara will be given

Stelara is intended for use under the guidance and supervision of a doctor experienced in the diagnosis and treatment of Crohn's disease or ulcerative colitis.

Stelara 130 mg concentrate for solution for infusion will be given to you by your doctor, through a drip in the vein of your arm (intravenous infusion) over at least one hour. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Stelara is given
Your doctor will decide how much Stelara you need to receive and for how long.

Adults aged 18 years or older
- The doctor will work out the recommended intravenous infusion dose for you based on your body weight.

Your body weight	Dose
≤ 55 kg	260 mg
> 55 kg to ≤ 85 kg	390 mg
> 85 kg	520 mg

- After the starting intravenous dose, you will have the next dose of 90 mg Stelara by an injection under your skin (subcutaneous injection) 8 weeks later, and then every 12 weeks therafter.

How Stelara is given
- The first dose of Stelara for treatment of Crohn's disease or ulcerative colitis is given by a doctor as a drip in the vein of an arm (intravenous infusion).

Talk to your doctor if you have any questions about receiving Stelara.

If you forget to use Stelara
If you forget or miss the appointment for receiving the dose, contact your doctor to reschedule your appointment.

If you stop using Stelara
It is not dangerous to stop using Stelara. However, if you stop, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.
- Serious allergic reactions ('anaphylaxis') are rare in people taking Stelara (may affect up to 1 in 1,000 people). Signs include:
  - difficulty breathing or swallowing

- low blood pressure, which can cause dizziness or light-headedness
- swelling of the face, lips, mouth or throat.

- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Stelara again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.

- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)
- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)
- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Stelara may make you less able to fight infections, and some infections could become serious. You must look out for signs of infection while you are using Stelara. These include:

- fever, flu-like symptoms, night sweats
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, or skin infections or shingles that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use Stelara until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people):

- Diarrhoea
- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching ('pruritus')
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people)**:**

- Tooth infections
- Vaginal yeast infection
- Depression
- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Feeling weak
- Drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary
- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)
- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1000 people)

- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Stelara

- Stelara 130 mg concentrate for solution for infusion is given in a hospital or clinic and patients should not need to store or handle it.
- Keep this medicine out of the sight and reach of children.
- Store in a refrigerator (2°C–8°C). Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- Do not shake the Stelara vials. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:

- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Stelara looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.
- If the seal is broken.

Stelara is for single use only. Any diluted infusion solution or unused product remaining in the vial and the syringe should be thrown away in accordance with local requirements.

6. Contents of the pack and other information

What Stelara contains

- The active substance is ustekinumab. Each vial contains130 mg ustekinumab in 26 mL.
- The other ingredients are EDTA disodium salt dihydrate, L-histidine, L-histidine monohydrochloride monohydrate, L-methionine, polysorbate 80, sucrose and water for injection.

What Stelara looks like and contents of the pack
Stelara is a clear, colourless to light yellow concentrate for solution for infusion. It is supplied as a carton pack containing 1 single-dose, glass 30 mL vial. Each vial contains 130 mg ustekinumab in 26 mL of concentrate for solution for infusion.

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Manufacturer
Janssen Biologics B.V.
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {MM/YYYY}.

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

The following information is intended for healthcare professionals only:

Traceability:

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Instructions for dilution:

STELARA concentrate for solution for infusion must be diluted, prepared and infused by a healthcare professional using aseptic technique.

1. Calculate the dose and the number of STELARA vials needed based on patient weight (see section 3, Table 1). Each 26 mL vial of STELARA contains 130 mg of ustekinumab.
2. Withdraw and then discard a volume of the sodium chloride 9 mg/mL (0.9%) solution from the 250 mL infusion bag equal to the volume of STELARA to be added (discard 26 mL sodium chloride for each vial of STELARA needed, for 2 vials- discard 52 mL, for 3 vials discard 78 mL, for 4 vials- discard 104 mL).
3. Withdraw 26 mL of STELARA from each vial needed and add it to the 250 mL infusion bag. The final volume in the infusion bag should be 250 mL. Gently mix.
4. Visually inspect the diluted solution before infusion. Do not use if visibly opaque particles, discoloration or foreign particles are observed.
5. Infuse the diluted solution over a period of at least one hour. Once diluted, the infusion should be completed within eight hours of the dilution in the infusion bag.
6. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.2 micrometer).
7. Each vial is for single use only and any unused medicinal product should be disposed of in accordance with local requirements.

Storage
If necessary, the diluted infusion solution may be stored at room temperature. The infusion should be completed within 8 hours of the dilution in the infusion bag. Do not freeze.

Package leaflet: Information for the user

STELARA 45 mg solution for injection
Ustekinumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine. If you are the parent or caregiver who will give Stelara to a child, please read this information carefully.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Stelara is and what it is used for
2. What you need to know before you use Stelara
3. How to use Stelara
4. Possible side effects
5. How to store Stelara
6. Contents of the pack and other information

1. What Stelara is and what it is used for

What Stelara is
Stelara contains the active substance ‘ustekinumab’, a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Stelara belongs to a group of medicines called ‘immunosuppressants’. These medicines work by weakening part of the immune system.

What Stelara is used for
Stelara is used to treat the following inflammatory diseases:
- Plaque psoriasis - in adults and children aged 6 years and older
- Psoriatic arthritis - in adults
- Moderate to severe Crohn’s disease - in adults
- Moderate to severe ulcerative colitis – in adults

Plaque psoriasis
Plaque psoriasis is a skin condition that causes inflammation affecting the skin and nails. Stelara will reduce the inflammation and other signs of the disease.

Stelara is used in adults with moderate to severe plaque psoriasis, who cannot use ciclosporin, methotrexate or phototherapy, or where these treatments did not work.

Stelara is used in children and adolescents aged 6 years and older with moderate to severe plaque psoriasis who are unable to tolerate phototherapy or other systemic therapies or where these treatments did not work.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Stelara to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.
- Slow down the damage to your joints.

Crohn's disease
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

Ulcerative colitis
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

2. What you need to know before you use Stelara

Do not use Stelara:
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks is important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Warnings and precautions
Talk to your doctor or pharmacist before using Stelara. Your doctor will check how well you are before each treatment. Make sure you tell your doctor about any illness you have before each treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Stelara. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Stelara can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Stelara. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Stelara tell your doctor:
- **If you ever had an allergic reaction to Stelara**. Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like Stelara weaken part of the immune system. This may increase the risk of cancer.
- **If you have or have had a recent infection**.
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis** – such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using these therapies together with Stelara has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.
- **If you are having or have ever had injections to treat allergies** – it is not known if Stelara may affect these.
- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Children and adolescents
Stelara is not recommended for use in children with psoriasis under 6 years of age, or for use in children under 18 years of age with psoriatic arthritis, Crohn's disease, or ulcerative colitis because it has not been studied in this age group.

Other medicines, vaccines and Stelara
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Stelara.

Pregnancy and breast-feeding
- It is preferable to avoid the use of Stelara in pregnancy. The effects of Stelara in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Stelara and for at least 15 weeks after the last Stelara treatment.
- Talk to your doctor if you are pregnant, think you may be pregnant or are planning to have a baby.
- Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use Stelara - do not do both.

Driving and using machines
Stelara has no or negligible influence on the ability to drive and use machines.

3. How to use Stelara

Stelara is intended for use under the guidance and supervision of a doctor experienced in treating conditions for which STELARA is intended.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Stelara is given
Your doctor will decide how much Stelara you need to use and for how long.

Adults aged 18 years or older
Psoriasis or Psoriatic Arthritis
- The recommended starting dose is 45 mg Stelara. Patients who weigh more than 100 kilograms (kg) may start on a dose of 90 mg instead of 45 mg.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks. The following doses are usually the same as the starting dose.

Crohn's disease or Ulcerative Colitis
- During treatment, the first dose of approximately 6 mg/kg Stelara will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, you will receive the next dose of 90 mg Stelara after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').
- In some patients, after the first injection under the skin, 90 mg Stelara may be given every 8 weeks. Your doctor will decide when you should receive your next dose.

Children and adolescents aged 6 years or older
Psoriasis

- The doctor will work out the right dose for you, including the amount (volume) of Stelara to be injected to give the right dose. The right dose for you will depend on your body weight at the time each dose is given.
- If you weigh less than 60 kg, the recommended dose is 0.75 mg of Stelara per kg body weight.
- If you weigh 60 kg to 100 kg, the recommended dose is 45 mg Stelara.
- If you weigh more than 100 kg, the recommended dose is 90 mg Stelara.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks.

How Stelara is given

- Stelara is given as an injection under the skin ('subcutaneously'). At the start of your treatment, medical or nursing staff may inject Stelara.
- However, you and your doctor may decide that you may inject Stelara yourself. In this case you will get training on how to inject Stelara yourself.
- For instructions on how to inject Stelara, see 'Instructions for administration' at the end of this leaflet.

Talk to your doctor if you have any questions about giving yourself an injection.

If you use more Stelara than you should
If you have used or been given too much Stelara, talk to a doctor or pharmacist straight away. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use Stelara
If you forget a dose, contact your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose.

If you stop using Stelara
It is not dangerous to stop using Stelara. However, if you stop, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.

- Serious allergic reactions ('anaphylaxis') are rare in people taking Stelara (may affect up to 1 in 1,000 people). Signs include:
  - difficulty breathing or swallowing
  - low blood pressure, which can cause dizziness or light-headedness
  - swelling of the face, lips, mouth or throat.
- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Stelara again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.

- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)
- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)
- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Stelara may make you less able to fight infections, and some infections could become serious. You must look out for signs of infection while you are using Stelara. These include:

- fever, flu-like symptoms, night sweats
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, or skin infections or shingles that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use Stelara until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people):

- Diarrhoea
- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching ('pruritus')
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people)**:**

- Tooth infections
- Vaginal yeast infection
- Depression
- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Feeling weak
- Drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary
- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)

- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1000 people)
- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Stelara

- Keep this medicine out of the sight and reach of children.
- Store in a refrigerator (2°C–8°C). Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- Do not shake the Stelara vials. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:
- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Stelara looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.
- If the seal is broken.

Stelara is for single use only. Any unused product remaining in the vial and the syringe should be thrown away. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Stelara contains
- The active substance is ustekinumab. Each vial contains 45 mg ustekinumab in 0.5 mL.
- The other ingredients are L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sucrose and water for injections.

What Stelara looks like and contents of the pack
Stelara is a clear to slightly opalescent (having a pearl-like shine), colourless to light yellow solution for injection. The solution may contain a few small translucent or white particles of protein. It is supplied as a carton pack containing 1 single-dose, glass 2 mL vial. Each vial contains 45 mg ustekinumab in 0.5 mL of solution for injection.

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Manufacturer
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This leaflet was last revised in {MM/YYYY}.

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

Instructions for administration

At the start of treatment, your healthcare provider will assist you with your first injection. However, you and your doctor may decide that you may inject Stelara yourself. If this happens, you will get training on how to inject Stelara. Talk to your doctor if you have any questions about giving yourself an injection.

- Do not mix Stelara with other liquids for injection
- Do not shake Stelara vials. This is because strong shaking may damage the medicine. Do not use the medicine if it has been shaken strongly.

1. Check the number of vials and prepare the materials:
Take the vial(s) out of the refrigerator. Let the vial stand for about half an hour. This will let the liquid come to a comfortable temperature for injection (room temperature).

Check the vial(s) to make sure:

- the number of vials and strength is correct
  - If your dose is 45 mg or less, you will get one 45 mg vial of Stelara
  - If your dose is 90 mg you will get two 45 mg vials of Stelara and you will need to give yourself two injections. Choose two different sites for these injections (for example one injection in the right thigh and the other injection in the left thigh), and give the injections one right after the other. Use a new needle and syringe for each injection.
- it is the right medicine
- it has not passed its expiry date
- the vial is not damaged and the seal is not broken
- the solution in the vial is clear to slightly opalescent (having a pearl-like shine) and colourless to light yellow
- the solution is not discoloured or cloudy and does not contain any foreign particles
- the solution is not frozen.

Children weighing less than 60 kg need a dose lower than 45 mg. Make sure you know the proper amount (volume) to remove from the vial and type of syringe needed for dosing. If you don't know the amount or type of syringe needed, contact your healthcare provider for further instruction.

Get everything together that you need and lay out on a clean surface. This includes a syringe, needle, antiseptic wipes, a cotton ball or gauze, and a sharps container (see Figure 1).

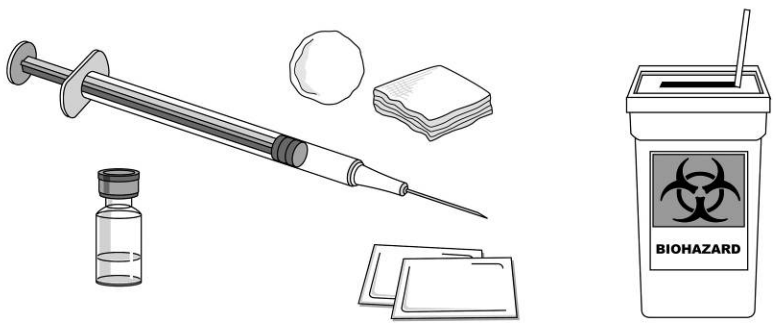
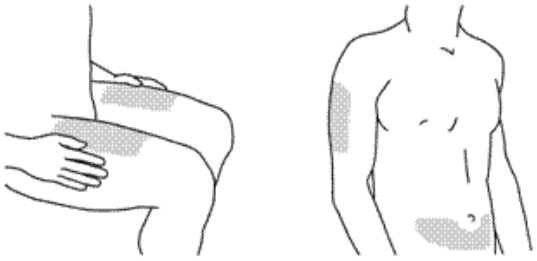


Figure 1

2. Choose and prepare the injection site:
Choose an injection site (see Figure 2)

- Stelara is given by injection under the skin (subcutaneously)
- Good places for the injection are the upper thigh or around the belly (abdomen) at least 5 cm away from the navel (belly button)

- If possible, do not use areas of skin that show signs of psoriasis
- If someone will assist in giving you the injection, then he or she may also choose the upper arms as an injection site



*Areas in gray are recommended injection sites.

Figure 2

Prepare the injection site
- Wash your hands very well with soap and warm water
- Wipe the injection site on the skin with an antiseptic wipe
- Do not touch this area again before giving the injection

3. Prepare the dose:
- Take the cap off the top of the vial (see Figure 3)



Figure 3

- Do not remove the stopper
- Clean the stopper with an antiseptic swab
- Put the vial on a flat surface.
- Pick up the syringe and remove the needle cover
- Do not touch the needle or let the needle touch anything
- Push the needle through the rubber stopper
- Turn the vial and the syringe upside down
- Pull on the syringe plunger to fill the syringe with the amount of liquid prescribed by your doctor
- It is important that the needle is always in the liquid. This stops air bubbles forming in the syringe (see Figure 4)

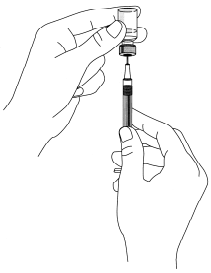


Figure 4

- Remove the needle from the vial
- Hold the syringe with the needle pointing up to see if it has any air bubbles inside
- If there are air bubbles, tap the side gently until the air bubbles go to the top of the syringe (see Figure 5)

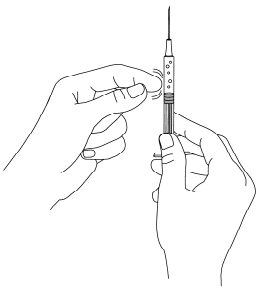


Figure 5

- Then press the plunger until all of the air (but none of the liquid) has been removed
- Do not lay the syringe down or allow the needle to touch anything.

4. Inject the dose:
- Gently pinch the cleaned skin between your thumb and index finger. Do not squeeze it tightly
- Push the needle into the pinched skin
- Push the plunger with your thumb as far as it will go to inject all of the liquid. Push it slowly and evenly, keeping the skin gently pinched
- When the plunger is pushed as far as it will go, take out the needle and let go of the skin

5. After the injection:
- Press an antiseptic wipe over the injection site for a few seconds after the injection
- There may be a small amount of blood or liquid at the injection site. This is normal
- You can press a cotton ball or gauze over the injection site and hold for 10 seconds
- Do not rub the skin at the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

6. Disposal:
- Used syringes and needles should be placed in a puncture-resistant container, like a sharps container. Never re-use needles and syringes, for your safety and health, and for the safety of others. Dispose of your sharps container according to your local regulations
- Empty vials, antiseptic wipes, and other supplies can be disposed of in your garbage.

Package leaflet: Information for the user

STELARA 90 mg solution for injection
Ustekinumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine. If you are the parent or caregiver who will give Stelara to a child, please read this information carefully.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Stelara is and what it is used for
2. What you need to know before you use Stelara
3. How to use Stelara
4. Possible side effects
5. How to store Stelara
6. Contents of the pack and other information

1. What Stelara is and what it is used for

What Stelara is
Stelara contains the active substance ‘ustekinumab’, a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Stelara belongs to a group of medicines called ‘immunosuppressants’. These medicines work by weakening part of the immune system.

What Stelara is used for
Stelara is used to treat the following inflammatory diseases:
- Plaque psoriasis - in adults and children aged 6 years and older
- Psoriatic arthritis - in adults
- Moderate to severe Crohn’s disease - in adults
- Moderate to severe ulcerative colitis – in adults

Plaque psoriasis
Plaque psoriasis is a skin condition that causes inflammation affecting the skin and nails. Stelara will reduce the inflammation and other signs of the disease.

Stelara is used in adults with moderate to severe plaque psoriasis, who cannot use ciclosporin, methotrexate or phototherapy, or where these treatments did not work.

Stelara is used in children and adolescents aged 6 years and older with moderate to severe plaque psoriasis who are unable to tolerate phototherapy or other systemic therapies or where these treatments did not work.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Stelara to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.
- Slow down the damage to your joints.

Crohn's disease
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

Ulcerative colitis
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

2. What you need to know before you use Stelara

Do not use Stelara:
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks is important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Warnings and precautions
Talk to your doctor or pharmacist before using Stelara. Your doctor will check how well you are before each treatment. Make sure you tell your doctor about any illness you have before each treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Stelara. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Stelara can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Stelara. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Stelara tell your doctor:
- **If you ever had an allergic reaction to Stelara**. Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like Stelara weaken part of the immune system. This may increase the risk of cancer.
- **If you have or have had a recent infection**.
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis** – such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using these therapies together with Stelara has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.
- **If you are having or have ever had injections to treat allergies** – it is not known if Stelara may affect these.
- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Children and adolescents
Stelara is not recommended for use in children with psoriasis under 6 years of age, or for use in children under 18 years of age with psoriatic arthritis, Crohn's disease, or ulcerative colitis because it has not been studied in this age group.

Other medicines, vaccines and Stelara
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Stelara.

Pregnancy and breast-feeding
- It is preferable to avoid the use of Stelara in pregnancy. The effects of Stelara in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Stelara and for at least 15 weeks after the last Stelara treatment.
- Talk to your doctor if you are pregnant, think you may be pregnant or are planning to have a baby.
- Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use Stelara - do not do both.

Driving and using machines
Stelara has no or negligible influence on the ability to drive and use machines.

3. How to use Stelara

Stelara is intended for use under the guidance and supervision of a doctor experienced in treating conditions for which STELARA is intended.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Stelara is given
Your doctor will decide how much Stelara you need to use and for how long.

Adults aged 18 years or older
Psoriasis or Psoriatic Arthritis
- The recommended starting dose is 45 mg Stelara. Patients who weigh more than 100 kilograms (kg) may start on a dose of 90 mg instead of 45 mg.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks. The following doses are usually the same as the starting dose.

Crohn's disease or Ulcerative Colitis
- During treatment, the first dose of approximately 6 mg/kg Stelara will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, you will receive the next dose of 90 mg Stelara after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').
- In some patients, after the first injection under the skin, 90 mg Stelara may be given every 8 weeks. Your doctor will decide when you should receive your next dose.

Children and adolescents aged 6 years or older
Psoriasis

- The doctor will work out the right dose for you, including the amount (volume) of Stelara to be injected to give the right dose. The right dose for you will depend on your body weight at the time each dose is given.
- A 45 mg vial is available if you need to receive less than the full 45 mg dose.
- If you weigh less than 60 kg, the recommended dose is 0.75 mg of Stelara per kg body weight.
- If you weigh 60 kg to 100 kg, the recommended dose is 45 mg Stelara.
- If you weigh more than 100 kg, the recommended dose is 90 mg Stelara.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks.

How Stelara is given

- Stelara is given as an injection under the skin ('subcutaneously'). At the start of your treatment, medical or nursing staff may inject Stelara.
- However, you and your doctor may decide that you may inject Stelara yourself. In this case you will get training on how to inject Stelara yourself.
- For instructions on how to inject Stelara, see 'Instructions for administration' at the end of this leaflet.

Talk to your doctor if you have any questions about giving yourself an injection.

If you use more Stelara than you should
If you have used or been given too much Stelara, talk to a doctor or pharmacist straight away. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use Stelara
If you forget a dose, contact your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose.

If you stop using Stelara
It is not dangerous to stop using Stelara. However, if you stop, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.

- Serious allergic reactions ('anaphylaxis') are rare in people taking Stelara (may affect up to 1 in 1,000 people). Signs include:
  - difficulty breathing or swallowing
  - low blood pressure, which can cause dizziness or light-headedness
  - swelling of the face, lips, mouth or throat.
- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Stelara

again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.

- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)
- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)
- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Stelara may make you less able to fight infections, and some infections could become serious. You must look out for signs of infection while you are using Stelara. These include:

- fever, flu-like symptoms, night sweats
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, or skin infections or shingles that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use Stelara until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people)**:**

- Diarrhoea
- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching ('pruritus')
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people)**:**

- Tooth infections
- Vaginal yeast infection
- Depression
- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Feeling weak
- Drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary

- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)
- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1000 people)
- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Stelara

- Keep this medicine out of the sight and reach of children.
- Store in a refrigerator (2°C–8°C). Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- Do not shake the Stelara vials. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:
- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Stelara looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.
- If the seal is broken.

Stelara is for single use only. Any unused product remaining in the vial and the syringe should be thrown away. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Stelara contains
- The active substance is ustekinumab. Each vial contains 90 mg ustekinumab in 1 mL.
- The other ingredients are L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sucrose and water for injections.

What Stelara looks like and contents of the pack
Stelara is a clear to slightly opalescent (having a pearl-like shine), colourless to light yellow solution for injection. The solution may contain a few small translucent or white particles of protein. It is supplied as a carton pack containing 1 single-dose, glass 2 mL vial. Each vial contains 90 mg ustekinumab in 1 mL of solution for injection.

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This leaflet was last revised in {MM/YYYY}.

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

Instructions for administration

At the start of treatment, your healthcare provider will assist you with your first injection. However, you and your doctor may decide that you may inject Stelara yourself. If this happens, you will get training on how to inject Stelara. Talk to your doctor if you have any questions about giving yourself an injection.

- Do not mix Stelara with other liquids for injection
- Do not shake Stelara vials. This is because strong shaking may damage the medicine. Do not use the medicine if it has been shaken strongly.

1. Check the number of vials and prepare the materials:
Take the vial(s) out of the refrigerator. Let the vial stand for about half an hour. This will let the liquid come to a comfortable temperature for injection (room temperature).

Check the vial(s) to make sure:

- the number of vials and strength is correct
  - If your dose is 90 mg you will get one 90 mg vial of Stelara.
- it is the right medicine
- it has not passed its expiry date
- the vial is not damaged and the seal is not broken
- the solution in the vial is clear to slightly opalescent (having a pearl-like shine) and colourless to light yellow
- the solution is not discoloured or cloudy and does not contain any foreign particles
- the solution is not frozen.

Get everything together that you need and lay out on a clean surface. This includes a syringe, needle, antiseptic wipes, a cotton ball or gauze, and a sharps container (see Figure 1).

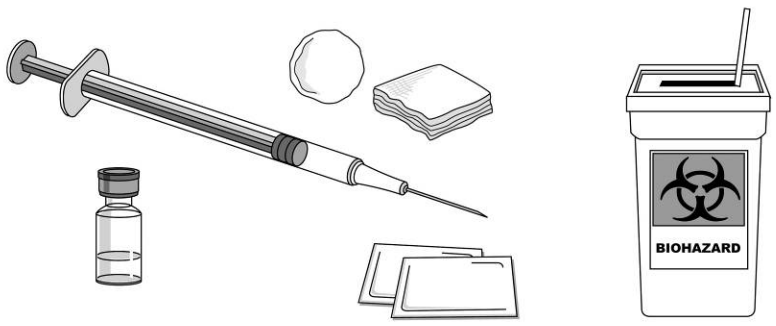
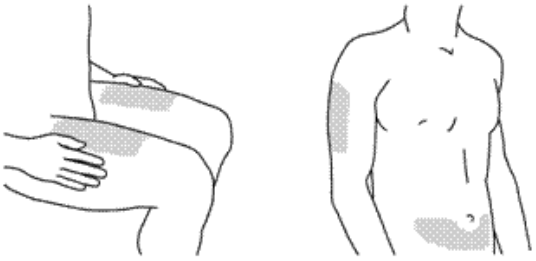


Figure 1

2. Choose and prepare the injection site:
Choose an injection site (see Figure 2)

- Stelara is given by injection under the skin (subcutaneously)
- Good places for the injection are the upper thigh or around the belly (abdomen) at least 5 cm away from the navel (belly button)
- If possible, do not use areas of skin that show signs of psoriasis
- If someone will assist in giving you the injection, then he or she may also choose the upper arms as an injection site.



*Areas in gray are recommended injection sites.

Figure 2

Prepare the injection site

- Wash your hands very well with soap and warm water
- Wipe the injection site on the skin with an antiseptic wipe
- Do not touch this area again before giving the injection.

3. Prepare the dose:

- Take the cap off the top of the vial (see Figure 3)



Figure 3

- Do not remove the stopper
- Clean the stopper with an antiseptic swab
- Put the vial on a flat surface.
- Pick up the syringe and remove the needle cover
- Do not touch the needle or let the needle touch anything
- Push the needle through the rubber stopper
- Turn the vial and the syringe upside down
- Pull on the syringe plunger to fill the syringe with the amount of liquid prescribed by your doctor
- It is important that the needle is always in the liquid. This stops air bubbles forming in the syringe (see Figure 4)

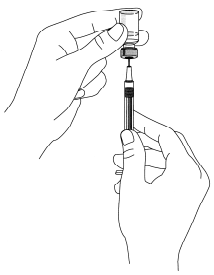


Figure 4

- Remove the needle from the vial

- Hold the syringe with the needle pointing up to see if it has any air bubbles inside
- If there are air bubbles, tap the side gently until the air bubbles go to the top of the syringe (see Figure 5)

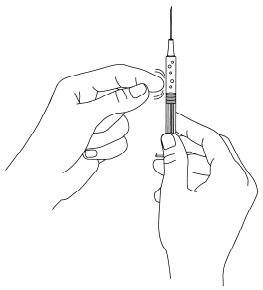


Figure 5

- Then press the plunger until all of the air (but none of the liquid) has been removed
- Do not lay the syringe down or allow the needle to touch anything.

4. Inject the dose:
- Gently pinch the cleaned skin between your thumb and index finger. Do not squeeze it tightly
- Push the needle into the pinched skin
- Push the plunger with your thumb as far as it will go to inject all of the liquid. Push it slowly and evenly, keeping the skin gently pinched
- When the plunger is pushed as far as it will go, take out the needle and let go of the skin

5. After the injection:
- Press an antiseptic wipe over the injection site for a few seconds after the injection
- There may be a small amount of blood or liquid at the injection site. This is normal
- You can press a cotton ball or gauze over the injection site and hold for 10 seconds
- Do not rub the skin at the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

6. Disposal:
- Used syringes and needles should be placed in a puncture-resistant container, like a sharps container. Never re-use needles and syringes, for your safety and health, and for the safety of others. Dispose of your sharps container according to your local regulations
- Empty vials, antiseptic wipes, and other supplies can be disposed of in your garbage.

Package leaflet: Information for the user

STELARA 45 mg solution for injection in pre-filled syringe
Ustekinumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine. If you are the parent or caregiver who will give Stelara to a child, please read this information carefully.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Stelara is and what it is used for
2. What you need to know before you use Stelara
3. How to use Stelara
4. Possible side effects
5. How to store Stelara
6. Contents of the pack and other information

1. What Stelara is and what it is used for

What Stelara is
Stelara contains the active substance ‘ustekinumab’, a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Stelara belongs to a group of medicines called ‘immunosuppressants’. These medicines work by weakening part of the immune system.

What Stelara is used for
Stelara is used to treat the following inflammatory diseases:
- Plaque psoriasis - in adults and children aged 6 years and older
- Psoriatic arthritis - in adults
- Moderate to severe Crohn’s disease - in adults
- Moderate to severe ulcerative colitis – in adults

Plaque psoriasis
Plaque psoriasis is a skin condition that causes inflammation affecting the skin and nails. Stelara will reduce the inflammation and other signs of the disease.

Stelara is used in adults with moderate to severe plaque psoriasis, who cannot use ciclosporin, methotrexate or phototherapy, or where these treatments did not work.

Stelara is used in children and adolescents aged 6 years and older with moderate to severe plaque psoriasis who are unable to tolerate phototherapy or other systemic therapies or where these treatments did not work.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Stelara to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.
- Slow down the damage to your joints.

Crohn's disease
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

Ulcerative colitis
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

2. What you need to know before you use Stelara

Do not use Stelara:
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks is important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Warnings and precautions
Talk to your doctor or pharmacist before using Stelara. Your doctor will check how well you are before each treatment. Make sure you tell your doctor about any illness you have before each treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Stelara. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Stelara can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Stelara. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Stelara tell your doctor:
- **If you ever had an allergic reaction to Stelara**. Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like Stelara weaken part of the immune system. This may increase the risk of cancer.
- **If you have or have had a recent infection.**
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you have ever had an allergic reaction to latex or Stelara injection** – the container of this medicinal product contains latex rubber, which may cause severe allergic reactions in people who are sensitive to latex. See 'Look out for serious side effects' in section 4 for the signs of an allergic reaction.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis** – such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using these therapies together with Stelara has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.

- **If you are having or have ever had injections to treat allergies** – it is not known if Stelara may affect these.
- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Children and adolescents
Stelara is not recommended for use in children with psoriasis under 6 years of age, or for use in children under 18 years of age with psoriatic arthritis, Crohn's disease, or ulcerative colitis because it has not been studied in this age group.

Other medicines, vaccines and Stelara
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Stelara.

Pregnancy and breast-feeding
- It is preferable to avoid the use of Stelara in pregnancy. The effects of Stelara in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Stelara and for at least 15 weeks after the last Stelara treatment.
- Talk to your doctor if you are pregnant, think you may be pregnant or are planning to have a baby.
- Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use Stelara - do not do both.

Driving and using machines
Stelara has no or negligible influence on the ability to drive and use machines.

3. How to use Stelara

Stelara is intended for use under the guidance and supervision of a doctor experienced in treating conditions for which STELARA is intended.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Stelara is given
Your doctor will decide how much Stelara you need to use and for how long.

Adults aged 18 years or older
Psoriasis or Psoriatic Arthritis
- The recommended starting dose is 45 mg Stelara. Patients who weigh more than 100 kilograms (kg) may start on a dose of 90 mg instead of 45 mg.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks. The following doses are usually the same as the starting dose.

Crohn's disease or Ulcerative Colitis
- During treatment, the first dose of approximately 6 mg/kg Stelara will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, you will receive the next dose of 90 mg Stelara after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').

- In some patients, after the first injection under the skin, 90 mg Stelara may be given every 8 weeks. Your doctor will decide when you should receive your next dose.

Children and adolescents aged 6 years or older
Psoriasis
- The doctor will work out the right dose for you, including the amount (volume) of Stelara to be injected to give the right dose. The right dose for you will depend on your body weight at the time each dose is given.
- A 45 mg vial is available for children who need to receive less than the full 45 mg dose.
- If you weigh less than 60 kg, the recommended dose is 0.75 mg of Stelara per kg body weight.
- If you weigh 60 kg to 100 kg, the recommended dose is 45 mg Stelara.
- If you weigh more than 100 kg, the recommended dose is 90 mg Stelara.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks.

How Stelara is given
- Stelara is given as an injection under the skin ('subcutaneously'). At the start of your treatment, medical or nursing staff may inject Stelara.
- However, you and your doctor may decide that you may inject Stelara yourself. In this case you will get training on how to inject Stelara yourself.
- For instructions on how to inject Stelara, see 'Instructions for administration' at the end of this leaflet.

Talk to your doctor if you have any questions about giving yourself an injection.

If you use more Stelara than you should
If you have used or been given too much Stelara, talk to a doctor or pharmacist straight away. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use Stelara
If you forget a dose, contact your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose.

If you stop using Stelara
It is not dangerous to stop using Stelara. However, if you stop, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.
- Serious allergic reactions ('anaphylaxis') are rare in people taking Stelara (may affect up to 1 in 1,000 people). Signs include:
  - difficulty breathing or swallowing
  - low blood pressure, which can cause dizziness or light-headedness
  - swelling of the face, lips, mouth or throat.
- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as

cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Stelara again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.

- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)
- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)
- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Stelara may make you less able to fight infections, and some infections could become serious. You must look out for signs of infection while you are using Stelara. These include:

- fever, flu-like symptoms, night sweats
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, or skin infections or shingles that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use Stelara until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people)**:**

- Diarrhoea
- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching ('pruritus')
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people)**:**

- Tooth infections
- Vaginal yeast infection
- Depression
- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given

- Feeling weak
- Drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary
- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)
- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1000 people)
- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Stelara

- Keep this medicine out of the sight and reach of children.
- Store in a refrigerator (2°C–8°C). Do not freeze.
- Keep the pre-filled syringe in the outer carton in order to protect from light.
- Do not shake Stelara pre-filled syringes. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:
- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Stelara looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.

Stelara is for single use only. Any unused product remaining in the syringe should be thrown away. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Stelara contains
- The active substance is ustekinumab. Each pre-filled syringe contains 45 mg ustekinumab in 0.5 mL.
- The other ingredients are L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sucrose and water for injections.

What Stelara looks like and contents of the pack
Stelara is a clear to slightly opalescent (having a pearl-like shine), colourless to light yellow solution for injection. The solution may contain a few small translucent or white particles of protein. It is supplied as a carton pack containing 1 single-dose, glass 1 mL pre-filled syringe. Each pre-filled syringe contains 45 mg ustekinumab in 0.5 mL of solution for injection.

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

Instructions for administration

At the start of treatment, your healthcare provider will assist you with your first injection. However, you and your doctor may decide that you may inject Stelara yourself. If this happens, you will get training on how to inject Stelara. Talk to your doctor if you have any questions about giving yourself an injection.

- Do not mix Stelara with other liquids for injection
- Do not shake Stelara pre-filled syringes. This is because strong shaking may damage the medicine. Do not use the medicine if it has been shaken strongly.

Figure 1 shows what the pre-filled syringe looks like.

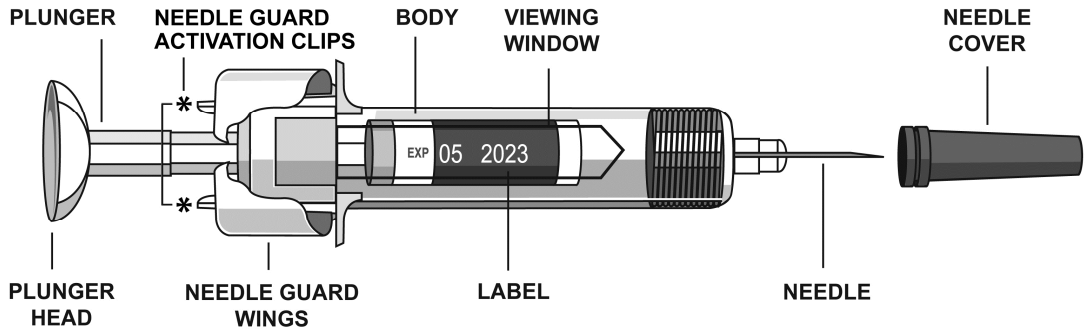


Figure 1

1. Check the number of pre-filled syringes and prepare the materials:

Preparing for use of the pre-filled syringe

- Take the pre-filled syringe(s) out of the refrigerator. Let the pre-filled syringe stand outside the box for about half an hour. This will let the liquid come to a comfortable temperature for injection (room temperature). Do not remove the syringe's needle cover while allowing it to reach room temperature
- Hold the pre-filled syringe by the body of the syringe with the covered needle pointing upward
- Do not hold by the plunger head, plunger, needle guard wings, or needle cover
- Do not pull back on the plunger at any time
- Do not remove the needle cover from the pre-filled syringe until instructed to do so
- Do not touch the needle guard activation clips (as indicated by asterisks * in Figure 1) to prevent prematurely covering the needle with the needle guard.

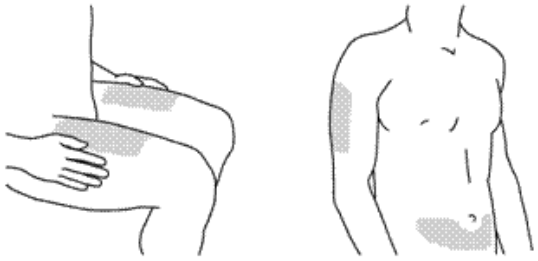
Check the pre-filled syringe(s) to make sure

- the number of pre-filled syringes and strength is correct
  - If your dose is 45 mg you will get one 45 mg pre-filled syringe of Stelara
  - If your dose is 90 mg you will get two 45 mg pre-filled syringes of Stelara and you will need to give yourself two injections. Choose two different sites for these injections (e.g. one injection in the right thigh and the other injection in the left thigh), and give the injections one right after the other.
- it is the right medicine
- it has not passed its expiry date
- the pre-filled syringe is not damaged
- the solution in the pre-filled syringe is clear to slightly opalescent (having a pearl-like shine) and colourless to light yellow
- the solution in the pre-filled syringe is not discoloured or cloudy and does not contain any foreign particles
- the solution in the pre-filled syringe is not frozen.

Get everything together that you need and lay out on a clean surface. This includes antiseptic wipes, a cotton ball or gauze, and a sharps container.

2. Choose and prepare the injection site:
Choose an injection site (see Figure 2)

- Stelara is given by injection under the skin (subcutaneously)
- Good places for the injection are the upper thigh or around the belly (abdomen) at least 5 cm away from the navel (belly button)
- If possible, do not use areas of skin that show signs of psoriasis
- If someone will assist in giving you the injection, then he or she may also choose the upper arms as an injection site



*Areas in gray are recommended injection sites.

Figure 2

Prepare the injection site

- Wash your hands very well with soap and warm water
- Wipe the injection site on the skin with an antiseptic wipe
- **Do not** touch this area again before giving the injection

3. Remove the needle cover (see Figure 3):

- The needle cover should **not** be removed until you are ready to inject the dose
- Pick up the pre-filled syringe, hold the body of the syringe with one hand
- Pull the needle cover straight off and throw it away. Do not touch the plunger while you do this

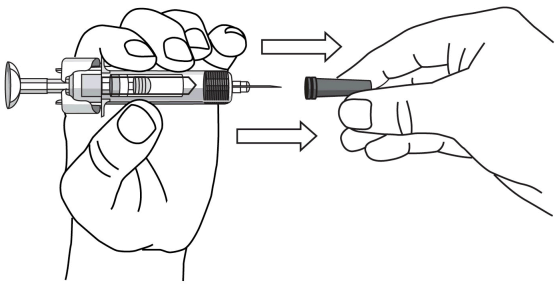


Figure 3

- You may notice an air bubble in the pre-filled syringe or a drop of liquid at the end of the needle. These are both normal and do not need to be removed
- Do not touch the needle or allow it to touch any surface
- Do not use the pre-filled syringe if it is dropped without the needle cover in place. If this happens, please contact your doctor or pharmacist
- Inject the dose promptly after removing the needle cover.

4. Inject the dose:

- Hold the pre-filled syringe with one hand between the middle and index fingers and place the thumb on top of the plunger head and use the other hand to gently pinch the cleaned skin between your thumb and index finger. Do not squeeze it tightly
- Do not pull back on the plunger at any time
- In a single and swift motion, insert the needle through the skin as far as it will go (see Figure 4)

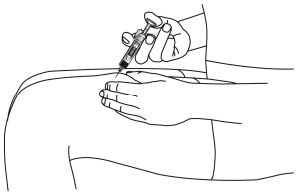


Figure 4

- Inject all of the medication by pushing in the plunger until the plunger head is completely between the needle guard wings (see Figure 5)

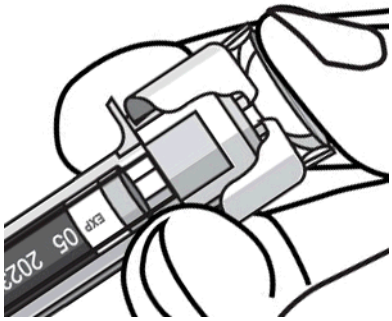


Figure 5

- When the plunger is pushed as far as it will go, continue to keep the pressure on the plunger head, take out the needle and let go of the skin (see Figure 6)

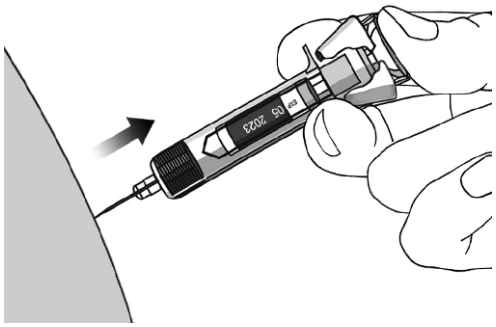


Figure 6

- Slowly take your thumb off the plunger head to allow the empty syringe to move up until the entire needle is covered by the needle guard, as shown by Figure 7:

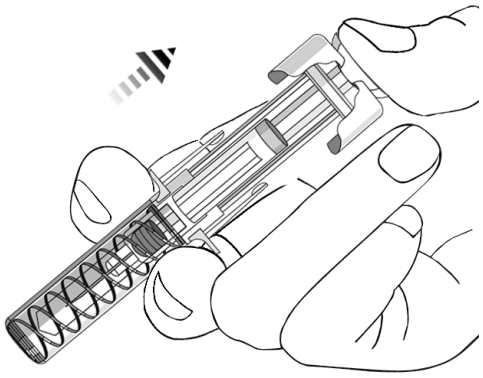


Figure 7

5. After the injection:

- Press an antiseptic wipe over the injection site for a few seconds after the injection.
- There may be a small amount of blood or liquid at the injection site. This is normal.
- You can press a cotton ball or gauze over the injection site and hold for 10 seconds.
- Do not rub the skin at the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

6. Disposal:

- Used syringes should be placed in a puncture-resistant container, like a sharps container (see Figure 8). Never re-use a syringe, for your safety and health and for the safety of others. Dispose of your sharps container according to your local regulations
- Antiseptic wipes and other supplies can be disposed of in your garbage.

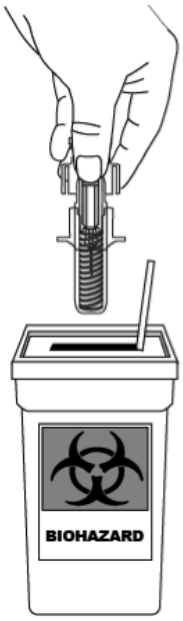


Figure 8

Package leaflet: Information for the user

STELARA 90 mg solution for injection in pre-filled syringe
Ustekinumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine. If you are the parent or caregiver who will give Stelara to a child, please read this information carefully.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Stelara is and what it is used for
2. What you need to know before you use Stelara
3. How to use Stelara
4. Possible side effects
5. How to store Stelara
6. Contents of the pack and other information

1. What Stelara is and what it is used for

What Stelara is
Stelara contains the active substance ‘ustekinumab’, a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Stelara belongs to a group of medicines called ‘immunosuppressants’. These medicines work by weakening part of the immune system.

What Stelara is used for
Stelara is used to treat the following inflammatory diseases:
- Plaque psoriasis - in adults and children aged 6 years and older
- Psoriatic arthritis - in adults
- Moderate to severe Crohn’s disease - in adults
- Moderate to severe ulcerative colitis – in adults

Plaque psoriasis
Plaque psoriasis is a skin condition that causes inflammation affecting the skin and nails. Stelara will reduce the inflammation and other signs of the disease.

Stelara is used in adults with moderate to severe plaque psoriasis, who cannot use ciclosporin, methotrexate or phototherapy, or where these treatments did not work.

Stelara is used in children and adolescents aged 6 years and older with moderate to severe plaque psoriasis who are unable to tolerate phototherapy or other systemic therapies or where these treatments did not work.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Stelara to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.
- Slow down the damage to your joints.

Crohn's disease
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

Ulcerative colitis
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

2. What you need to know before you use Stelara

Do not use Stelara:
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks is important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Warnings and precautions
Talk to your doctor or pharmacist before using Stelara. Your doctor will check how well you are before each treatment. Make sure you tell your doctor about any illness you have before each treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Stelara. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Stelara can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Stelara. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Stelara tell your doctor:
- **If you ever had an allergic reaction to Stelara**. Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like Stelara weaken part of the immune system. This may increase the risk of cancer.
- **If you have or have had a recent infection.**
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you have ever had an allergic reaction to latex or Stelara injection** – the container of this medicinal product contains latex rubber, which may cause severe allergic reactions in people who are sensitive to latex. See 'Look out for serious side effects' in section 4 for the signs of an allergic reaction.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis** – such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using these therapies together with Stelara has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.

- **If you are having or have ever had injections to treat allergies** – it is not known if Stelara may affect these.
- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Children and adolescents
Stelara is not recommended for use in children with psoriasis under 6 years of age, or for use in children under 18 years of age with psoriatic arthritis, Crohn's disease, or ulcerative colitis because it has not been studied in this age group.

Other medicines, vaccines and Stelara
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Stelara.

Pregnancy and breast-feeding
- It is preferable to avoid the use of Stelara in pregnancy. The effects of Stelara in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Stelara and for at least 15 weeks after the last Stelara treatment.
- Talk to your doctor if you are pregnant, think you may be pregnant or are planning to have a baby.
- Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use Stelara -do not do both.

Driving and using machines
Stelara has no or negligible influence on the ability to drive and use machines.

3. How to use Stelara

Stelara is intended for use under the guidance and supervision of a doctor experienced in treating conditions for which STELARA is intended.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Stelara is given
Your doctor will decide how much Stelara you need to use and for how long.

Adults aged 18 years or older
Psoriasis or Psoriatic Arthritis
- The recommended starting dose is 45 mg Stelara. Patients who weigh more than 100 kilograms (kg) may start on a dose of 90 mg instead of 45 mg.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks. The following doses are usually the same as the starting dose.

Crohn's disease or Ulcerative Colitis
- During treatment, the first dose of approximately 6 mg/kg Stelara will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, you will receive the next dose of 90 mg Stelara after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').

- In some patients, after the first injection under the skin, 90 mg Stelara may be given every 8 weeks. Your doctor will decide when you should receive your next dose.

Children and adolescents aged 6 years or older
Psoriasis
- The doctor will work out the right dose for you, including the amount (volume) of Stelara to be injected to give the right dose. The right dose for you will depend on your body weight at the time each dose is given.
- A 45 mg vial is available for children who need to receive less than the full 45 mg dose.
- If you weigh less than 60 kg, the recommended dose is 0.75 mg of Stelara per kg body weight.
- If you weigh 60 kg to 100 kg, the recommended dose is 45 mg Stelara.
- If you weigh more than 100 kg, the recommended dose is 90 mg Stelara.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks.

How Stelara is given
- Stelara is given as an injection under the skin ('subcutaneously'). At the start of your treatment, medical or nursing staff may inject Stelara.
- However, you and your doctor may decide that you may inject Stelara yourself. In this case you will get training on how to inject Stelara yourself.
- For instructions on how to inject Stelara, see 'Instructions for administration' at the end of this leaflet.

Talk to your doctor if you have any questions about giving yourself an injection.

If you use more Stelara than you should
If you have used or been given too much Stelara, talk to a doctor or pharmacist straight away. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use Stelara
If you forget a dose, contact your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose.

If you stop using Stelara
It is not dangerous to stop using Stelara. However, if you stop, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.
- Serious allergic reactions ('anaphylaxis') are rare in people taking Stelara (may affect up to 1 in 1,000 people). Signs include:
  - difficulty breathing or swallowing
  - low blood pressure, which can cause dizziness or light-headedness
  - swelling of the face, lips, mouth or throat.
- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as

cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Stelara again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.

- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)
- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)
- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Stelara may make you less able to fight infections, and some infections could become serious. You must look out for signs of infection while you are using Stelara. These include:

- fever, flu-like symptoms, night sweats
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, or skin infections or shingles that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use Stelara until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people)**:**

- Diarrhoea
- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching ('pruritus')
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people)**:**

- Tooth infections
- Vaginal yeast infection
- Depression
- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Feeling weak

- Drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary
- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)
- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1000 people)
- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Stelara

- Keep this medicine out of the sight and reach of children.
- Store in a refrigerator (2°C–8°C). Do not freeze.
- Keep the pre-filled syringe in the outer carton in order to protect from light.
- Do not shake Stelara pre-filled syringes. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:
- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Stelara looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.

Stelara is for single use only. Any unused product remaining in the syringe should be thrown away. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Stelara contains
- The active substance is ustekinumab. Each pre-filled syringe contains 90 mg ustekinumab in 1 mL.
- The other ingredients are L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sucrose and water for injections.

What Stelara looks like and contents of the pack
Stelara is a clear to slightly opalescent (having a pearl-like shine), colourless to light yellow solution for injection. The solution may contain a few small translucent or white particles of protein. It is supplied as a carton pack containing 1 single-dose, glass 1 mL pre-filled syringe. Each pre-filled syringe contains 90 mg ustekinumab in 1 mL of solution for injection.

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This leaflet was last revised in {MM/YYYY}.

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

Instructions for administration

At the start of treatment, your healthcare provider will assist you with your first injection. However, you and your doctor may decide that you may inject Stelara yourself. If this happens, you will get training on how to inject Stelara. Talk to your doctor if you have any questions about giving yourself an injection.

- Do not mix Stelara with other liquids for injection
- Do not shake Stelara pre-filled syringes. This is because strong shaking may damage the medicine. Do not use the medicine if it has been shaken strongly.

Figure 1 shows what the pre-filled syringe looks like.

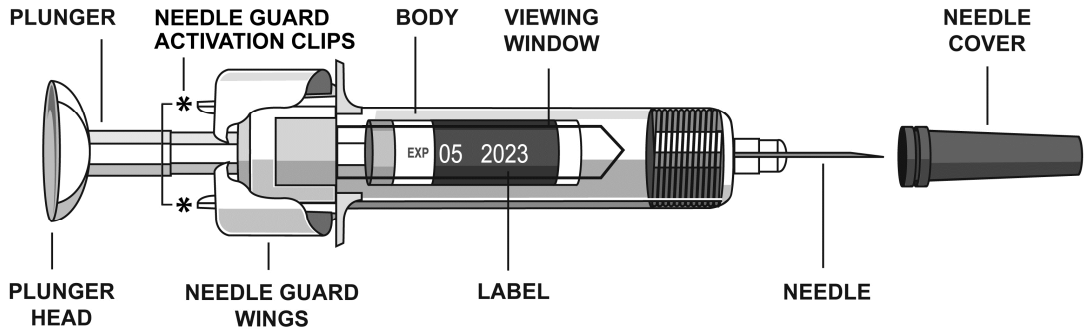


Figure 1

1. Check the number of pre-filled syringes and prepare the materials:
Preparing for use of the pre-filled syringe

- Take the pre-filled syringe(s) out of the refrigerator. Let the pre-filled syringe stand outside the box for about half an hour. This will let the liquid come to a comfortable temperature for injection (room temperature). Do not remove the syringe's needle cover while allowing it to reach room temperature
- Hold the pre-filled syringe by the body of the syringe with the covered needle pointing upward
- Do not hold by the plunger head, plunger, needle guard wings, or needle cover
- Do not pull back on the plunger at any time
- Do not remove the needle cover from the pre-filled syringe until instructed to do so
- Do not touch the needle guard activation clips (as indicated by asterisks * in Figure 1) to prevent prematurely covering the needle with the needle guard.

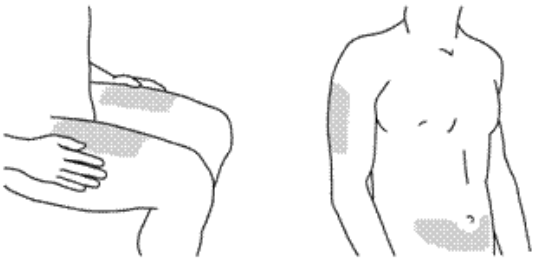
Check the pre-filled syringe(s) to make sure

- the number of pre-filled syringes and strength is correct
  - If your dose is 90 mg you will get one 90 mg pre-filled syringe of Stelara.
- it is the right medicine
- it has not passed its expiry date
- the pre-filled syringe is not damaged
- the solution in the pre-filled syringe is clear to slightly opalescent (having a pearl-like shine) and colourless to light yellow
- the solution in the pre-filled syringe is not discoloured or cloudy and does not contain any foreign particles
- the solution in the pre-filled syringe is not frozen.

Get everything together that you need and lay out on a clean surface. This includes antiseptic wipes, a cotton ball or gauze, and a sharps container.

2. Choose and prepare the injection site:
Choose an injection site (see Figure 2)

- Stelara is given by injection under the skin (subcutaneously)
- Good places for the injection are the upper thigh or around the belly (abdomen) at least 5 cm away from the navel (belly button)
- If possible, do not use areas of skin that show signs of psoriasis
- If someone will assist in giving you the injection, then he or she may also choose the upper arms as an injection site.



*Areas in gray are recommended injection sites.

Figure 2

Prepare the injection site
- Wash your hands very well with soap and warm water
- Wipe the injection site on the skin with an antiseptic wipe
- **Do not** touch this area again before giving the injection.

3. Remove the needle cover (see Figure 3):
- The needle cover should **not** be removed until you are ready to inject the dose
- Pick up the pre-filled syringe, hold the body of the syringe with one hand
- Pull the needle cover straight off and throw it away. Do not touch the plunger while you do this

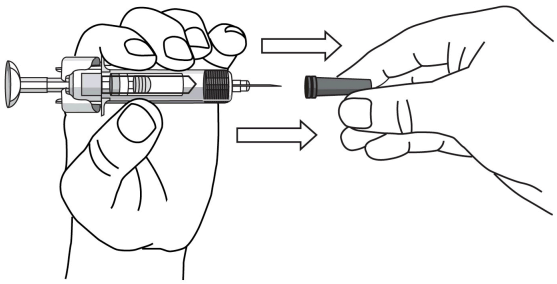


Figure 3

- You may notice an air bubble in the pre-filled syringe or a drop of liquid at the end of the needle. These are both normal and do not need to be removed
- Do not touch the needle or allow it to touch any surface
- Do not use the pre-filled syringe if it is dropped without the needle cover in place. If this happens, please contact your doctor or pharmacist
- Inject the dose promptly after removing the needle cover.

4. Inject the dose:
- Hold the pre-filled syringe with one hand between the middle and index fingers and place the thumb on top of the plunger head and use the other hand to gently pinch the cleaned skin between your thumb and index finger. Do not squeeze it tightly
- Do not pull back on the plunger at any time
- In a single and swift motion, insert the needle through the skin as far as it will go (see Figure 4)

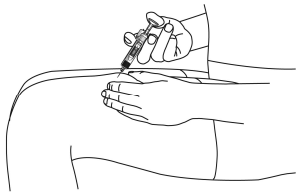


Figure 4

- Inject all of the medication by pushing in the plunger until the plunger head is completely between the needle guard wings (see Figure 5)

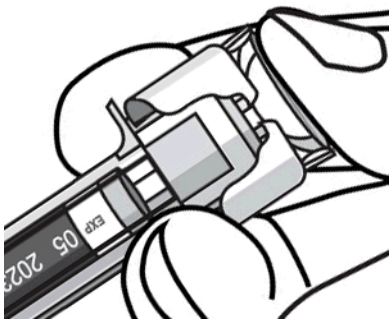


Figure 5

- When the plunger is pushed as far as it will go, continue to keep the pressure on the plunger head, take out the needle and let go of the skin (see Figure 6)

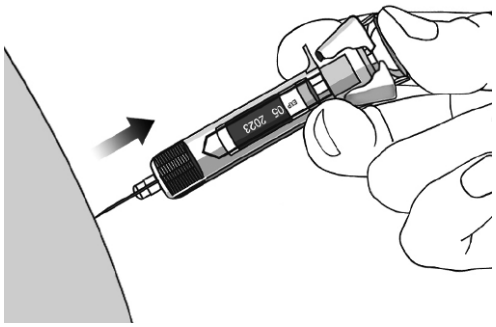


Figure 6

- Slowly take your thumb off the plunger head to allow the empty syringe to move up until the entire needle is covered by the needle guard, as shown by Figure 7:

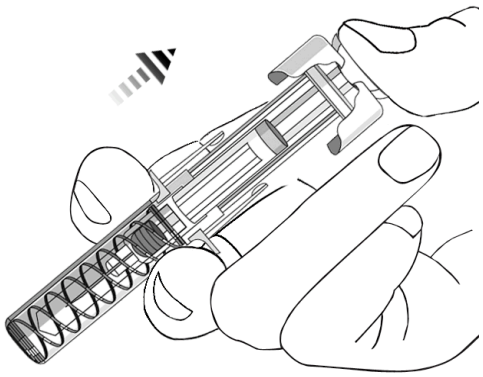


Figure 7

5. After the injection:

- Press an antiseptic wipe over the injection site for a few seconds after the injection.
- There may be a small amount of blood or liquid at the injection site. This is normal.
- You can press a cotton ball or gauze over the injection site and hold for 10 seconds.
- Do not rub the skin at the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

6. Disposal:

- Used syringes should be placed in a puncture-resistant container, like a sharps container (see Figure 8). Never re-use a syringe, for your safety and health and for the safety of others. Dispose of your sharps container according to your local regulations
- Antiseptic wipes and other supplies can be disposed of in your garbage.

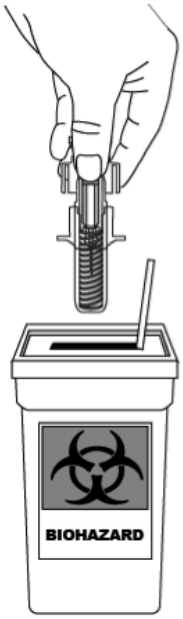


Figure 8

1.7　同種同効品一覧表

販売名	ステラーラ点滴静注 130mg	ステラーラ皮下注 45mg シリンジ	エンタイビオ点滴静注用 300mg	ゼルヤンツ錠 5mg
一般名	ウステキヌマブ（遺伝子組換え）	ウステキヌマブ（遺伝子組換え）	ベドリズマブ（遺伝子組換え）	トファシチニブクエン酸塩
会社名	製造販売元　ヤンセンファーマ株式会社 販売元　　田辺三菱製薬株式会社	製造販売元　ヤンセンファーマ株式会社 販売元　　田辺三菱製薬株式会社	武田薬品工業株式会社	ファイザー株式会社
効能又は効果	○中等症から重症の活動期クローン病の導入療法（既存治療で効果不十分な場合に限る） ○中等症から重症の潰瘍性大腸炎の寛解導入療法（既存治療で効果不十分な場合に限る）	○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 ○中等症から重症の活動期クローン病の維持療法（既存治療で効果不十分な場合に限る） ○中等症から重症の潰瘍性大腸炎の維持療法（既存治療で効果不十分な場合に限る）	○中等症から重症の潰瘍性大腸炎の治療及び維持療法(既存治療で効果不十分な場合に限る) ○中等症から重症の活動期クローン病の治療及び維持療法(既存治療で効果不十分な場合に限る)	○既存治療で効果不十分な関節リウマチ ○中等症から重症の潰瘍性大腸炎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）
添付文書改訂日	―	―	2019 年 5 月改訂	2019 年 9 月改訂

<table>
<tr><td>販売名</td><td>シンポニー皮下注 50mg シリンジ
同皮下注 50mg オートインジェクター</td><td>ヒュミラ皮下注 40mg シリンジ 0.4mL
同皮下注 80mg シリンジ 0.8mL
同皮下注 40mg ペン 0.4mL
同皮下注 80mg ペン 0.8mL</td><td>レミケード点滴静注用 100</td><td></td></tr>
<tr><td>一般名</td><td>ゴリムマブ（遺伝子組換え）</td><td>アダリムマブ（遺伝子組換え）</td><td>インフリキシマブ（遺伝子組換え）</td><td></td></tr>
<tr><td>会社名</td><td>製造販売元　ヤンセンファーマ株式会社
発売元　　田辺三菱製薬株式会社</td><td>製造販売（輸入）元　アッヴィ合同会社
販売元　　エーザイ株式会社
プロモーション提携　EA ファーマ株式会社</td><td>製造販売元　田辺三菱製薬株式会社
製造元　　Janssen Biotech, Inc.</td><td></td></tr>
<tr><td>効能又は効果</td><td>○既存治療で効果不十分な関節リウマチ（関節の構造的損傷の防止を含む）
○中等症から重症の潰瘍性大腸炎の改善及び維持療法（既存治療で効果不十分な場合に限る）</td><td>ヒュミラ皮下注20mgシリンジ0.2mL
ヒュミラ皮下注40mgシリンジ0.4mL
ヒュミラ皮下注40mgペン0.4mL
既存治療で効果不十分な下記疾患
多関節に活動性を有する若年性特発性関節炎
ヒュミラ皮下注40mgシリンジ0.4mL
ヒュミラ皮下注80mgシリンジ0.8mL
ヒュミラ皮下注40mgペン0.4mL
ヒュミラ皮下注80mgペン0.8mL
関節リウマチ(関節の構造的損傷の防止を含む)
化膿性汗腺炎
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，膿疱性乾癬
強直性脊椎炎
腸管型ベーチェット病
非感染性の中間部，後部又は汎ぶどう膜炎
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)
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)
(参考)
<table>
<tr><td></td><td colspan="3">ヒュミラ皮下注</td></tr>
<tr><td></td><td>20mgシリンジ 0.2mL</td><td>40mgシリンジ 0.4mL
40mgペン 0.4mL</td><td>80mgシリンジ 0.8mL
80mgペン 0.8mL</td></tr>
<tr><td>関節リウマチ</td><td>－</td><td>○</td><td>○</td></tr>
<tr><td>化膿性汗腺炎</td><td>－</td><td>○</td><td>○</td></tr>
<tr><td>尋常性乾癬，関節症性乾癬，膿疱性乾癬</td><td>－</td><td>○</td><td>○</td></tr>
<tr><td>強直性脊椎炎</td><td>－</td><td>○</td><td>○</td></tr>
<tr><td>多関節に活動性を有する若年性特発性関節炎</td><td>○</td><td>○</td><td>－</td></tr>
<tr><td>腸管型ベーチェット病</td><td>－</td><td>○</td><td>○</td></tr>
<tr><td>クローン病</td><td>－</td><td>○</td><td>○</td></tr>
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40mgペン 0.4mL</td><td>80mgシリンジ 0.8mL
80mgペン 0.8mL</td></tr>
<tr><td>潰瘍性大腸炎</td><td>－</td><td>○</td><td>○</td></tr>
<tr><td>非感染性の中間部，後部又は汎ぶどう膜炎</td><td>－</td><td>○</td><td>○</td></tr>
</table></td><td>既存治療で効果不十分な下記疾患
○ 関節リウマチ（関節の構造的損傷の防止を含む）
○ ベーチェット病による難治性網膜ぶどう膜炎
○ 尋常性乾癬、関節症性乾癬、膿疱性乾癬、乾癬性紅皮症
○ 強直性脊椎炎
○ 腸管型ベーチェット病、神経型ベーチェット病、血管型ベーチェット病
○ 川崎病の急性期
○ 次のいずれかの状態を示すクローン病の治療及び維持療法（既存治療で効果不十分な場合に限る）
中等度から重度の活動期にある患者
外瘻を有する患者
○ 中等症から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）</td><td></td></tr>
<tr><td>添付文書改訂日</td><td>2019 年 11 月改訂</td><td>2019 年 4 月改訂</td><td>2019 年 5 月改訂</td><td></td></tr>
</table>

201x 年 x 月改訂（第 1 版）
貯　　法：2～8℃で保存すること
有効期間：36 ヵ月

日本標準商品分類番号
873999

ヒト型抗ヒト IL-12/23p40 モノクローナル抗体製剤

生物由来製品
劇薬
処方箋医薬品※

ウステキヌマブ（遺伝子組換え）製剤

ステラーラ®点滴静注 130mg

Stelara® Intravenous Infusion

※ 注意－医師等の処方箋により使用すること

承認番号	22900AMX00514000
販売開始	2017 年 5 月

1. 警告

1.1 本剤は IL-12/23 の作用を選択的に抑制する薬剤であるため、感染のリスクを増大させる可能性がある。また、結核の既往歴を有する患者では結核を活動化させる可能性がある。また、本剤との関連性は明らかではないが、悪性腫瘍の発現が報告されている。本剤が疾病を完治させる薬剤でないことも含め、これらの情報を患者に十分説明し、患者が理解したことを確認した上で、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。また、本剤投与後に副作用が発現した場合には、主治医に連絡するよう患者に注意を与えること。[2.1、8.1-8.3、9.1.1-9.1.3、11.1.2、11.1.3、15.1.5 参照]

1.2 重篤な感染症
ウイルス、細菌及び真菌による重篤な感染症が報告されているため、十分な観察を行うなど感染症の発症に注意すること。[2.1、8.1、9.1.1、11.1.2 参照]

1.3 結核等の感染症について診療経験を有する内科等の医師と十分な連携をとり使用すること。[2.2、8.2、9.1.2、11.1.3 参照]

1.4 本剤の治療を開始する前に、適応疾患の既存治療の適用を十分勘案すること。[5.1、5.2 参照]

1.5 本剤についての十分な知識と適応疾患の治療の知識・経験をもつ医師が使用すること。

2. 禁忌（次の患者には投与しないこと）

2.1 重篤な感染症の患者［症状を悪化させるおそれがある。］
［1.1、1.2、8.1、11.1.2 参照］

2.2 活動性結核の患者［症状を悪化させるおそれがある。］
［1.3、8.2、11.1.3 参照］

2.3 本剤の成分に対し過敏症の既往歴のある患者

3. 組成・性状

3.1 組成

販売名	ステラーラ点滴静注 130mg
有効成分	（1 バイアル 26mL 中） ウステキヌマブ（遺伝子組換え）130mg 含有
添加剤	精製白糖 2210mg、L-ヒスチジン 20mg、L-ヒスチジン塩酸塩水和物 27mg、ポリソルベート 80 10.4mg、L-メチオニン 10.4mg、エデト酸ナトリウム水和物 0.52mg

本剤はマウスミエローマ（Sp2/0）細胞株を用いて製造される。

3.2 製剤の性状

色・性状	無色～淡黄色の澄明な液
pH	5.7～6.3
浸透圧比	約 1（生理食塩液に対する比）

4. 効能又は効果

○中等症から重症の活動期クローン病の導入療法（既存治療で効果不十分な場合に限る）
○中等症から重症の潰瘍性大腸炎の寛解導入療法（既存治療で効果不十分な場合に限る）

5. 効能又は効果に関連する注意

〈クローン病〉

5.1 過去の治療において、栄養療法、他の薬物療法（5-アミノサリチル酸製剤、ステロイド、アザチオプリン等）等による適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に投与すること。[1.4 参照]

〈潰瘍性大腸炎〉

5.2 過去の治療において、他の薬物療法（ステロイド、アザチオプリン等）等による適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に投与すること。[1.4 参照]

6. 用法及び用量

通常、成人にはウステキヌマブ（遺伝子組換え）として、導入療法の初回に、以下に示す用量を単回点滴静注する。

患者体重	投与量
55kg 以下	260mg
55kg を超える 85kg 以下	390mg
85kg を超える	520mg

7. 用法及び用量に関連する注意

7.1 維持療法については、本剤初回投与の 8 週後、ウステキヌマブ（遺伝子組換え）皮下投与用製剤の投与を行う。維持療法における用法・用量は、ウステキヌマブ（遺伝子組換え）皮下投与用製剤の添付文書を参照すること。

7.2 本剤と他の生物製剤の併用について安全性及び有効性は確立していないので併用を避けること。

8. 重要な基本的注意

8.1 本剤は IL-12/23 の作用を選択的に抑制する薬剤であり、感染のリスクを増大させる可能性がある。そのため、本剤の投与に際しては、十分な観察を行い、感染症の発症や増悪に注意すること。感染の徴候又は症状があらわれた場合には、直ちに主治医に連絡するよう患者を指導すること。[1.1、1.2、2.1、9.1.1、11.1.2 参照]

8.2 本剤投与に先立って結核に関する十分な問診及び胸部 X 線検査に加え、インターフェロン-γ 遊離試験又はツベルクリン反応検査を行い、適宜胸部 CT 検査等を行うことにより、結核感染の有無を確認すること。
また、本剤投与中も、胸部 X 線検査等の適切な検査を定期的に行うなど結核症の発現には十分に注意し、結核を疑う症状（持続する咳、体重減少、発熱等）が発現した場合には速やかに担当医に連絡するよう患者に指導すること。[1.1、1.3、2.2、9.1.2、11.1.3 参照]

8.3 本剤は IL-12/23 の作用を選択的に抑制する薬剤であり、悪性腫瘍発現の可能性があり、臨床試験において皮膚及び皮膚以外の悪性腫瘍の発現が報告されている。本剤との因果関係は明確ではないが、悪性腫瘍の発現には注意すること。[1.1、9.1.3、15.1.5 参照]

8.4 生ワクチン接種に起因する感染症発現の可能性を否定できないので、本剤による治療中は、生ワクチンを接種しないこと。

8.5 他の生物製剤から変更する場合は感染症の徴候について患者の状態を十分に観察すること。

8.6 本剤投与中又は投与当日に Infusion Reaction（発熱、悪寒、嘔気、嘔吐、頭痛、発疹等）が発現する可能性があるため、患者の状態を十分に観察し、異常が認められた場合には直ちに投与を中止し、適切な処置（抗ヒスタミン薬、解熱鎮痛薬の投与等）を行うこと。

最新の添付文書を参照すること

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 感染症（重篤な感染症を除く）の患者、感染症が疑われる又は再発性感染症の既往歴のある患者
感染症を悪化又は顕在化させるおそれがある。[1.1、1.2、8.1、11.1.2 参照]

9.1.2 結核の既往歴を有する患者又は結核感染が疑われる患者
(1)結核の既往歴を有する患者では、結核を活動化させるおそれがある。[1.1、1.3、8.2、11.1.3 参照]
(2)結核の既往歴を有する場合又は結核感染が疑われる場合には、結核の診療経験がある医師に相談すること。下記のいずれかの患者には、結核等の感染症について診療経験を有する医師と連携の下、原則として本剤の投与開始前に適切な抗結核薬を投与すること。[1.1、1.3、8.2、11.1.3 参照]
・胸部画像検査で陳旧性結核に合致するか推定される陰影を有する患者
・結核の治療歴（肺外結核を含む）を有する患者
・インターフェロン-γ 遊離試験やツベルクリン反応検査等の検査により、既感染が強く疑われる患者
・結核患者との濃厚接触歴を有する患者

9.1.3 悪性腫瘍の既往歴のある患者、悪性腫瘍を発現し、本剤投与継続を考慮している患者
悪性腫瘍の既往歴のある患者を対象とする試験は実施されていない。[1.1、8.3 参照]

9.1.4 アレルゲン免疫療法を受けた患者
アレルゲン免疫療法を受けた患者における本剤の使用については評価されていないが、本剤はアレルゲン免疫療法に影響を与える可能性がある。特にアナフィラキシーに対するアレルゲン免疫療法を受けている又は過去に受けたことのある患者については注意すること。

9.5 妊婦

妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。本剤はカニクイザルにおいて胎児への移行が報告されているが、胚・胎児毒性及び催奇形性は認められていない。

9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。本剤のヒトにおける乳汁への移行は不明であるが、動物実験（サル）で乳汁中へ移行することが報告されている。

9.7 小児等

小児等の患者を対象とした臨床試験は実施していない。

9.8 高齢者

感染症等の副作用の発現に留意し、十分な観察を行うこと。一般に生理機能が低下している。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 **アナフィラキシー**（頻度不明）
発疹、蕁麻疹、血管浮腫等があらわれることがある。

11.1.2 **重篤な感染症**（1%未満）
ウイルス、細菌あるいは真菌による重篤な感染症（蜂巣炎、憩室炎、骨髄炎、胃腸炎、肺炎及び尿路感染等）があらわれることがある。重篤な感染症が発現した場合には、感染が回復するまで本剤の投与をしないこと。[1.1、1.2、2.1、8.1、9.1.1 参照]

11.1.3 **結核**（頻度不明）
結核が発現又は再活性化する可能性がある。[1.1、1.3、2.2、8.2、9.1.2 参照]

11.1.4 **間質性肺炎**（頻度不明）
咳嗽、呼吸困難、発熱、肺音の異常（捻髪音）等が認められた場合には、速やかに胸部 X 線、胸部 CT、血清マーカー等の検査を実施すること。間質性肺炎が疑われた場合には投与を中止し、副腎皮質ホルモン剤の投与等の適切な処置を行うこと。

11.2 その他の副作用

	1%以上	1%未満	頻度不明
感染症及び寄生虫症	鼻咽頭炎	上気道感染、外陰腟真菌感染、帯状疱疹、副鼻腔炎	歯肉炎
精神障害			うつ病
神経系障害	頭痛	浮動性めまい	
呼吸器、胸郭及び縦隔障害		咽喉頭疼痛、鼻閉	好酸球性肺炎
胃腸障害	悪心	嘔吐、下痢	
皮膚及び皮下組織障害	そう痒症	発疹、蕁麻疹、ざ瘡	膿疱性乾癬、乾癬性紅皮症
筋骨格系及び結合組織障害		関節痛、筋痛、背部痛	
全身障害及び投与局所様態	疲労	無力症、注射部位反応	

14. 適用上の注意

14.1 薬剤調製時の注意

14.1.1 患者の体重に基づき投与量及び必要な本剤のバイアルの数を算出する。

14.1.2 日局生理食塩液の 250mL 点滴バッグから、追加する本剤と同量分を抜き取る。

14.1.3 必要なバイアルごとに本剤 26mL を 250mL 点滴バッグに加え、穏やかに混合する。総液量は 250mL とする。

14.2 薬剤投与時の注意

14.2.1 投与前に本剤の希釈液を目視で確認すること。不透明粒子や変色又は異物が認められた場合は使用しないこと。

14.2.2 本剤の希釈液を 1 時間以上かけて投与すること。

14.2.3 調製後は 8 時間以内に投与完了すること。

14.2.4 本剤は無菌・パイロジェンフリーで蛋白結合性の低いインラインフィルター（ポアサイズ 0.2μm）を用いて投与すること。

14.2.5 他の薬剤と同じ静注ラインで同時注入はしないこと。

14.2.6 本剤のバイアルは 1 回使い切りである。未使用残液については適切に廃棄すること。

15. その他の注意

15.1 臨床使用に基づく情報

15.1.1 尋常性乾癬（関節症性乾癬を合併した患者を含む）を対象としたウステキヌマブ皮下投与用製剤の国内臨床試験は、72 週間までの期間で実施されている。また、尋常性乾癬を対象としたウステキヌマブ皮下投与用製剤の海外臨床試験は、5 年間までの期間で実施されており、関節症性乾癬を対象とした海外臨床試験は 24 ヵ月までの期間で実施されている。また、クローン病及び潰瘍性大腸炎では、それぞれ国際共同臨床試験（本剤単回投与後にウステキヌマブ皮下投与用製剤を反復投与）は、52 週間までの期間で実施されている。これらの期間を超えたウステキヌマブ製剤の長期投与時の安全性は確立していない。

15.1.2 尋常性乾癬（関節症性乾癬を合併した患者を含む）を対象としたウステキヌマブ皮下投与用製剤の国内臨床試験において、153 例中 10 例（6.5%）が 72 週目までに抗ウステキヌマブ抗体陽性となり、尋常性乾癬及び関節症性乾癬を対象とした海外臨床試験においても、ウステキヌマブ皮下投与用製剤投与により 5.2～12.4%の患者が抗ウステキヌマブ抗体陽性となった。抗ウステキヌマブ抗体が陽性となった患者では効果が減弱化する傾向がみられた。また、約 1 年間の本剤及びウステキヌマブ皮下投与用製剤の投与により、クローン病を対象とした国際共同試験において 2.9%、潰瘍性大腸炎を対象とした国際共同試験において 4.6%の患者がそれぞれ抗ウステキヌマブ抗体陽性となった。抗ウステキヌマブ抗体が陽性となった患者では効果が減弱化する可能性がある。

15.1.3 尋常性乾癬を対象としたウステキヌマブ皮下投与用製剤の海外臨床試験において、糖尿病を合併する患者では皮下投与後の血清中ウステキヌマブのトラフ濃度が低く、効果が

低い傾向がみられた。

15.1.4 本剤との関連性は明らかではないが、海外において可逆性後白質脳症症候群（RPLS）の症例が報告されている。

15.1.5 海外の尋常性乾癬、関節症性乾癬、クローン病、潰瘍性大腸炎を対象とした臨床試験（第Ⅱ相及び第Ⅲ相試験）において、プラセボ対照期間の非黒色腫皮膚癌を除く悪性腫瘍の発現頻度は、ウステキヌマブ投与群が0.11/100人年(1例/929人年)、プラセボ投与群が0.23/100人年（1例/434人年）であった。非黒色腫皮膚癌の発現頻度は、ウステキヌマブ投与群が0.43/100人年（4例/929人年)、プラセボ投与群が0.46/100人年（2例/433人年）であった。また、対照及び非対照期間において、6709名（11561人年）にウステキヌマブが投与された。その追跡調査中央値は1.0年で、尋常性乾癬を対象とした臨床試験では3.3年、関節症性乾癬を対象とした臨床試験では1.0年、クローン病を対象とした臨床試験では0.6年、潰瘍性大腸炎を対象とした臨床試験では1.0年であった。非黒色腫皮膚癌を除く悪性腫瘍の発現頻度は、0.54/100人年（62例/11561人年）で、主なものは前立腺癌、結腸直腸癌、黒色腫、乳癌であった。ウステキヌマブ投与群で報告された悪性腫瘍の発現頻度は、一般人口で予測される発現頻度と同様であった（標準化発生比：0.93［95%信頼区間：0.71、1.20］年齢、性別、人種により補正)。非黒色腫皮膚癌の発現頻度は0.49/100人年（56例/11545人年）であった。皮膚基底細胞癌と皮膚有棘細胞癌の発現比率は3:1であり一般人口で予測される発現頻度と同様であった。［1.1、8.3参照］

15.2 非臨床試験に基づく情報

15.2.1 げっ歯類のIL-12及びIL-23に対して中和活性を示さないため、がん原性試験は実施されていない。げっ歯類のモデルにおいて、IL-12/IL-23p40の阻害により、悪性腫瘍の増大が報告されている[1]。また、IL-12及びIL-23の両方の遺伝子を欠損させたマウスでは、紫外線による皮膚癌の発生時期が早まり、発生頻度も増加することが報告されている[2]。

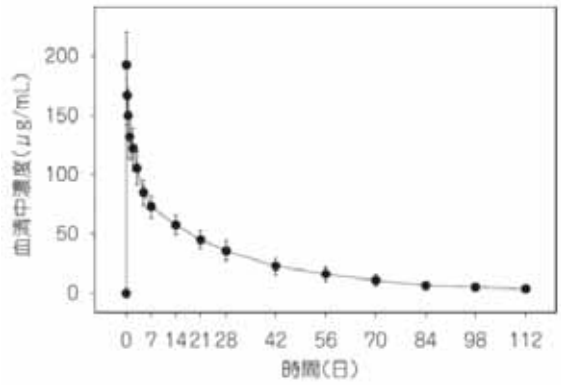
16. 薬物動態

16.1 血中濃度

〈効能共通〉

16.1.1 単回投与

健康成人に本剤6mg/kg※を単回静脈内投与したときの血中濃度推移と薬物動態パラメータは以下であった。[3]（外国人データ）



外国人健康成人に本剤を単回静脈内投与したときの血清中ウステキヌマブ濃度推移（平均値±標準偏差、69例）

薬物動態パラメータ（外国人データ）

AUC_{∞} （μg・day/mL）	3132.4 注) (690.2)
$t_{1/2}$ (day)	24.7 注) (6.2)

平均値（標準偏差）、69例（注) 68例）

※本剤の体重別用量群（承認用量）：体重55kg以下=本剤260mg、体重55kg超85kg以下=本剤390mg、体重85kg超=本剤520mg

〈クローン病〉

16.1.2 単回投与（国際共同臨床試験）

日本人及び外国人のクローン病患者に、用法・用量に従って本剤を単回静脈内投与したとき、血清中ウステキヌマブ濃度は投与1時間後に113（23.7）μg/mL（n=28）及び126（34.1）μg/mL（n=412）、8週後に4.04（2.92）μg/mL（n=15）及び7.09（4.57）μg/mL（n=292）を示した。[4]［平均値（標準偏差)］

〈潰瘍性大腸炎〉

16.1.3 単回投与（国際共同臨床試験）

日本人及び外国人の潰瘍性大腸炎患者に、用法・用量に従って本剤を単回静脈内投与したとき、血清中ウステキヌマブ濃度は投与1時間後に129(27.4)μg/mL(n=39)及び126(33.3)μg/mL（n=273)、8週後に7.40（4.04）μg/mL（n=36）及び9.14（5.50）μg/mL（n=224）を示した。［平均値（標準偏差)］[5]

16.4 代謝

ウステキヌマブは、ヒトIgG1由来の抗体であることから、他の免疫グロブリン[6]と同様に代謝されると推察される。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈クローン病〉

17.1.1 第Ⅲ相国際共同臨床試験（CRD3001試験）

中等症から重症の活動期のクローン病患者（日本人症例56例を含む）を対象とし、プラセボ、本剤130mg又は体重別用量（6mg/kg）[a]を0週目に単回静脈内投与した導入試験を実施した。抗TNF薬で効果不十分又は忍容性がなかった患者を対象とした。6週目にclinical response[注1)]が得られた被験者の割合は、プラセボ群の21.5%に対して、本剤130mg群で34.3%、本剤体重別用量（6mg/kg）[a]群で33.3%であった。[7]

注1） Crohn’s Disease Activity Index（CDAI）スコアのベースラインからの100ポイント以上の減少(ベースラインのCDAIスコアが220ポイント以上248ポイント以下の被験者については、CDAIスコアが150ポイント未満を達成していた場合、clinical responseが得られたとみなした)

投与量	プラセボ	130mg [b]	体重別用量（6mg/kg）[a]
Clinical response rate（6週目）	21.5% (53/247例)	34.3% [c] (84/245例)	33.3% [c] (83/249例)

a)：本剤の体重別用量群(承認用量)：体重55kg以下=本剤260mg、体重55kg超85kg以下=本剤390mg、体重85kg超=本剤520mg

b)：国内未承認用量

c)：p<0.01、対プラセボ群、Cochran-Mantel-Haenszelカイ二乗検定

本剤130mg群の副作用発現頻度は、26.0%（64例/246例）であった。主要な副作用は、頭痛7例（2.8%)、関節痛5例（2.0%)、鼻咽頭炎4例（1.6%)、発疹4例（1.6%)、上気道感染3例（1.2%)、そう痒症3例（1.2%)、筋痛3例（1.2%）であった。

本剤体重別用量（6mg/kg）群の副作用発現頻度は、28.1%（70例/249例）であった。主要な副作用は、頭痛9例（3.6%)、嘔吐6例(2.4%)、悪心5例（2.0%)、疲労5例（2.0%)、上気道感染4例（1.2%）であった。

17.1.2 第Ⅲ相国際共同臨床試験（CRD3002試験）

中等症から重症の活動期のクローン病患者（日本人症例26例を含む）を対象とし、プラセボ、本剤130mg又は体重別用量（6mg/kg）[a]を0週目に単回静脈内投与した導入試験を実施した。既存治療（コルチコステロイド又は免疫調節剤）で効果不十分であり、かつ抗TNF薬による治療歴がないか又は抗TNF薬治療歴を有するものの効果不十分又は忍容性がないことが示されていない患者を対象とした。6週目にclinical response[注1)]が得られた被験者の割合は、プラセボ群の28.7%に対して、本剤130mg群で51.7%、本剤体重別用量（6mg/kg）[a]群で55.5%であった。[8]

注1） Crohn’s Disease Activity Index（CDAI）スコアのベースラインからの100ポイント以上の減少(ベースラインのCDAIスコアが220ポイント以上248ポイン

ト以下の被験者については、CDAI スコアが 150 ポイント未満を達成していた場合、clinical response が得られたとみなした）

投与量	プラセボ	130mg [b)]	体重別用量（6mg/kg） [a)]
Clinical response rate（6 週目）	28.7%（60/209 例）	51.7% [c)]（108/209 例）	55.5% [c)]（116/209 例）

a）：本剤の体重別用量群（承認用量）：体重 55kg 以下=本剤 260mg、体重 55kg 超 85kg 以下=本剤 390mg、体重 85kg 超=本剤 520mg
b）：国内未承認用量
c）：p<0.001、対プラセボ群、Cochran-Mantel-Haenszel カイ二乗検定

本剤 130mg 群の副作用発現頻度は、13.2%（28 例/212 例）であった。主要な副作用は、頭痛 7 例（3.3%）、悪心 3 例（1.4%）、無力症 3 例（1.4%）、上気道感染 2 例（0.9%）であった。
本剤体重別用量（6mg/kg）群の副作用発現頻度は、12.1%（25 例/207 例）であった。主要な副作用は、頭痛 6 例（2.9%）、上気道感染 3 例（1.4%）、悪心 3 例（1.4%）、鼻咽頭炎 2 例（1.0%）、嘔吐 2 例（1.0%）、疲労 2 例（1.0%）であった。

〈潰瘍性大腸炎〉

17.1.3 第Ⅲ相国際共同臨床試験（UC03001 試験）

中等症から重症の活動期の潰瘍性大腸炎患者（日本人症例 107 例を含む）を対象とし、プラセボ、本剤 130mg 又は体重別用量（6mg/kg） [b)]を 0 週目に単回静脈内投与した導入試験を実施した。生物学的製剤（抗 TNF 薬又はベドリズマブ）又は既存治療（コルチコステロイド又は免疫調節薬）で効果不十分又は忍容性がなかった患者を対象とした。8 週目に clinical remission [注 1)] が得られた被験者の割合は、プラセボ群の 5.3%に対して、本剤 130mg 群で 15.6%、本剤体重別用量（6mg/kg） [b)]群で 15.5%であった。[5)]

注1） Mayo スコアが 2 以下、かついずれのサブスコアも 1 を超えていない場合

投与量	プラセボ	130mg [c)]	体重別用量（6mg/kg） [b)]
Clinical remission（8 週目）	5.3%（17/319 例）	15.6%[a)]（50/320 例）	15.5%[a)]（50/322 例）

a）：p<0.001、対プラセボ群、Cochran-Mantel-Haenszel カイ二乗検定
b）：本剤の体重別用量群（承認用量）：体重 55kg 以下=本剤 260mg、体重 55kg 超 85kg 以下=本剤 390mg、体重 85kg 超=本剤 520mg
c）：国内未承認用量

本剤 130mg 群の副作用発現頻度は、11.2%（36 例/321 例）であった。主要な副作用は、頭痛 7 例（2.2%）、そう痒症 5 例（1.6%）、疲労 3 例（0.9%）、悪心 3 例（0.9%）、浮動性めまい 2 例（0.6%）、無力症 2 例（0.6%）であった。
本剤体重別用量（6mg/kg）群の副作用発現頻度は、14.1%（45 例/320 例）であった。主要な副作用は、上気道感染 5 例（1.6%）疲労 4 例（1.3%）、そう痒症 3 例（0.9%）、頭痛 3 例（0.9%）、発疹 3 例(0.9%)、ざ瘡 3 例(0.9%)であった。

18. 薬効薬理

18.1 作用機序

In vitro 試験において、本剤はヒトインターロイキン（IL）-12 及び IL-23 を構成する p40 たん白サブユニットに特異的かつ高い親和性で結合し [9)]、IL-12 及び IL-23 受容体複合体への結合を阻害した [10)]。

18.2 薬理作用

In vitro 試験において、IL-12 及び IL-23 によって活性化されるヘルパーT 細胞及びナチュラルキラー細胞などの免疫担当細胞の細胞内シグナル伝達並びに IFN-γ、IL-17A、IL-17F 及び IL-22 の分泌を抑制した [11)]。

19. 有効成分に関する理化学的知見

一般的名称：ウステキヌマブ（遺伝子組換え）
[Ustekinumab (Genetical Recombination)]
分子式：H 鎖 $C_{2207}H_{3410}N_{582}O_{671}S_{17}$
L 鎖 $C_{1034}H_{1596}N_{274}O_{337}S_{6}$
分子量：148,079～149,690
本　質：ウステキヌマブは、ヒトインターロイキン-12 及びインターロイキン-23 の p40 サブユニットに対する遺伝子組換えヒト IgG1 モノクローナル抗体である。
ウステキヌマブは、マウスミエローマ（Sp2/0）細胞により産生される。
ウステキヌマブは、449 個のアミノ酸残基からなる H 鎖（γ1 鎖）2 分子及び 214 個のアミノ酸残基からなる L 鎖（κ 鎖）2 分子で構成される糖タンパク質（分子量：148,079～149,690）である。

20. 取扱い上の注意

20.1 激しく振盪しないこと。
20.2 本剤は遮光保存する必要があるため、使用直前に外箱から取り出すこと。
20.3 凍結しないこと。

21. 承認条件

医薬品リスク管理計画を策定の上、適切に実施すること。

22. 包装

26mL［1 バイアル］

23. 主要文献

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2) Maeda A, et al.：Cancer Res. 2006; 66: 2962-2969
3) 社内資料：健康成人におけるウステキヌマブ製剤の薬物動態比較試験（2017 年 3 月 30 日承認、CTD2.7.1.2）
4) 社内資料：クローン病に対する国際共同臨床試験の薬物濃度データの併合結果（2017 年 3 月 30 日承認）
5) 社内資料：国際共同第Ⅲ相臨床試験成績（UC03001 寛解導入試験）（2020 年 3 月承認、CTD2.7.6.1）
6) Tabrizi MA, et al.：Drug Discov Today. 2006; 11: 81-88
7) 社内資料：国際共同第Ⅲ相臨床試験成績（CRD3001）（2017 年 3 月 30 日承認、CTD2.7.6.2）
8) 社内資料：国際共同第Ⅲ相臨床試験成績（CRD3002）（2017 年 3 月 30 日承認、CTD2.7.6.3）
9) Luo J, et al.：J Mol Biol. 2010; 402: 797-812
10) 社内資料：ウステキヌマブのヒト IL-12 及び IL-23 中和作用機序（2017 年 3 月 30 日承認、CTD2.6.2.1）
11) 社内資料：ウステキヌマブのヒト IL-12 及び IL-23 中和作用の機能的効果（2017 年 3 月 30 日承認、CTD2.6.2.1）

24. 文献請求先及び問い合わせ先

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26. 製造販売業者等

26.1 製造販売元

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販売開始	2011 年 3 月

1. 警告

1.1 本剤は IL-12/23 の作用を選択的に抑制する薬剤であるため、感染のリスクを増大させる可能性がある。また、結核の既往歴を有する患者では結核を活動化させる可能性がある。また、本剤との関連性は明らかではないが、悪性腫瘍の発現が報告されている。本剤が疾病を完治させる薬剤でないことも含め、これらの情報を患者に十分説明し、患者が理解したことを確認した上で、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。また、本剤投与後に副作用が発現した場合には、主治医に連絡するよう患者に注意を与えること。[2.1、8.1-8.3、9.1.1-9.1.3、11.1.2、11.1.3、15.1.6 参照]

1.2 重篤な感染症
ウイルス、細菌及び真菌による重篤な感染症が報告されているため、十分な観察を行うなど感染症の発症に注意すること。[2.1、8.1、9.1.1、11.1.2 参照]

1.3 結核等の感染症について診療経験を有する内科等の医師と十分な連携をとり使用すること。[2.2、8.2、9.1.2、11.1.3 参照]

1.4 本剤の治療を開始する前に、適応疾患の既存治療の適応を十分勘案すること。[5.1、5.2、5.3 参照]

1.5 本剤についての十分な知識と適応疾患の治療の知識・経験をもつ医師が使用すること。

2. 禁忌（次の患者には投与しないこと）

2.1 重篤な感染症の患者［症状を悪化させるおそれがある。］
［1.1、1.2、8.1、11.1.2 参照］

2.2 活動性結核の患者［症状を悪化させるおそれがある。］
［1.3、8.2、11.1.3 参照］

2.3 本剤の成分に対し過敏症の既往歴のある患者

3. 組成・性状

3.1 組成

販売名	ステラーラ皮下注 45mg シリンジ
有効成分	（1 シリンジ 0.5mL 中） ウステキヌマブ（遺伝子組換え）45mg 含有
添加剤	精製白糖 38mg、L-ヒスチジン 0.5mg、ポリソルベート 80 0.02mg

本剤はマウスミエローマ（Sp2/0）細胞株を用いて製造される。

3.2 製剤の性状

色・性状	無色～淡黄色の澄明又はわずかに混濁した液
pH	5.7～6.3
浸透圧比	約 1（生理食塩液に対する比）

4. 効能又は効果

○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
○中等症から重症の活動期クローン病の維持療法（既存治療で効果不十分な場合に限る）
○中等症から重症の潰瘍性大腸炎の維持療法（既存治療で効果不十分な場合に限る）

5. 効能又は効果に関連する注意

〈尋常性乾癬及び関節症性乾癬〉

5.1 以下のいずれかを満たす尋常性乾癬又は関節症性乾癬患者に投与すること。[1.4 参照]
・紫外線療法を含む既存の全身療法（生物製剤を除く）で十分な効果が得られず、皮疹が体表面積の 10%以上に及ぶ患者。
・難治性の皮疹又は関節症状を有する患者。

〈クローン病〉

5.2 過去の治療において、栄養療法、他の薬物療法（5-アミノサリチル酸製剤、ステロイド、アザチオプリン等）等による適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に投与すること。[1.4 参照]

〈潰瘍性大腸炎〉

5.3 過去の治療において、他の薬物療法（ステロイド、アザチオプリン等）等による適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に投与すること。[1.4 参照]

6. 用法及び用量

〈尋常性乾癬及び関節症性乾癬〉
通常、成人にはウステキヌマブ（遺伝子組換え）として 1 回 45mg を皮下投与する。初回投与及びその 4 週後に投与し、以降 12 週間隔で投与する。
ただし、効果不十分な場合には 1 回 90mg を投与することができる。

〈クローン病/潰瘍性大腸炎〉
ウステキヌマブ(遺伝子組換え)の点滴静注製剤を投与8週後に、通常、成人にはウステキヌマブ（遺伝子組換え）として 90mg を皮下投与し、以降は 12 週間隔で 90mg を皮下投与する。なお、効果が減弱した場合には、投与間隔を 8 週間に短縮できる。

7. 用法及び用量に関連する注意

〈効能共通〉

7.1 本剤と他の生物製剤の併用について安全性及び有効性は確立していないので併用を避けること。

〈尋常性乾癬及び関節症性乾癬〉

7.2 本剤による治療反応が得られない場合、投与開始から 28 週以内には増量を含めて治療計画を再考すること。また、増量を行っても十分な治療反応が得られない場合、本剤の投与継続を慎重に再考すること。

〈クローン病/ 潰瘍性大腸炎〉

7.3 ウステキヌマブ（遺伝子組換え）点滴静注製剤による導入療法の初回投与 8 週後に、本剤の皮下投与を開始すること。（導入療法における用法・用量は、ウステキヌマブ(遺伝子組換え)の点滴静注製剤の添付文書を参照すること。）

7.4 本剤の 8 週間隔への投与間隔短縮は、本剤の皮下投与中に効果が減弱した患者に対し、本剤の皮下投与開始から 8 週以降に行うことができる。本剤の投与間隔を短縮しても 16 週以内に治療効果が得られない場合、投与を継続しても効果が得られない可能性があることから、本剤の投与継続の必要性を検討すること。

7.5 本剤の皮下投与開始後、本剤の 2 回目の皮下投与までに治療反応がない場合、投与を継続しても効果が得られない可能性があることから、本剤の投与継続の必要性を検討すること。

8. 重要な基本的注意

8.1 本剤は IL-12/23 の作用を選択的に抑制する薬剤であり、感

最新の添付文書を参照すること

染のリスクを増大させる可能性がある。そのため、本剤の投与に際しては、十分な観察を行い、感染症の発症や増悪に注意すること。感染の徴候又は症状があらわれた場合には、直ちに主治医に連絡するよう患者を指導すること。[1.1、1.2、2.1、9.1.1、11.1.2 参照]

8.2 本剤投与に先立って結核に関する十分な問診及び胸部X線検査に加え、インターフェロン-γ 遊離試験又はツベルクリン反応検査を行い、適宜胸部 CT 検査等を行うことにより、結核感染の有無を確認すること。
また、本剤投与中も、胸部X線検査等の適切な検査を定期的に行うなど結核症の発現には十分に注意し、結核を疑う症状（持続する咳、体重減少、発熱等）が発現した場合には速やかに担当医に連絡するよう患者に指導すること。[1.1、1.3、2.2、9.1.2、11.1.3 参照]

8.3 本剤は IL-12/23 の作用を選択的に抑制する薬剤であり、悪性腫瘍発現の可能性があり、臨床試験において皮膚及び皮膚以外の悪性腫瘍の発現が報告されている。本剤との因果関係は明確ではないが、悪性腫瘍の発現には注意すること。[1.1、9.1.3、15.1.6 参照]

8.4 生ワクチン接種に起因する感染症発現の可能性を否定できないので、本剤による治療中は、生ワクチンを接種しないこと。

8.5 他の生物製剤から変更する場合は感染症の徴候について患者の状態を十分に観察すること。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 感染症（重篤な感染症を除く）の患者、感染症が疑われる又は再発性感染症の既往歴のある患者
感染症を悪化又は顕在化させるおそれがある。[1.1、1.2、8.1、11.1.2 参照]

9.1.2 結核の既往歴を有する患者又は結核感染が疑われる患者
(1)結核の既往歴を有する患者では、結核を活動化させるおそれがある。[1.1、1.3、8.2、11.1.3 参照]
(2)結核の既往歴を有する場合又は結核感染が疑われる場合には、結核の診療経験がある医師に相談すること。下記のいずれかの患者には、結核等の感染症について診療経験を有する医師と連携の下、原則として本剤の投与開始前に適切な抗結核薬を投与すること。[1.1、1.3、8.2、11.1.3 参照]
・胸部画像検査で陳旧性結核に合致するか推定される陰影を有する患者
・結核の治療歴（肺外結核を含む）を有する患者
・インターフェロン-γ 遊離試験やツベルクリン反応検査等の検査により、既感染が強く疑われる患者
・結核患者との濃厚接触歴を有する患者

9.1.3 悪性腫瘍の既往歴のある患者、悪性腫瘍を発現し、本剤投与継続を考慮している患者
悪性腫瘍の既往歴のある患者を対象とする試験は実施されていない。[1.1、8.3 参照]

9.1.4 アレルゲン免疫療法を受けた患者
アレルゲン免疫療法を受けた患者における本剤の使用については評価されていないが、本剤はアレルゲン免疫療法に影響を与える可能性がある。特にアナフィラキシーに対するアレルゲン免疫療法を受けている又は過去に受けたことのある患者については注意すること。

9.1.5 ラテックス過敏症の既往歴又は可能性のある患者
アレルギー反応を起こすことがあるので注意すること。注射針部分のカバーは、乾燥天然ゴム（ラテックス類縁物質）を含む。

9.5 妊婦
妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。本剤はカニクイザルにおいて胎児への移行が報告されているが、胚・胎児毒性及び催奇形性は認められていない。

9.6 授乳婦
治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。本剤のヒトにおける乳汁への移行は不明であるが、動物実験（サル）で乳汁中へ移行することが報告されている。

9.7 小児等
小児等の患者を対象とした臨床試験は実施していない。

9.8 高齢者
感染症等の副作用の発現に留意し、十分な観察を行うこと。一般に生理機能が低下している。

11. 副作用
次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 アナフィラキシー（頻度不明）
発疹、蕁麻疹、血管浮腫等があらわれることがある。

11.1.2 重篤な感染症（1～5%未満）
ウイルス、細菌あるいは真菌による重篤な感染症（蜂巣炎、憩室炎、骨髄炎、胃腸炎、肺炎及び尿路感染等）があらわれることがある。重篤な感染症が発現した場合には、感染が回復するまで本剤の投与をしないこと。[1.1、1.2、2.1、8.1、9.1.1 参照]

11.1.3 結核（頻度不明）
結核が発現又は再活性化する可能性がある。[1.1、1.3、2.2、8.2、9.1.2 参照]

11.1.4 間質性肺炎（頻度不明）
咳嗽、呼吸困難、発熱、肺音の異常（捻髪音）等が認められた場合には、速やかに胸部X線、胸部CT、血清マーカー等の検査を実施すること。間質性肺炎が疑われた場合には投与を中止し、副腎皮質ホルモン剤の投与等の適切な処置を行うこと。

11.2 その他の副作用

	5%以上	1～5%未満	1%未満	頻度不明
感染症及び寄生虫症	鼻咽頭炎	上気道感染	外陰腟真菌感染、副鼻腔炎、帯状疱疹、歯肉炎	
精神障害			うつ病	
神経系障害		頭痛、浮動性めまい		
呼吸器、胸郭及び縦隔障害		咽喉頭疼痛	鼻閉	好酸球性肺炎
胃腸障害		悪心、嘔吐	下痢	
皮膚及び皮下組織障害		発疹、そう痒症	ざ瘡、蕁麻疹	膿疱性乾癬、乾癬性紅皮症
筋骨格系及び結合組織障害		関節痛	筋痛、背部痛	
全身障害及び投与局所様態		注射部位反応、疲労	無力症	

14. 適用上の注意

14.1 薬剤投与前の注意
14.1.1 投与前に冷蔵庫から取り出し室温に戻しておくことが望ましい。

14.2 薬剤投与時の注意
14.2.1 皮膚が敏感な部位、皮膚に異常がある部位、乾癬の部位には注射しないこと。
14.2.2 投与部位は、上腕部、腹部、大腿部又は臀部が望ましい。同一箇所へ繰り返し注射することは避けること。

15. その他の注意

15.1 臨床使用に基づく情報
15.1.1 尋常性乾癬（関節症性乾癬を合併した患者を含む）を対

象としたウステキヌマブ皮下投与用製剤の国内臨床試験は、72 週間までの期間で実施されている。また、尋常性乾癬を対象としたウステキヌマブ皮下投与用製剤の海外臨床試験は、5 年間までの期間で実施されており、関節症性乾癬を対象とした海外臨床試験は 24 ヵ月までの期間で実施されている。また、クローン病及び潰瘍性大腸炎では、それぞれを対象とした本剤の国際共同臨床試験（ウステキヌマブ静注用製剤を単回投与後に本剤を反復投与）は、52 週間までの期間で実施されている。これらの期間を超えたウステキヌマブ製剤の長期投与時の安全性は確立していない。

15.1.2 尋常性乾癬（関節症性乾癬を合併した患者を含む）を対象とした国内臨床試験において、本剤投与により 153 例中 10 例（6.5%）が 72 週目までに抗ウステキヌマブ抗体陽性となり、尋常性乾癬及び関節症性乾癬を対象とした海外臨床試験においても、本剤投与により 5.2～12.4%の患者が抗ウステキヌマブ抗体陽性となった。抗ウステキヌマブ抗体が陽性となった患者では効果が減弱化する傾向がみられた。また、約 1 年間の本剤及びウステキヌマブ点滴静注製剤の投与により、クローン病を対象とした国際共同試験において 2.9%、潰瘍性大腸炎を対象とした国際共同試験において 4.6%の患者がそれぞれ抗ウステキヌマブ抗体陽性となった。抗ウステキヌマブ抗体が陽性となった患者では効果が減弱化する可能性がある。

15.1.3 尋常性乾癬を対象とした海外臨床試験において、糖尿病を合併する患者では皮下投与後の血清中ウステキヌマブのトラフ濃度が低く、効果が低い傾向がみられた。

15.1.4 尋常性乾癬に対し免疫抑制剤又は光線療法と併用した場合の安全性及び有効性は確立していない。

15.1.5 本剤との関連性は明らかではないが、海外において可逆性後白質脳症症候群（RPLS）の症例が報告されている。

15.1.6 海外の尋常性乾癬、関節症性乾癬、クローン病、潰瘍性大腸炎を対象とした臨床試験（第Ⅱ相及び第Ⅲ相試験）において、プラセボ対照期間の非黒色腫皮膚癌を除く悪性腫瘍の発現頻度は、本剤投与群が 0.11/100 人年（1 例/929 人年）、プラセボ投与群が 0.23/100 人年（1 例/434 人年）であった。非黒色腫皮膚癌の発現頻度は、本剤投与群が 0.43/100 人年（4 例/929 人年）、プラセボ投与群が 0.46/100 人年（2 例/433 人年）であった。また、対照及び非対照期間において、6709 名（11561 人年）に本剤が投与された。その追跡調査中央値は 1.0 年で、尋常性乾癬を対象とした臨床試験では 3.3 年、関節症性乾癬を対象とした臨床試験では 1.0 年、クローン病を対象とした臨床試験では 0.6 年、潰瘍性大腸炎を対象とした臨床試験では 1.0 年であった。非黒色腫皮膚癌を除く悪性腫瘍の発現頻度は、0.54/100 人年（62 例/11561 人年）で、主なものは前立腺癌、結腸直腸癌、黒色腫、乳癌であった。本剤投与群で報告された悪性腫瘍の発現頻度は、一般人口で予測される発現頻度と同様であった（標準化発生比：0.93［95%信頼区間：0.71、1.20］年齢、性別、人種により補正）。非黒色腫皮膚癌の発現頻度は 0.49/100 人年（56 例/11545 人年）であった。皮膚基底細胞癌と皮膚有棘細胞癌の発現比率は 3:1 であり一般人口で予測される発現頻度と同様であった。［1.1、8.3 参照］

15.2 非臨床試験に基づく情報

15.2.1 げっ歯類の IL-12 及び IL-23 に対して中和活性を示さないため、がん原性試験は実施されていない。げっ歯類のモデルにおいて、IL-12/IL-23p40 の阻害により、悪性腫瘍の増大が報告されている[1]。また、IL-12 及び IL-23 の両方の遺伝子を欠損させたマウスでは、紫外線による皮膚癌の発生時期が早まり、発生頻度も増加することが報告されている[2]。

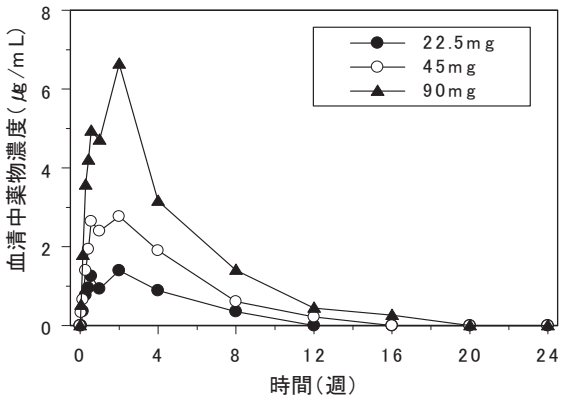
16. 薬物動態

16.1 血中濃度

〈尋常性乾癬及び関節症性乾癬〉

16.1.1 単回投与

乾癬患者に本剤 22.5mg※、45mg 及び 90mg を単回皮下投与したとき、血清中ウステキヌマブ濃度は投与 6.99～10.49 日後に最高濃度に達した後、約 3 週の消失半減期で低下した。血清中ウステキヌマブの C_{max} 及び AUC_{∞} は、22.5～90mg の用量範囲において用量にほぼ比例して増加した。[3]



乾癬患者に本剤を単回皮下投与したときの
血清中ウステキヌマブ濃度推移（中央値、各 6 例）

薬物動態パラメータ

用量	22.5mg※	45mg	90mg
C_{max} (μg/mL)	1.44 (1.21～1.70)	2.77 (2.63～3.38)	9.58 (7.23～10.20)
T_{max} (day)	6.99 (4.76～12.24)	10.48 (4.73～14.00)	10.49 (6.98～13.99)
AUC_{∞} (μg·day/mL)	61.3 (49.2～75.8)	109.4 (96.9～171.9)	242.7 (195.7～272.3)

中央値（四分位範囲）、各 6 例
※本剤の承認用量は 1 回 45/ 90mg である。

16.1.2 反復投与

乾癬患者に 0、4 週及びその後 12 週毎に 52 週目まで本剤 45mg 又は 90mg を反復皮下投与したとき、血清中ウステキヌマブ濃度は投与開始 28 週目までに定常状態に達した。本剤 45mg 又は 90mg を反復皮下投与したとき、定常状態における血清中ウステキヌマブのトラフ濃度の中央値はそれぞれ 0.25～0.31 及び 0.55～0.76 μg/mL であり、用量にほぼ比例して上昇した。[4]

16.1.3 体重の影響

乾癬患者において、体重 100kg 超の患者に本剤 90mg を投与したときの血清中ウステキヌマブのトラフ濃度は体重 100kg 以下の患者に本剤 45mg を投与したときと同程度であった。（外国人データ）[5]

〈クローン病〉

16.1.4 反復投与（国際共同臨床試験）

日本人及び外国人のクローン病患者に、本剤の点滴静注 8 週後、及びその後 8 週毎又は 12 週毎に本剤 90mg を皮下投与したとき、血清中ウステキヌマブ濃度は 2 回目の皮下投与前までに定常状態に達した。日本人及び外国人のクローン病患者に本剤 90mg を 8 週間隔で反復皮下投与したとき、定常状態における血清中ウステキヌマブのトラフ濃度の中央値はそれぞれ 1.02～2.14 μg/mL（n=7～9）及び 1.98～2.26 μg/mL（n=74～115）であった。日本人及び外国人のクローン病患者に本剤 90mg を 12 週間隔で反復皮下投与したとき、定常状態における血清中ウステキヌマブのトラフ濃度の中央値はそれぞれ 0.37～0.70 μg/mL（n=6～7）及び 0.62～0.76 μg/mL（n=75～103）であった。[6]

〈潰瘍性大腸炎〉

16.1.5 反復投与（国際共同臨床試験）

日本人及び外国人の潰瘍性大腸炎患者に、本剤の点滴静注 8 週後、及びその後 8 週毎又は 12 週毎に本剤 90mg を皮下投与したとき、血清中ウステキヌマブ濃度は 2 回目の皮下投与前までに定常状態に達した。日本人及び外国人の潰瘍性大腸炎患者に本剤 90mg を 8 週間隔で反復皮下投与したとき、定常状態における血清中ウステキヌマブのトラフ濃度の中央値はそれぞれ 2.46～2.96 μg/mL（n=17～18）及び 2.69～3.12 μg/mL（n=131～148）であった。日本人及び外国人の潰瘍性大腸炎患者に本剤 90mg を 12 週間隔で反復皮下投与したとき、定常状態における血清中ウステキヌマブのトラフ濃度の中央値はそれぞれ 0.86～1.03 μg/mL（n=17～19）及び 0.93～1.23 μg/mL（n=122～141）であった。[7]

16.2 吸収

乾癬患者に本剤を単回静脈内投与（0.09、0.27、0.9、4.5mg/kg）又は単回皮下投与（0.27、0.675、1.35、2.7mg/kg）したときの血清中ウステキヌマブ濃度を用いて算出した、ウステキヌマブを皮下投与したときの絶対的バイオアベイラビリティは約57.2%と推定された。（外国人データ）

16.4 代謝

ウステキヌマブは、ヒト IgG1 由来の抗体であることから、他の免疫グロブリン[8]と同様に代謝されると推察される。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈尋常性乾癬及び関節症性乾癬〉

17.1.1 国内臨床試験（第Ⅱ/Ⅲ相試験）

中等症から重症の局面型皮疹を有する尋常性乾癬及び関節症性乾癬（局面型皮疹の病変が体表面積（BSA）の 10%以上、かつ PASI スコアが 12 以上）患者を対象とし、プラセボ、ウステキヌマブ 45mg 及び 90mg を 0、4 週に投与し、以降 12 週毎にウステキヌマブを 52 週まで投与したプラセボ対照二重盲検比較試験を実施した。12 週後の PASI[注1)]スコアがベースラインから 75%以上改善した患者の割合（以下、PASI75）を下表に示す。12 週後の本剤投与群における PASI75 は、プラセボ群に比べて有意に高かった。その後、緩やかに上昇した後 64 週目までほぼ一定の値で推移した。[4]

注 1)Psoriasis Area and Severity Index

投与量	プラセボ	45mg	90mg
12 週後 PASI75	6.5% (2/31 例)	59.4% a) (38/64 例)	67.7% a) (42/62 例)

a)：p<0.0001、対プラセボ群、Fisher の正確検定

本剤 45mg 群の副作用発現頻度は、87.5%（56 例/64 例）であった。主要な副作用は、鼻咽頭炎 27 例(42.2%)、関節痛 6 例(9.4%)、頭痛 5 例（7.8%）、下痢 4 例（6.3%）、そう痒症 2 例（3.1%）であった。

本剤 90mg 群の副作用発現頻度は、87.1%（54 例/62 例）であった。主要な副作用は、鼻咽頭炎 26 例(41.9%)、ざ瘡 3 例(4.8%)、上気道感染 2 例(3.2%)、蕁麻疹 2 例(3.2%)、背部痛 2 例(3.2%)であった。

〈クローン病〉

17.1.2 国際共同臨床試験（第Ⅲ相試験）

中等症から重症の活動期のクローン病患者（日本人症例 20 例を含む）を対象とした本剤の導入試験から移行した被験者を対象に、プラセボ又は本剤 90mg（8 週間隔又は 12 週間隔）を皮下投与した維持試験を実施した。本剤の導入試験で 8 週目に clinical response[注1)]が得られた被験者における本試験 44 週目の clinical remission rate[注2)]を下表に示す。44 週目に clinical remission が得られた被験者の割合は、プラセボ群の 35.9%に対して、本剤 90mg の 8 週間隔投与群で 53.5%、本剤 90mg の 12 週間隔投与群で 48.8%であった。[6]

注 1)Crohn’s Disease Activity Index（CDAI）スコアのベースラインからの 100 ポイント以上の減少（ベースラインの CDAI スコアが 220 ポイント以上 248 ポイント以下の被験者については、CDAI スコアが 150 ポイント未満を達成していた場合、clinical response が得られたとみなした）

注 2)CDAI スコア<150 ポイント

投与量	プラセボ	90 mg 8 週間隔投与	90 mg 12 週間隔投与
Clinical remission rate	35.9% (47/131 例)	53.5% a) (68/127 例)	48.8%b) (63/129 例)

a)：p<0.01、対プラセボ群、Cochran-Mantel-Haenszel カイ二乗検定
b)：p<0.05、対プラセボ群、Cochran-Mantel-Haenszel カイ二乗検定

本剤 90mg 8 週間隔投与群の副作用発現頻度は、29.8%（39 例/131 例）であった。主要な副作用は、上気道感染 6 例(4.6%)、頭痛 5 例（3.8%）、鼻咽頭炎 4 例（3.1%）、外陰膣真菌感染 3 例（2.3%）、悪心 3 例（2.3%）であった。

本剤 90mg 12 週間隔投与群の副作用発現頻度は、25.8%（34 例/132 例）であった。主な副作用は、頭痛 4 例（3.0%）、疲労 3 例（2.3%）、悪心 3 例（2.3%）、上気道感染 2 例（1.5%）、鼻咽頭炎 2 例（1.5%）、発疹 2 例（1.5%）であった。

〈潰瘍性大腸炎〉

17.1.3 国際共同臨床試験（第Ⅲ相試験）

中等症から重症の活動期の潰瘍性大腸炎患者（日本人症例 92 例を含む）を対象とした本剤の導入試験から移行した被験者を対象に、プラセボ又は本剤 90 mg(8 週間隔又は 12 週間隔)を皮下投与した維持試験を実施した。44 週目に clinical remission[注1)]が得られた被験者の割合は、プラセボ群の 24.0%に対して、本剤 90 mg の 8 週間隔投与群で 43.8%、本剤 90 mg の 12 週間隔投与群で 38.4%であった。[7]

注1) Mayo スコアが 2 以下、かついずれのサブスコアも 1 を超えていない場合

投与量	プラセボ	90 mg 8 週間隔投与	90 mg 12 週間隔投与
Clinical remission	24.0% (42/175 例)	43.8%a) (77/176 例)	38.4%b) (66/172 例)

a)：p<0.001、対プラセボ群、Cochran-Mantel-Haenszel カイ二乗検定
b)：p<0.01、対プラセボ群、Cochran-Mantel-Haenszel カイ二乗検定

本剤 90mg 8 週間隔投与群の副作用発現頻度は、26.1%（46 例/176 例）であった。主要な副作用は、上気道感染 5 例(2.8%)、発疹 5 例（2.8%）、ざ瘡 3 例（1.7%）、頭痛 3 例（1.7%）、注射部位反応 3 例（1.7%）であった。

本剤 90mg 12 週間隔投与群の副作用発現頻度は、17.4%（30 例/172 例）であった。主な副作用は、疲労 3 例（1.7%）、関節痛 3 例(1.7%)、頭痛 3 例(1.7%)、上気道感染 2 例(1.2%)、発疹 2 例（1.2%）であった。

18. 薬効薬理

18.1 作用機序

In vitro 試験において、本剤はヒトインターロイキン（IL）-12 及び IL-23 を構成する p40 たん白サブユニットに特異的かつ高い親和性で結合し[9]、IL-12 及び IL-23 受容体複合体への結合を阻害した[10]。

18.2 薬理作用

In vitro 試験において、IL-12 及び IL-23 によって活性化されるヘルパーT 細胞及びナチュラルキラー細胞などの免疫担当細胞の細胞内シグナル伝達並びに IFN-γ、IL-17A、IL-17F 及び IL-22 の分泌を抑制した[11]。

19. 有効成分に関する理化学的知見

一般的名称：ウステキヌマブ（遺伝子組換え）
[Ustekinumab (Genetical Recombination)]

分子式：H 鎖 $C_{2207}H_{3410}N_{582}O_{671}S_{17}$
L 鎖 $C_{1034}H_{1596}N_{274}O_{337}S_{6}$

分子量：148,079～149,690

本　質：ウステキヌマブは、ヒトインターロイキン-12 及びインターロイキン-23 の p40 サブユニットに対する遺伝子組換えヒト IgG1 モノクローナル抗体である。
ウステキヌマブは、マウスミエローマ（Sp2/0）細胞により産生される。
ウステキヌマブは、449 個のアミノ酸残基からなる H 鎖（γ1 鎖）2 分子及び 214 個のアミノ酸残基からなる L 鎖（κ 鎖）2 分子で構成される糖タンパク質（分子量：148,079～149,690）である。

20. 取扱い上の注意

20.1 激しく振盪しないこと。

20.2 本剤は遮光保存する必要があるため、使用直前に外箱から取り出すこと。

20.3 凍結しないこと。

21. 承認条件

21.1 医薬品リスク管理計画を策定の上、適切に実施すること。

〈尋常性乾癬及び関節症性乾癬〉

21.2 大規模な製造販売後調査を実施し、本剤の安全性について十分に検討するとともに、感染症等の発現を含めた長期投与時の安全性及び有効性について検討すること。

22. 包装

0.5mL［1シリンジ］

23. 主要文献

1) Langowsk JL, et al.: Nature. 2006; 442: 461-465
2) Maeda A, et al.: Cancer Res. 2006; 66: 2962-2969
3) 社内資料：国内第Ⅰ相臨床試験成績（JNS009-JPN-01）（2011年1月21日承認、CTD2.5.3.2）
4) 社内資料：国内第Ⅱ/Ⅲ相臨床試験成績（JNS009-JPN-02）（2011年1月21日承認、CTD2.7.6.7）
5) 社内資料：外国第Ⅲ相臨床試験成績（PHOENIX 1）（2011年1月21日承認、CTD2.5.3.3）
6) 社内資料：国際共同第Ⅲ相臨床試験成績（CRD3003）（2017年3月30日承認、CTD2.7.6.4）
7) 社内資料：国際共同第Ⅲ相臨床試験成績（UCO3001 寛解維持試験）（2020年3月承認、CTD2.7.6.2）
8) Tabrizi MA, et al.: Drug Discov Today. 2006; 11: 81-88
9) Luo J, et al.: J Mol Biol. 2010; 402: 797-812
10) 社内資料：ウステキヌマブのヒトIL-12及びIL-23中和作用機序（2011年1月21日承認、CTD2.6.2.1）
11) 社内資料：ウステキヌマブのヒトIL-12及びIL-23中和作用の機能的効果（2011年1月21日承認、CTD2.6.2.1）

24. 文献請求先及び問い合わせ先

〈乾癬・クローン病・潰瘍性大腸炎に関するお問い合わせ〉

ヤンセンファーマ株式会社　メディカルインフォメーションセンター
〒101-0065 東京都千代田区西神田3-5-2
フリーダイヤル　0120-183-275
www.janssenpro.jp

〈クローン病に関するお問い合わせ〉

田辺三菱製薬株式会社くすり相談センター
〒541-8505 大阪市中央区道修町3-2-10
フリーダイヤル　0120-753-280
受付時間9：00～17：30（土・日・祝日及び会社休日を除く）

26. 製造販売業者等

26.1 製造販売元

ヤンセンファーマ株式会社
〒101-0065 東京都千代田区西神田3-5-2

26.2 販売元

田辺三菱製薬株式会社
〒541-8505 大阪市中央区道修町3-2-10

製造販売元
ヤンセンファーマ株式会社
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販売元
田辺三菱製薬株式会社
大阪市中央区道修町3-2-10

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1.8　添付文書（案）

1.8.1　効能・効果（案），用法・用量（案）及びその設定根拠

1.8.1.1　効能・効果（案）及びその設定根拠

(1) 効能・効果（案）

中等症から重症の潰瘍性大腸炎の寛解導入療法（既存治療で効果不十分な場合に限る）

(2) 設定根拠

本剤の効能・効果（案）は，既存治療（コルチコステロイド又は免疫調節薬）又は生物学的製剤で効果不十分あるいは忍容性がない中等症から重症の活動期潰瘍性大腸炎患者を対象としたランダム化，二重盲検，プラセボ対照，並行群間，多施設共同試験である第 III 相国際共同試験（CNTO1275UCO3001 試験）の寛解導入試験の結果に基づいて設定された。

本試験に組み入れられた被験者の人口統計学的特性及びベースラインの疾患特性は，中等症から重症の潰瘍性大腸炎患者集団の特性の代表的なものであった。組み入れられた被験者のほぼ半数（51.1%）は，ベースラインにおいて生物学的製剤治療の無効歴があった。

主要評価項目である 8 週目に clinical remission が得られた被験者の割合は，プラセボ群と比較して 130 mg 群及び～6 mg/kg 群で有意に高かった（いずれも $p<0.001$）【2.5.4.4.1.1】。さらに 3 つの主な副次評価項目である 8 週目に内視鏡的治癒が得られた被験者の割合，8 週目に clinical response が得られた被験者の割合及びベースラインから 8 週目までの IBDQ 総スコアの変化量のいずれにおいても，プラセボ群と比較して 130 mg 群及び～6 mg/kg 群で有意に高かった（いずれも $p<0.001$）【2.5.4.4.1】。生物学的製剤治療無効歴の有無別の部分集団にて評価した場合でも，無効歴あり又はなしのいずれにおいても，8 週目で clinical remission，内視鏡的治癒，clinical response 及び粘膜治癒が得られた被験者の割合は，プラセボ群と比較して 130 mg 群及び～6 mg/kg 群で高かった【2.5.4.4.1.7】。

日本人集団においても，主要評価項目及び 3 つの主な副次評価項目において，プラセボ群と比較して 130 mg 群及び～6 mg/kg 群で改善が認められた【2.5.4.4.1.1，2.5.4.4.1.3】。

本剤 130 mg 及び本剤～6 mg/kg を単回静脈内投与した際の安全性は良好であり，用量による違いは認められず，日本人の安全性プロファイルについては，全体集団で認められたものと類似していた。

以上より，本剤の効能・効果（案）を「中等症から重症の潰瘍性大腸炎の寛解導入療法（既存治療で効果不十分な場合に限る）」とした。

1.8.1.2　用法・用量（案）及びその設定根拠

(1) 用法・用量（案）

通常、成人にはウステキヌマブ（遺伝子組換え）として、導入療法の初回に、以下に示す用量を単回点滴静注する。

患者体重	投与量
55 kg 以下	260 mg
55 kg を超える 85 kg 以下	390 mg
85 kg を超える	520 mg

(2) 設定根拠

様々な背景の潰瘍性大腸炎患者を対象に，寛解導入試験において，130 mg 群及び～6 mg/kg 群のいずれの投与においても幅広い評価項目で早期かつ臨床的に意味のある改善が認められたが，全体的には，本剤 130 mg 投与に比べ本剤～6 mg/kg 投与により高い有効性を示した。以下に，いくつかの重要な評価項目で，低用量である本剤 130 mg 投与と比較して本剤～6 mg/kg 投与のベネフィットが上回っていたことを示す【2.7.3.4】。

- Clinical response 及び Mayo 直腸出血サブスコアが 0 の被験者の割合がより高かった。
- 便中炎症バイオマーカーの低下量がより大きかった。
- 抗 TNF 薬が一次無効の被験者（アンメットニーズが高く，臨床的に重要な部分集団）で有効性がより高かった。
- 曝露量と薬物応答の関係から，本剤～6 mg/kg 投与によって得られるより高い曝露量が，clinical remission，clinical response，及び内視鏡的治癒などの臨床転帰においてより高い改善率を示すことが示唆された。

日本人集団においても，全体集団と同様に Mayo 直腸出血サブスコアが 0 の被験者の割合のベースラインからの増加，炎症マーカーの低下量など幾つかの重要な有効性評価項目で，～6 mg/kg 群は 130 mg 群と比較して高い有効性が認められた。また，曝露量と薬物応答の関係の結果から，高曝露量の集団で clinical response が得られた被験者の割合が高くなる傾向，及び Mayo スコアのベースラインからの変化量が大きくなる傾向が認められ，全体集団と同様に高曝露量で高い有効性が期待できると考えられた。

本剤の寛解導入試験で潰瘍性大腸炎患者に本剤 130 mg 及び本剤～6 mg/kg を単回静脈内投与した際の安全性は良好であり，用量による違いは認められなかった。

日本人の安全性プロファイルについては，全体集団で認められたものと類似しており，両本剤群でプラセボ群と比較して大きな懸念は認められず，用量による違いは認められなかった。

以上より，本剤の用法・用量（案）を 1.8.1.2(1)に記載したとおりとした。

1.8.2　使用上の注意（案）及びその設定根拠

使用上の注意 (新記載要領に基づく第 1 版)	使用上の注意（案） (新記載要領に基づく第 1 版からの変更箇所) （下線：追記箇所、取消線：削除箇所）	設定根拠
1. 警告	**1. 警告**	
1.1 本剤は IL-12/23 の作用を選択的に抑制する薬剤であるため、感染のリスクを増大させる可能性がある。また、結核の既往歴を有する患者では結核を活動化させる可能性がある。また、本剤との関連性は明らかではないが、悪性腫瘍の発現が報告されている。本剤が疾病を完治させる薬剤でないことも含め、これらの情報を患者に十分説明し、患者が理解したことを確認した上で、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。また、本剤投与後に副作用が発現した場合には、主治医に連絡するよう患者に注意を与えること。［2.1、8.1-8.3、9.1.1-9.1.3、11.1.2、11.1.3、15.1.5 参照］ 1.2 重篤な感染症 ウイルス、細菌及び真菌による重篤な感染症が報告されているため、十分な観察を行うなど感染症の発症に注意すること。［2.1、8.1、9.1.1、11.1.2 参照］ 1.3 結核等の感染症について診療経験を有する内科等の医師と十分な連携をとり使用すること。［2.2、8.2、9.1.2、11.1.3 参照］ 1.4 クローン病患者に本剤の治療を開始する前に、栄養療法、ステロイド、免疫調節剤等の使用を十分に勘案すること。また、本剤についての十分な知識とクローン病の治療経験を持つ医師が使用すること。	1.1 本剤は IL-12/23 の作用を選択的に抑制する薬剤であるため、感染のリスクを増大させる可能性がある。また、結核の既往歴を有する患者では結核を活動化させる可能性がある。また、本剤との関連性は明らかではないが、悪性腫瘍の発現が報告されている。本剤が疾病を完治させる薬剤でないことも含め、これらの情報を患者に十分説明し、患者が理解したことを確認した上で、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。また、本剤投与後に副作用が発現した場合には、主治医に連絡するよう患者に注意を与えること。［2.1、8.1-8.3、9.1.1-9.1.3、11.1.2、11.1.3、15.1.5 参照］ 1.2 重篤な感染症 ウイルス、細菌及び真菌による重篤な感染症が報告されているため、十分な観察を行うなど感染症の発症に注意すること。［2.1、8.1、9.1.1、11.1.2 参照］ 1.3 結核等の感染症について診療経験を有する内科等の医師と十分な連携をとり使用すること。［2.2、8.2、9.1.2、11.1.3 参照］ 1.4 本剤の治療を開始する前に、適応疾患の既存治療の適用を十分勘案すること~~クローン病患者に本剤の治療を開始する前に、栄養療法、ステロイド、免疫調節剤等の使用を十分に勘案すること。また、本剤についての十分な知識とクローン病の治療経験を持つ医師が使用すること~~。［5.1、5.2 参照］ 1.5 本剤についての十分な知識と適応疾患の治療の知識・経験をもつ医師が使用すること。	本剤の薬剤プロファイル，類薬の添付文書の記載に基づき設定した。
5. 効能又は効果に関連する注意	5. 効能又は効果に関連する注意	

使用上の注意 (新記載要領に基づく第 1 版)	使用上の注意（案） (新記載要領に基づく第 1 版からの変更箇所) （下線：追記箇所、取消線：削除箇所）	設定根拠
5.1 過去の治療において、栄養療法、他の薬物療法（5-アミノサリチル酸製剤、ステロイド、アザチオプリン等）等による適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に投与すること。	＜クローン病＞ 5.1 過去の治療において、栄養療法、他の薬物療法（5-アミノサリチル酸製剤、ステロイド、アザチオプリン等）等による適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に投与すること。［1. 4 参照］ ＜潰瘍性大腸炎＞ 5.2 過去の治療において、他の薬物療法（ステロイド、アザチオプリン等）等による適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に投与すること。［1. 4 参照］	本試験の選択基準等を基に設定した。
11. 副作用 次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。 11.1 重大な副作用 11.1.1 アナフィラキシー（頻度不明） 発疹、蕁麻疹、血管浮腫等があらわれることがある。 11.1.2 重篤な感染症（1%未満） ウイルス、細菌あるいは真菌による重篤な感染症（蜂巣炎、憩室炎、骨髄炎、胃腸炎、肺炎及び尿路感染等）があらわれることがある。重篤な感染症が発現した場合には、感染が回復するまで本剤の投与をしないこと。［1.1、1.2、2.1、8.1、9.1.1 参照］ 11.1.3 結核（頻度不明） 結核が発現又は再活性化する可能性がある。［1.1、1.3、2.2、8.2、9.1.2 参照］ 11.1.4 間質性肺炎（頻度不明） 咳嗽、呼吸困難、発熱、肺音の異常（捻髪音）等が認められた場合には、速やかに胸部 X 線、胸部 CT、血清マーカー等の検査を実施すること。間質性	11. 副作用 次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。 11.1 重大な副作用 11.1.1 アナフィラキシー（頻度不明） 発疹、蕁麻疹、血管浮腫等があらわれることがある。 11.1.2 重篤な感染症（1%未満） ウイルス、細菌あるいは真菌による重篤な感染症（蜂巣炎、憩室炎、骨髄炎、胃腸炎、肺炎及び尿路感染等）があらわれることがある。重篤な感染症が発現した場合には、感染が回復するまで本剤の投与をしないこと。［1.1、1.2、2.1、8.1、9.1.1 参照］ 11.1.3 結核（頻度不明） 結核が発現又は再活性化する可能性がある。［1.1、1.3、2.2、8.2、9.1.2 参照］ 11.1.4 間質性肺炎（頻度不明） 咳嗽、呼吸困難、発熱、肺音の異常（捻髪音）等が認められた場合には、速やかに胸部 X 線、胸部 CT、血清マーカー等の検査を実施すること。間質性	潰瘍性大腸炎を対象とした臨床試験での発現状況も踏まえ，本剤の CCDS に基づき副鼻腔炎を新たにその他の副作用の項に追記した。 また，本申請とは別に CCDS 改訂に基づき機構相談し、了承いただいた好酸球性肺炎を新たにその他の副作用の項に追記した~~副鼻腔炎の頻度についても，本剤の CCDS の記載に基づき，プラセボ又は実薬対照期間における下記の第二相及び第三相臨床試験の併合解析の有害事象としての発現頻度に基づき設定した~~。 ・潰瘍性大腸炎患者を対象とした臨床試験（0-8 週）：UCO3001 ・クローン病患者を対象とした臨床試験（0-8 週）：C0379T07（プラセボ対照期間のみ），C0743T26, CRD3001, CRD3002（0-8 週） ・乾癬患者を対象とした臨床試験（0-12 週）：C0379T04, C0743T08, C0743T09, C0743T12 の 0 週時にウステキヌマブの投与を受けた患者 ・関節症性乾癬患者を対象とした臨床試験（0-16 週）：C0379T10, CNTO1275PSA3001, CNTO1275PSA3002

<table>
<tr><th>使用上の注意
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（下線：追記箇所、取消線：削除箇所）</th><th>設定根拠</th></tr>
<tr><td>肺炎が疑われた場合には投与を中止し、副腎皮質ホルモン剤の投与等の適切な処置を行うこと。
11.2 その他の副作用
<table><tr><th></th><th>1%以上</th><th>1%未満</th><th>頻度不明</th></tr><tr><td>感染症及び寄生虫症</td><td>上気道感染、鼻咽頭炎</td><td>帯状疱疹、外陰腟真菌感染</td><td>歯肉炎</td></tr><tr><td>精神障害</td><td></td><td></td><td>うつ病</td></tr><tr><td>神経系障害</td><td>頭痛</td><td>浮動性めまい</td><td></td></tr><tr><td>呼吸器、胸郭及び縦隔障害</td><td></td><td>咽喉頭疼痛、鼻閉</td><td></td></tr><tr><td>胃腸障害</td><td>悪心、嘔吐</td><td>下痢</td><td></td></tr><tr><td>皮膚及び皮下組織障害</td><td>発疹</td><td>蕁麻疹、そう痒症、ざ瘡</td><td>膿疱性乾癬、乾癬性紅皮症</td></tr><tr><td>筋骨格系及び結合組織障害</td><td></td><td>関節痛、筋痛、背部痛</td><td></td></tr><tr><td>全身障害及び投与局所様態</td><td>疲労</td><td>無力症、注射部位反応</td><td></td></tr></table></td><td>肺炎が疑われた場合には投与を中止し、副腎皮質ホルモン剤の投与等の適切な処置を行うこと。
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<tr><td>15. その他の注意
15.1 臨床使用に基づく情報
15.1.1 尋常性乾癬（関節症性乾癬を合併した患者を含む）を対象としたウステキヌマブ皮下投与用製剤の国内臨床試験は、72 週間までの期間で実施されている。また、尋常性乾癬を対象としたウステキヌマブ皮下投与用製剤の海外臨床試験は、5 年間までの期間で実施されており、関節症性乾癬を対象とした海外臨床試験は 24 ヵ月までの期間で実施されている。また、クローン病を対象とした国際共同臨床試験（本剤単回投与後にウステキヌマブ皮下投与用製剤を反復投与）は、52 週間までの期間で実施されている。これらの期間を超えた本剤の長期投与時の安全性は確立していない。
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15.1.2 尋常性乾癬（関節症性乾</td><td>15.1.1 潰瘍性大腸炎を対象とした UCO3001 試験結果に基づき追記した。

15.1.2 潰瘍性大腸炎を対象とした UCO3001 試験での抗ウステキヌマブ抗体の発現頻度を追記し，尋常性乾癬，関節症性乾癬，クローン病及び潰瘍性大腸炎患者に対する注意喚起について明確化した。

15.1.6 潰瘍性大腸炎を対象とした UCO3001 試験を含め統合解析した悪性腫瘍の発現頻度に変更した。</td></tr>
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与用製剤の国内臨床試験において、153 例中 10 例（6.5%）が 72 週目までに抗ウステキヌマブ抗体陽性となり、尋常性乾癬及び関節症性乾癬を対象とした海外臨床試験においても、ウステキヌマブ皮下投与用製剤投与により 5.2～12.4%の患者が抗ウステキヌマブ抗体陽性となった。クローン病を対象とした国際共同臨床試験において、本剤及びウステキヌマブ皮下投与用製剤の投与により 3%未満の患者が抗ウステキヌマブ抗体陽性となった。抗ウステキヌマブ抗体が陽性となった患者では効果が減弱化する傾向がみられた。 15.1.3 尋常性乾癬を対象としたウステキヌマブ皮下投与用製剤の海外臨床試験において、糖尿病を合併する患者では皮下投与後の血清中ウステキヌマブのトラフ濃度が低く、効果が低い傾向がみられた。 15.1.4 本剤との関連性は明らかではないが、海外において可逆性後白質脳症症候群（RPLS）の症例が報告されている。 15.1.5 海外の尋常性乾癬、関節症性乾癬、クローン病を対象とした臨床試験（第Ⅱ相及び第Ⅲ相試験）において、プラセボ対照期間の非黒色腫皮膚癌を除く悪性腫瘍の発現頻度は、ウステキヌマブ投与群が 0.12/100 人年（1 例/829 人年）、プラセボ投与群が 0.26/100 人年（1 例/385 人年）であった。非黒色腫皮膚癌の発現頻度は、ウステキヌマブ投与群が 0.48/100 人年（4 例/829 人年）、プラセボ投与群が 0.52/100 人年（2 例/385 人年）であった。また、対照及び非対照期間において、5884 名（10935 人年）にウステキヌマブが投与された。その追跡調査中央値は 1 年で、尋常性乾癬を対象とした臨床試験では 3.2 年、関節症性乾癬を対象とした	癬を合併した患者を含む）を対象としたウステキヌマブ皮下投与用製剤の国内臨床試験において、153 例中 10 例（6.5%）が 72 週目までに抗ウステキヌマブ抗体陽性となり、尋常性乾癬及び関節症性乾癬を対象とした海外臨床試験においても、ウステキヌマブ皮下投与用製剤投与により 5.2～12.4%の患者が抗ウステキヌマブ抗体陽性となった。抗ウステキヌマブ抗体が陽性となった患者では効果が減弱化する傾向がみられた。~~クローン病を対象とした国際共同臨床試験において、本剤及びウステキヌマブ皮下投与用製剤の投与により 3%未満の患者が抗ウステキヌマブ抗体陽性となった。抗ウステキヌマブ抗体が陽性となった患者では効果が減弱化する傾向がみられた。~~また、約 1 年間の本剤及びウステキヌマブ皮下投与用製剤の投与により、クローン病を対象とした国際共同試験において 2.9%、潰瘍性大腸炎を対象とした国際共同試験において 4.6%の患者がそれぞれ抗ウステキヌマブ抗体陽性となった。抗ウステキヌマブ抗体が陽性となった患者では効果が減弱化する可能性がある。 15.1.3 尋常性乾癬を対象としたウステキヌマブ皮下投与用製剤の海外臨床試験において、糖尿病を合併する患者では皮下投与後の血清中ウステキヌマブのトラフ濃度が低く、効果が低い傾向がみられた。 15.1.4 本剤との関連性は明らかではないが、海外において可逆性後白質脳症症候群（RPLS）の症例が報告されている。 15.1.5 海外の尋常性乾癬、関節症性乾癬、クローン病、潰瘍性大腸炎を対象とした臨床試験（第Ⅱ相及び第Ⅲ相試験）において、プラセボ対照期間の非黒色腫皮膚癌を除く悪性腫瘍の発	

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臨床試験では 1 年、クローン病を対象とした臨床試験では 0.6 年であった。非黒色腫皮膚癌を除く悪性腫瘍の発現頻度は、0.53/100 人年（58 例/10935 人年）で、主なものは前立腺癌、黒色腫、結腸直腸癌、乳癌であった。ウステキヌマブ投与群で報告された悪性腫瘍の発現頻度は、一般人口で予測される発現頻度と同様であった（標準化発生比：0.87［95%信頼区間：0.66、1.14］年齢、性別、人種により補正）。非黒色腫皮膚癌の発現頻度は 0.49/100 人年（53 例/10919 人年）であった。皮膚基底細胞癌と皮膚有棘細胞癌の発現比率は 4：1 であり一般人口で予測される発現頻度と同様であった。［1.1、8.3 参照］ 15.2 非臨床使用に基づく情報 15.2.1 げっ歯類の IL-12 及び IL-23 に対して中和活性を示さないため、がん原性試験は実施されていない。げっ歯類のモデルにおいて、IL-12/IL-23p40 の阻害により、悪性腫瘍の増大が報告されている [1)]。また、IL-12 及び IL-23 の両方の遺伝子を欠損させたマウスでは、紫外線による皮膚癌の発生時期が早まり、発生頻度も増加することが報告されている [2)]。	現頻度は、ウステキヌマブ投与群が 0.1112/100 人年（1 例/929829 人年）、プラセボ投与群が 0.2326/100 人年（1 例/434385 人年）であった。非黒色腫皮膚癌の発現頻度は、ウステキヌマブ投与群が 0.4348/100 人年（4 例/929829 人年）、プラセボ投与群が 0.4652/100 人年（2 例/433385 人年）であった。また、対照及び非対照期間において、67095884 名（1156110935 人年）にウステキヌマブが投与された。その追跡調査中央値は 1.0 年で、尋常性乾癬を対象とした臨床試験では 3.32 年、関節症性乾癬を対象とした臨床試験では 1.0 年、クローン病を対象とした臨床試験では 0.6 年、潰瘍性大腸炎を対象とした臨床試験では 1.0 年であった。非黒色腫皮膚癌を除く悪性腫瘍の発現頻度は、0.5453/100 人年（6258 例/1156110935 人年）で、主なものは前立腺癌、黒色腫、結腸直腸癌、黒色腫、乳癌であった。ウステキヌマブ投与群で報告された悪性腫瘍の発現頻度は、一般人口で予測される発現頻度と同様であった（標準化発生比：0.9387［95%信頼区間：0.7166、1.2014］年齢、性別、人種により補正）。非黒色腫皮膚癌の発現頻度は 0.49/100 人年（5653 例/1154510919 人年）であった。皮膚基底細胞癌と皮膚有棘細胞癌の発現比率は 34：1 であり一般人口で予測される発現頻度と同様であった。 ［1.1、8.3 参照］ 15.2 非臨床使用試験に基づく情報 15.2.1 げっ歯類の IL-12 及び IL-23 に対して中和活性を示さないため、がん原性試験は実施されていない。げっ歯類のモデルにおいて、IL-12/IL-23p40 の阻害により、悪性腫瘍の増大が報	

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	告されている[1)]。また、IL-12 及び IL-23 の両方の遺伝子を欠損させたマウスでは、紫外線による皮膚癌の発生時期が早まり、発生頻度も増加することが報告されている[2)]。	

上記以外の項目は変更なし

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1.8 添付文書（案）

1.8.1 効能・効果（案），用法・用量（案）及びその設定根拠

1.8.1.1 効能・効果（案）及びその設定根拠

(1) 効能・効果（案）

中等症から重症の潰瘍性大腸炎の維持療法（既存治療で効果不十分な場合に限る）

(2) 設定根拠

本剤の効能・効果（案）は，既存治療（コルチコステロイド又は免疫調節薬）又は生物学的製剤で効果不十分又は忍容性がない中等症から重症の活動期潰瘍性大腸炎患者を対象としたランダム化，二重盲検，プラセボ対照，並行群間，多施設共同試験である第 III 相国際共同試験（CNTO1275UCO3001 試験）の寛解維持試験の結果に基づいて設定された。本試験では，寛解導入試験で clinical response が得られた被験者を対象とし，主要な有効性解析は，そのうち再ランダム化された被験者（寛解導入試験でいずれかの本剤群に割付けられ 8 週目に clinical response が得られた被験者及び寛解導入試験でプラセボ群に割り付けられ 8 週目に clinical response が得られず～6 mg/kg を追加投与されたのち 16 週目に clinical response が得られた被験者）にて実施した。

寛解維持試験に組み入れられた全被験者が寛解導入試験からの移行であり，再ランダム化集団の寛解導入試験ベースラインでの人口統計学的特性，疾患特性，併用薬及び前治療薬は，寛解導入試験で認められたこれらの特性とおおむね一致していた。ベースラインにおいて生物学的製剤治療無効歴ありであった被験者は 47.6%であった。

本剤の寛解維持試験の主要評価項目である 44 週目に clinical remission が得られた被験者の割合は，プラセボ群と比較して 90 mg q12w 群及び 90 mg q8w 群で有意に高かった（いずれも $p<0.01$）【2.5.4.4.2.1】。さらに 4 つの主な副次評価項目のうち，44 週目まで clinical response を維持した被験者の割合，44 週目に内視鏡的治癒が得られた被験者の割合，44 週目にコルチコステロイド free remission が得られた被験者の割合は，プラセボ群と比較して両本剤群で有意に高く，寛解維持試験のベースラインで clinical remission が得られていた被験者のうち 44 週目まで clinical remission を維持した被験者の割合では，プラセボ群と比較して 90 mg q12w 群で有意に高かった。生物学的製剤治療無効歴あり又はなしのいずれの被験者においても，主要評価項目及び主な副次評価項目を達成した被験者の割合並びに 44 週目に粘膜治癒が得られた被験者の割合は，プラセボ群と比較して 90 mg q12w 群及び 90 mg q8w 群で高かった【2.5.4.4.2.6】。

日本人集団において，主要評価項目である 44 週目に clinical remission が得られた被験者の割合は， 90 mg q12w 群でプラセボ群より高く，90 mg q8w 群でプラセボと同程度であった。ただし，主な副次評価項目のうち 44 週目まで clinical response を維持した被験者の割合，44 週目に内視鏡的治癒が得られた被験者の割合は，両本剤群でプラセボ群より高かった【2.5.4.4.2.1】。さらに，各種炎症マーカー及び健康関連 QOL といった指標においても両本剤群でプラセボ群より高い効果を示した【2.5.4.4.2.2，2.5.4.4.2.3】。

本剤 90 mg を q12w 及び q8w で皮下投与した際の安全性プロファイルはクローン病患者にて認められたものと一貫しており，両本剤群とプラセボ群の間に重要な安全性に関する違いは認めら

れなかった。日本人集団で認められた安全性プロファイルは全体集団で認められた安全性プロファイルと類似していた。

以上より，本剤の効能・効果（案）を「中等症から重症の潰瘍性大腸炎の維持療法（既存治療で効果不十分な場合に限る）」とした。

1.8.1.2 用法・用量（案）及びその設定根拠

(1) 用法・用量（案）

ウステキヌマブ（遺伝子組換え）の点滴静注製剤を投与 8 週後に、通常、成人にはウステキヌマブ（遺伝子組換え）として 90 mg を皮下投与し、以降は 12 週間隔で 90 mg を皮下投与する。なお、効果が減弱した場合には、投与間隔を 8 週間に短縮できる。

(2) 設定根拠

寛解維持試験で本剤群に再ランダム化されたすべての被験者が，寛解導入療法としての本剤の点滴静脈内投与を受けた 8 週後（すなわち寛解維持試験の 0 週目）に本剤 90 mg の皮下投与を受け，それ以降，盲検下で本剤 90 mg q8w もしくは 90 mg q12w の皮下投与を受けた。

本剤 90 mg q8w 及び 90 mg q12w 投与は，いずれも臨床的に意味のあるベネフィットをもたらした。しかしながら，本剤 90 mg q8w 投与は，以下に示す一部の重要な評価項目において，全体集団にてより高い有効性を示した【2.7.3.4】。

- 内視鏡的治癒及び粘膜治癒などの客観性の高い評価項目
- Partial Mayo remission の維持，コルチコステロイド free remission 及び寛解維持試験のベースラインでコルチコステロイドを併用していた被験者におけるコルチコステロイドの中止などの厳密な評価項目
- Symptomatic remission などの 44 週目まで経時的に有効性を評価する評価項目
- Treatment failure の基準に該当した被験者の割合
- 定常状態の血清中ウステキヌマブのトラフ濃度と clinical remission，内視鏡的治癒及び粘膜治癒にて認められた曝露量と薬物応答の間の正の関係
- 寛解維持試験のベースラインで clinical remission，symptomatic remission 又は内視鏡的治癒が得られていなかった部分集団での 44 週目の clinical remission，symptomatic remission 又は内視鏡的治癒

このことから，全体的には本剤 90 mg q8w 投与が有効性の対象集団全体でより高い有効性を示し，必要に応じてすべての患者が利用可能な用法・用量であるべきと考える。

ただし，以下に示すとおり，本剤 90 mg q12w 投与の方が寛解維持療法を開始する用法・用量として適切と考えられる場合も認められた。

- 寛解維持試験のベースラインで clinical remission，symptomatic remission 又は内視鏡的治癒が得られていた部分集団では，44 週目の clinical remission，symptomatic remission 又は内視鏡的治癒で 90 mg q12w 群及び 90 mg q8w 群の有効性は同様であった【2.5.4.4.2.6】。

・ 44 週目の clinical remission 及び 44 週目の symptomatic remission について寛解維持試験ベースラインのそれぞれの remission の有無で評価すると，寛解維持試験ベースラインでそれぞれの remission が得られていた部分集団では，曝露量と薬物応答の間に明確な正の関係が認められなかった【2.5.4.4.2.7】。

このことから，一つの固定された投与レジメンだけではなく，患者の状態に応じた投与レジメンを選択可能とすべきと考えられた。

本剤 90 mg q12w から本剤 90 mg q8w へ投与頻度を増加させた場合の有効性への影響については寛解維持試験で検討してないが，以下に示すとおり，潰瘍性大腸炎の適応に対してもクローン病と同様に本剤 90 mg q12w 投与にて clinical response を消失する，又は効果が不十分である患者に対して，本剤 90 mg q8w 投与への用量調整を行うことは妥当であると考えられる。

・ 潰瘍性大腸炎の試験においても，クローン病の試験と同様，clinical response を消失した被験者での血清中ウステキヌマブのトラフ濃度が，clinical response を消失していない被験者に比べて低かった【2.5.3.1.2，2.7.2.3.1.4】。また，潰瘍性大腸炎の試験データを用いた母集団薬物動態解析の結果，潰瘍性大腸炎患者においても用量調整により高い血清中ウステキヌマブ濃度が得られ，理論的により高い有効性が期待されることが示された【2.5.3.1.3，2.7.2.3.1.4】。

・ 寛解維持試験において曝露量と薬物応答の間に正の関係が認められ，本剤の高い曝露量が有効性の改善（特に clinical remission，内視鏡的治癒，及び粘膜治癒等の評価項目）に繋がることが示され，より高頻度の投与が高い曝露量と関連していることが示された【2.5.3.2】。

・ クローン病の第 III 相寛解維持試験において，本剤 90 mg q12w から本剤 90 mg q8w 投与への用量調整により血清中ウステキヌマブのトラフ濃度中央値が増加し，用量調整により臨床転帰の改善を示したデータが得られており，これは投与頻度の増加によって得られるベネフィット及び曝露量と薬物応答の関係のさらなる裏付けになると考える。

・ 寛解維持試験のベースライン時に再ランダム化された被験者において，長期継続投与期で用量調節が行われた被験者では用量調節によるベネフィットが認められた【2.7.3.7.2】。また，長期継続投与期にて治験薬の投与を受けた被験者の 44 週目から 96 週目までの安全性プロファイルは，本剤の既知の安全性プロファイルとおおむね一致しており，安全性に関する新たな所見は認められなかった【2.7.4.7】。

安全性では，90 mg q8w 群で有害事象を発現した被験者の割合は，プラセボ群とおおむね同様であったが，90 mg q12w 群で有害事象を発現した被験者の割合は，90 mg q8w 群又はプラセボ群よりも低かった。両本剤群間で重篤な有害事象又は重篤な感染症の発現頻度に大きな違いは認められず，全投与群を通じてこれらの事象の発現頻度は低かった。全体として，本剤 90 mg を q8w 及び q12w で投与した際の安全性プロファイルに臨床的に意味のある差は認められなかったことから，安全性の観点からも，両用量・用法を推奨することは可能と考える。

日本人集団においては，特に 90 mg q12w 群で一貫して全体集団と同程度の有効性が認められた。このため，クローン病と同様に本剤 90 mg q12w 投与が基本となる維持療法であると考えら

れた。日本人集団では寛解維持試験のベースラインで投与群間の不均衡も認められ，90 mg q8w 群が必ずしも 90 mg q12w 群と比較して高い有効性を示さなかったものの，全体集団では 90 mg q8w 群で 90 mg q12w 群と比較して一貫して高い有効性が認められた。さらに，日本人集団では，以下に示すような有効性，安全性及び薬物動態に関する全体集団と類似した傾向が認められた。

- 客観性の高い評価項目（内視鏡的治癒等）及び厳密な評価項目（partial Mayo remission の維持等）では，clinical remission で認められた 90 mg q8w 群と 90 mg q12w 群の群間差と比較して，これらの両本剤群間差は小さかったことから，全体集団と日本人集団で一定の類似性が認められた【2.7.3.4.2.2】。
- 寛解維持試験のベースラインで clinical remission，symptomatic remission 又は内視鏡的治癒を得られていなかった部分集団では，44 週目のこれらの臨床転帰で 90 mg q8w 群と 90 mg q12w 群の群間差が小さくなる傾向が認められ，これは全体集団の傾向と矛盾しないと考える【2.7.3.3.3.2】。
- 曝露量と薬物応答の解析の結果，四分位区分ごとの被験者数が少なく，曝露量と clinical remission を達成した被験者の割合には明確な正の関係が認められなかったが，Mayo スコアの減少については，日本人の高曝露量の集団で Mayo スコアがより減少する傾向が認められた【2.7.3.2.2.7】。
- 90 mg q8w 群と 90 mg q12w 群のトラフ値の比較から，日本人集団においても全体集団と同様に，高用量群である 90 mg q8w 群では 90 mg q12w 群と比較し，約 3 倍の曝露量が認められた【2.7.2.2.1.1】。
- 日本人集団で認められた安全性プロファイルは，全体集団で認められた安全性プロファイルと類似していた。

これらのことから，日本人においても本剤 90 mg q8w 投与による有効性が期待でき，推奨すべき用法・用量として，本剤 90 mg q12w 投与を基本とし，患者の状態に応じて本剤 90 mg q8w 投与を可能とすることは一定のベネフィットをもたらすと考える。

最後に，以下に示した医師及び患者に対して考えられ得るベネフィットから，潰瘍性大腸炎とクローン病の両疾患に対して，共通の用法・用量を使用することは妥当と考えられる。

- 多くの場合，炎症性腸疾患患者（潰瘍性大腸炎又はクローン病患者）は同じ医師により診察を受け，同様の治療薬の用法・用量が用いられている。治療薬は通常低用量（又は低頻度）から開始され，効果不十分の場合，用量又は頻度をあげるといった治療方針は両疾患でおおむね類似している。これはクローン病におけるインフリキシマブ及びアダリムマブ，潰瘍性大腸炎におけるトファシチニブといった，クローン病及び潰瘍性大腸炎の適応症にて承認されているその他の薬剤の添付文書にも反映されている。
- 炎症性腸疾患の患者の中には少なからず診断時に indeterminate colitis と診断される患者もおり，その治療初期には，クローン病か潰瘍性大腸炎か明確に区別できないケースも存在するため，これらの症例に対しても治療全体を通じて一貫した治療が行えることが望ましいと考えられる【2.5.1.2.3】。

上記を総合的に判断して，クローン病にて既に承認された用法・用量と同様に，本剤の用法・用量（案）を 1.8.1.2(1) に記載したとおりとした。

1.8.2　使用上の注意（案）及びその設定根拠

使用上の注意 (新記載要領に基づく第 1 版)	使用上の注意（案） (新記載要領に基づく第 1 版からの変更箇所) （下線：追記箇所、取消線：削除箇所）	設定根拠
1. 警告	**1. 警告**	
1.1 本剤は IL-12/23 の作用を選択的に抑制する薬剤であるため、感染のリスクを増大させる可能性がある。また、結核の既往歴を有する患者では結核を活動化させる可能性がある。また、本剤との関連性は明らかではないが、悪性腫瘍の発現が報告されている。本剤が疾病を完治させる薬剤でないことも含め、これらの情報を患者に十分説明し、患者が理解したことを確認した上で、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。また、本剤投与後に副作用が発現した場合には、主治医に連絡するよう患者に注意を与えること。［2.1、8.1-8.3、9.1.1-9.1.3、11.1.2、11.1.3、15.1.6 参照］ 1.2 重篤な感染症 ウイルス、細菌及び真菌による重篤な感染症が報告されているため、十分な観察を行うなど感染症の発症に注意すること。［2.1、8.1、9.1.1、11.1.2 参照］ 1.3 結核等の感染症について診療経験を有する内科等の医師と十分な連携をとり使用すること。［2.2、8.2、9.1.2、11.1.3 参照］ 1.4 尋常性乾癬及び関節症性乾癬患者では、本剤の治療を開始する前に、紫外線療法を含む既存の全身療法（生物製剤を除く）の適用を十分に勘案すること。また、本剤についての十分な知識と乾癬の治療経験をもつ医師が使用すること。 1.5 クローン病患者では、本剤の治療を開始する前に、栄養療法、ステロイド、免疫調節剤等の使用を十分に勘案すること。また、本剤についての十分な知	1.1 本剤は IL-12/23 の作用を選択的に抑制する薬剤であるため、感染のリスクを増大させる可能性がある。また、結核の既往歴を有する患者では結核を活動化させる可能性がある。また、本剤との関連性は明らかではないが、悪性腫瘍の発現が報告されている。本剤が疾病を完治させる薬剤でないことも含め、これらの情報を患者に十分説明し、患者が理解したことを確認した上で、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。また、本剤投与後に副作用が発現した場合には、主治医に連絡するよう患者に注意を与えること。［2.1、8.1-8.3、9.1.1-9.1.3、11.1.2、11.1.3、15.1.6 参照］ 1.2 重篤な感染症 ウイルス、細菌及び真菌による重篤な感染症が報告されているため、十分な観察を行うなど感染症の発症に注意すること。［2.1、8.1、9.1.1、11.1.2 参照］ 1.3 結核等の感染症について診療経験を有する内科等の医師と十分な連携をとり使用すること。［2.2、8.2、9.1.2、11.1.3 参照］ 1.4 ~~尋常性乾癬及び関節症性乾癬患者では、~~本剤の治療を開始する前に、適応疾患の既存治療の適応を十分勘案すること~~紫外線療法を含む既存の全身療法（生物製剤を除く）の適用を十分に勘案すること。また、本剤についての十分な知識と乾癬の治療経験をもつ医師が使用すること~~。［5.1、5.2、5.3 参照］ 1.5 ~~クローン病患者では、本剤の治療を開始する前に、栄養療法、ステロイド、免疫調節剤等~~	本剤の薬剤プロファイル，類薬の添付文書の記載に基づき設定した。

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識とクローン病の治療経験をもつ医師が使用すること。	~~の使用を十分に勘案すること。また、~~本剤についての十分な知識と適応疾患~~クローン病~~の治療の知識・経験をもつ医師が使用すること。	
5. 効能又は効果に関連する注意	5. 効能又は効果に関連する注意	
〈尋常性乾癬及び関節症性乾癬〉 5.1 以下のいずれかを満たす尋常性乾癬又は関節症性乾癬患者に投与すること。 ・紫外線療法を含む既存の全身療法（生物製剤を除く）で十分な効果が得られず、皮疹が体表面積の 10%以上に及ぶ患者。 ・難治性の皮疹又は関節症状を有する患者。 〈クローン病〉 5.2 過去の治療において、栄養療法、他の薬物療法（5-アミノサリチル酸製剤、ステロイド、アザチオプリン等）等による適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に投与すること。	〈尋常性乾癬及び関節症性乾癬〉 5.1 以下のいずれかを満たす尋常性乾癬又は関節症性乾癬患者に投与すること。［1. 4 参照］ ・紫外線療法を含む既存の全身療法（生物製剤を除く）で十分な効果が得られず、皮疹が体表面積の 10%以上に及ぶ患者。 ・難治性の皮疹又は関節症状を有する患者。 〈クローン病〉 5.2 過去の治療において、栄養療法、他の薬物療法（5-アミノサリチル酸製剤、ステロイド、アザチオプリン等）等による適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に投与すること。［1. 4 参照］ 〈潰瘍性大腸炎〉 5.3 過去の治療において、他の薬物療法(ステロイド、アザチオプリン等）等による適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に投与すること。［1. 4 参照］	本試験の選択基準等を基に設定した。
7. 用法及び用量に関連する注意	7. 用法及び用量に関連する注意	
〈効能共通〉 7.1 本剤と他の生物製剤の併用について安全性及び有効性は確立していないので併用を避けること。 〈尋常性乾癬及び関節症性乾癬〉 7.2 本剤による治療反応が得られない場合、投与開始から 28 週以内には増量を含めて治療計画を再考すること。また、増量を行っても十分な治療反応が得られない場合、本剤の投与継続	〈効能共通〉 7.1 本剤と他の生物製剤の併用について安全性及び有効性は確立していないので併用を避けること。 〈尋常性乾癬及び関節症性乾癬〉 7.2 本剤による治療反応が得られない場合、投与開始から 28 週以内には増量を含めて治療計画を再考すること。また、増量を行っても十分な治療反応が得られない場合、本剤の投与継続	1.8.1.2 (2)を及び以下の考察を基に設定した。 寛解維持試験における Delayed responder の評価から，8 週目に clinical response が得られなかったとしても，8 週目に本剤 90 mg の追加の皮下投与を受けることで効果が得られる被験者が認められた【2.5.4.4.1.4】。その後も本剤 90 mg q8w 投与を継続することで，44 週を通じて clinical response を維持し，さらには 44 週目の clinical remission

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を慎重に再考すること。 〈クローン病〉 7.3 ウステキヌマブ（遺伝子組換え）点滴静注製剤による導入療法の初回投与 8 週後に、本剤の皮下投与を開始すること。 （導入療法における用法・用量は、ウステキヌマブ（遺伝子組換え）の点滴静注製剤の添付文書を参照すること。） 7.4 本剤の 8 週間隔への投与間隔短縮は、本剤の皮下投与中に効果が減弱した患者に対し、本剤の皮下投与開始から 8 週以降に行うことができる。本剤の投与間隔を短縮しても 16 週以内に治療効果が得られない場合、投与を継続しても効果が得られない可能性があることから、本剤の投与継続の必要性を検討すること。 7.5 本剤の皮下投与開始後、本剤の 2 回目の皮下投与までに治療反応がない場合、投与を継続しても効果が得られない可能性があることから、本剤の投与継続の必要性を検討すること。	を慎重に再考すること。 〈クローン病／潰瘍性大腸炎〉 7.3 ウステキヌマブ（遺伝子組換え）点滴静注製剤による導入療法の初回投与 8 週後に、本剤の皮下投与を開始すること。 （導入療法における用法・用量は、ウステキヌマブ（遺伝子組換え）の点滴静注製剤の添付文書を参照すること。） 7.4 本剤の 8 週間隔への投与間隔短縮は、本剤の皮下投与中に効果が減弱した患者に対し、本剤の皮下投与開始から 8 週以降に行うことができる。本剤の投与間隔を短縮しても 16 週以内に治療効果が得られない場合、投与を継続しても効果が得られない可能性があることから、本剤の投与継続の必要性を検討すること。 7.5 本剤の皮下投与開始後、本剤の 2 回目の皮下投与までに治療反応がない場合、投与を継続しても効果が得られない可能性があることから、本剤の投与継続の必要性を検討すること。	の達成を含む，その他の有効性指標を達成した被験者が認められたこと【2.5.4.4.2.4】から，クローン病と同様に，有効性の最終評価及び投与継続の決定は，静脈内投与による寛解導入療法の開始後 16 週間（8 週目に本剤 90 mg を追加皮下投与）まで待つことが適切であると考えた。維持療法時の投与継続の判断を簡便にするために，維持療法中に投与間隔を短縮した場合も同様の判断で投与継続の可否を決定することが適切と考えた。
11. 副作用 次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。 11.1 重大な副作用 11.1.1 アナフィラキシー（頻度不明） 発疹、蕁麻疹、血管浮腫等があらわれることがある。 11.1.2 重篤な感染症（1～5%未満） ウイルス、細菌あるいは真菌による重篤な感染症（蜂巣炎、憩室炎、骨髄炎、胃腸炎、肺炎及び尿路感染等）があらわれることがある。重篤な感染症が発現した場合には、感染が回復するまで本剤の投与をしないこと。［1.1、1.2、2.1、8.1、9.1.1 参	11. 副作用 次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。 11.1 重大な副作用 11.1.1 アナフィラキシー（頻度不明） 発疹、蕁麻疹、血管浮腫等があらわれることがある。 11.1.2 重篤な感染症（1～5%未満） ウイルス、細菌あるいは真菌による重篤な感染症（蜂巣炎、憩室炎、骨髄炎、胃腸炎、肺炎及び尿路感染等）があらわれることがある。重篤な感染症が発現した場合には、感染が回復するまで本剤の投与をしないこと。［1.1、1.2、2.1、8.1、9.1.1 参	潰瘍性大腸炎を対象とした臨床試験での発現状況も踏まえ、本剤の CCDS に基づき副鼻腔炎を新たにその他の副作用の項に追記した。 また、本申請とは別に CCDS 改訂に基づき機構相談し、了承いただいた好酸球性肺炎を新たにその他の副作用の項に追記した副鼻腔炎の頻度についても，~~本剤の CCDS の記載に基づき，プラセボ又は実薬対照期間における下記の第二相及び第三相臨床試験の併合解析の有害事象としての発現頻度に基づき設定した~~。 ・潰瘍性大腸炎患者を対象とした臨床試験（0-8 週）：UCO3001 ・クローン病患者を対象とした臨床試験（0-8 週）：C0379T07（プラセボ対照期間のみ）， ・潰瘍性大腸炎患者を対象とした臨床試験（0-8 週）：UCO3001

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<td>C0743T26, CRD3001, CRD3002（0-8 週）
・乾癬患者を対象とした臨床試験（0-12 週）：C0379T04, C0743T08, C0743T09, C0743T12 の 0 週時にウステキヌマブの投与を受けた患者
・関節症性乾癬患者を対象とした臨床試験（0-16 週）：C0379T10, CNTO1275PSA3001, CNTO1275PSA3002
また、副鼻腔炎を含むその他の副作用の発現頻度は、現行の添付文書に基づき、乾癬承認時の集計及びクローン病を対象とした 3001、3002、3003 試験~~（日本人症例のみ）~~と潰瘍性大腸炎を対象とした UCO3001 試験において、ウステキヌマブと合理的に関連性がある有害事象（可能性小、可能性大、ほぼ確実）の集計に基づき設定している~~おり、変更はない~~。</td>
</tr>
<tr>
<td>15. その他の注意
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週間までの期間で実施されている。また、尋常性乾癬を対象としたウステキヌマブ皮下投与用製剤の海外臨床試験は、5 年間までの期間で実施されており、関節症性乾癬を対象とした海外臨床試験は 24 ヵ月までの期間で実施されている。また、クローン病を対象とした本剤の国際共同臨床試験は、52 週間までの期間で実施されている。これらの期間を超えた本剤の長期投与時の安全性は確立していない。 15.1.2 尋常性乾癬（関節症性乾癬を合併した患者を含む）を対象とした国内臨床試験において、本剤投与により 153 例中 10 例（6.5%)が 72 週目までに抗ウステキヌマブ抗体陽性となり、尋常性乾癬及び関節症性乾癬を対象とした海外臨床試験においても、本剤投与により 5.2～12.4%の患者が抗ウステキヌマブ抗体陽性となった。クローン病を対象とした国際共同臨床試験において、3%未満の患者がウステキヌマブ点滴静注製剤及び本剤投与により抗ウステキヌマブ抗体陽性となった。抗ウステキヌマブ抗体が陽性となった患者では効果が減弱化する傾向がみられた。 15.1.3 尋常性乾癬を対象とした海外臨床試験において、糖尿病を合併する患者では皮下投与後の血清中ウステキヌマブのトラフ濃度が低く、効果が低い傾向がみられた。 15.1.4 尋常性乾癬に対し免疫抑制剤又は光線療法と併用した場合の安全性及び有効性は確立していない。 15.1.5 本剤との関連性は明らかではないが、海外において可逆性後白質脳症症候群（RPLS）の症例が報告されている。 15.1.6 海外の尋常性乾癬、関節	週間までの期間で実施されている。また、尋常性乾癬を対象としたウステキヌマブ皮下投与用製剤の海外臨床試験は、5 年間までの期間で実施されており、関節症性乾癬を対象とした海外臨床試験は 24 ヵ月までの期間で実施されている。また、クローン病及び潰瘍性大腸炎では、それぞれを対象とした本剤の国際共同臨床試験（ウステキヌマブ静注用製剤を単回投与後に本剤を反復投与）は、52 週間までの期間で実施されている。これらの期間を超えたウステキヌマブ製剤~~本剤~~の長期投与時の安全性は確立していない。 15.1.2 尋常性乾癬（関節症性乾癬を合併した患者を含む）を対象とした国内臨床試験において、本剤投与により 153 例中 10 例（6.5%)が 72 週目までに抗ウステキヌマブ抗体陽性となり、尋常性乾癬及び関節症性乾癬を対象とした海外臨床試験においても、本剤投与により 5.2～12.4%の患者が抗ウステキヌマブ抗体陽性となった。抗ウステキヌマブ抗体が陽性となった患者では効果が減弱化する傾向がみられた。~~クローン病を対象とした国際共同臨床試験において、3%未満の患者がウステキヌマブ点滴静注製剤及び本剤投与により抗ウステキヌマブ抗体陽性となった。抗ウステキヌマブ抗体が陽性となった患者では効果が減弱化する傾向がみられた。~~また、約 1 年間の本剤及びウステキヌマブ点滴静注製剤の投与により、クローン病を対象とした国際共同試験において 2.9%、潰瘍性大腸炎を対象とした国際共同試験において 4.6%の患者がそれぞれ抗ウステキヌマブ抗体陽性となった。抗ウステキヌマブ抗体が陽性となった患者では効果が減弱化する可能性がある。	キヌマブ抗体の発現頻度を追記し，尋常性乾癬，関節症性乾癬，クローン病及び潰瘍性大腸炎患者に対する注意喚起について明確化した。 15.1.6 潰瘍性大腸炎を対象とした UCO3001 試験を含め統合解析した悪性腫瘍の発現頻度に変更した。

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症性乾癬、クローン病を対象とした臨床試験（第 II 相及び第 III 相試験）において、プラセボ対照期間の非黒色腫皮膚癌を除く悪性腫瘍の発現頻度は、本剤投与群が 0.12/100 人年（1 例/829 人年）、プラセボ投与群が 0.26/100 人年（1 例/385 人年）であった。非黒色腫皮膚癌の発現頻度は、本剤投与群が 0.48/100 人年（4 例/829 人年）、プラセボ投与群が 0.52/100 人年（2 例/385 人年）であった。また、対照及び非対照期間において、5884 名（10935 人年）に本剤が投与された。その追跡調査中央値は 1 年で、尋常性乾癬を対象とした臨床試験では 3.2 年、関節症性乾癬を対象とした臨床試験では 1 年、クローン病を対象とした臨床試験では 0.6 年であった。非黒色腫皮膚癌を除く悪性腫瘍の発現頻度は、0.53/100 人年（58 例/10935 人年）で、主なものは前立腺癌、黒色腫、結腸直腸癌、乳癌であった。本剤投与群で報告された悪性腫瘍の発現頻度は、一般人口で予測される発現頻度と同様であった（標準化発生比：0.87［95%信頼区間：0.66、1.14］年齢、性別、人種により補正）。非黒色腫皮膚癌の発現頻度は 0.49/100 人年（53 例/10919 人年）であった。皮膚基底細胞癌と皮膚有棘細胞癌の発現比率は 4:1 であり一般人口で予測される発現頻度と同様であった。［1.1、8.3 参照］ 15.2 非臨床試験に基づく情報 15.2.1 げっ歯類の IL-12 及び IL-23 に対して中和活性を示さないため、がん原性試験は実施されていない。げっ歯類のモデルにおいて、IL-12/IL-23p40 の阻害により、悪性腫瘍の増大が報告されている[1)]。また、IL-12	15.1.3 尋常性乾癬を対象とした海外臨床試験において、糖尿病を合併する患者では皮下投与後の血清中ウステキヌマブのトラフ濃度が低く、効果が低い傾向がみられた。 15.1.4 尋常性乾癬に対し免疫抑制剤又は光線療法と併用した場合の安全性及び有効性は確立していない。 15.1.5 本剤との関連性は明らかではないが、海外において可逆性後白質脳症症候群（RPLS）の症例が報告されている。 15.1.6 海外の尋常性乾癬、関節症性乾癬、クローン病、潰瘍性大腸炎を対象とした臨床試験（第 II 相及び第 III 相試験）において、プラセボ対照期間の非黒色腫皮膚癌を除く悪性腫瘍の発現頻度は、本剤投与群が 0.11~~12~~/100 人年（1 例/929~~829~~ 人年）、プラセボ投与群が 0.23~~26~~/100 人年（1 例/434~~385~~ 人年）であった。非黒色腫皮膚癌の発現頻度は、本剤投与群が 0.43~~48~~/100 人年（4 例/929~~829~~ 人年）、プラセボ投与群が 0.46~~52~~/100 人年（2 例/433~~385~~ 人年）であった。また、対照及び非対照期間において、6709~~5884~~ 名（11561~~10935~~ 人年）に本剤が投与された。その追跡調査中央値は 1.0 年で、尋常性乾癬を対象とした臨床試験では 3.3~~2~~ 年、関節症性乾癬を対象とした臨床試験では 1.0 年、クローン病を対象とした臨床試験では 0.6 年、潰瘍性大腸炎を対象とした臨床試験では 1.0 年であった。非黒色腫皮膚癌を除く悪性腫瘍の発現頻度は、0.54~~53~~/100 人年（62~~58~~ 例/11561~~10935~~ 人年）で、主なものは前立腺癌、~~黒色腫、~~結腸直腸癌、黒色腫、乳癌であった。本剤投与群で報告された悪性腫瘍の発現頻度は、一般人口で予測される発現頻度と同様であった（標準化発	

使用上の注意 (新記載要領に基づく第 1 版)	使用上の注意（案） (新記載要領に基づく第 1 版からの変更箇所) （下線：追記箇所、取消線：削除箇所）	設定根拠
及び IL-23 の両方の遺伝子を欠損させたマウスでは、紫外線による皮膚癌の発生時期が早まり、発生頻度も増加することが報告されている [2)]。	生比：0.93~~87~~［95%信頼区間：0.71~~66~~、1.20~~14~~］年齢、性別、人種により補正）。非黒色腫皮膚癌の発現頻度は 0.49/100 人年（56~~53~~例/11545~~10919~~人年）であった。皮膚基底細胞癌と皮膚有棘細胞癌の発現比率は 3~~4~~:1 であり一般人口で予測される発現頻度と同様であった。 ［1.1、8.3 参照］ 15.2 非臨床試験に基づく情報 15.2.1 げっ歯類の IL-12 及び IL-23 に対して中和活性を示さないため、がん原性試験は実施されていない。げっ歯類のモデルにおいて、IL-12/IL-23p40 の阻害により、悪性腫瘍の増大が報告されている [1)]。また、IL-12 及び IL-23 の両方の遺伝子を欠損させたマウスでは、紫外線による皮膚癌の発生時期が早まり、発生頻度も増加することが報告されている [2)]。	

上記以外の項目は変更なし

1.9　一般的名称に係る文書

平成 23 年 1 月 21 日承認時資料第 1 部 1.9 参照。

1.10 毒薬・劇薬等の指定審査資料のまとめ

毒薬・劇薬等の指定審査に係る資料について，本申請に係る内容を次ページより示す。

【現行】

<table>
<tr><td>化学名・別名</td><td>ウステキヌマブ（遺伝子組換え）</td></tr>
<tr><td>構造式</td><td>別紙</td></tr>
<tr><td>効能・効果</td><td>中等症から重症の活動期クローン病の導入療法（既存治療で 効果不十分な場合に限る）</td></tr>
<tr><td>用法・用量</td><td>通常，成人にはウステキヌマブ（遺伝子組換え）として，導入療法の初回に，以下に示す用量を単回点滴静注する。

<table>
<tr><td>患者体重</td><td>投与量</td></tr>
<tr><td>55kg 以下</td><td>260 mg</td></tr>
<tr><td>55kg を超える 85kg 以下</td><td>390 mg</td></tr>
<tr><td>85kg を超える</td><td>520 mg</td></tr>
</table>
</td></tr>
<tr><td>劇薬等の指定</td><td></td></tr>
<tr><td>市販名及び有効成分・分量</td><td>市販名：ステラーラ点滴静注 130mg（1 バイアル中 130mg 含有）
有効成分：ウステキヌマブ（遺伝子組換え）</td></tr>
<tr><td>毒性</td><td>単回投与毒性
<table>
<tr><td>動物種</td><td>投与経路</td><td>概略の致死量 1)
（mg/kg）</td></tr>
<tr><td>サ　ル</td><td>静脈内投与</td><td>♂：>9</td></tr>
</table>
1)：単回静脈内投与による薬物動態試験の結果から求めた。

反復投与毒性
<table>
<tr><td>動物種</td><td>投与期間
投与経路</td><td>性別</td><td>投与量 1)
（mg/kg）</td><td>無毒性量
（mg/kg）</td><td>主な所見</td></tr>
<tr><td>サ　ル</td><td>4 週間
静脈内投与</td><td>♂♀</td><td>0, 9, 45</td><td>♂♀：45</td><td>特記すべき所見なし</td></tr>
</table>
1)：週 1 回投与</td></tr>
<tr><td>副作用</td><td>クローン病
副作用発現率（臨床検査値異常変動を含む）　188／941 例＝20.0%
［国際共同第Ⅲ相試験（CNTO1275CRD3001 試験及び CNTO1275CRD3002 試験）］

<table>
<tr><td>副作用の種類</td><td>例数</td><td>臨床検査値異常の種類</td><td>例数</td></tr>
<tr><td>頭痛</td><td>29 例</td><td>体温上昇</td><td>2 例</td></tr>
<tr><td>悪心</td><td>14 例</td><td>肝機能検査異常</td><td>2 例</td></tr>
<tr><td>上気道感染</td><td>12 例</td><td>アラニンアミノトランスフェラーゼ増加</td><td>1 例</td></tr>
<tr><td>嘔吐</td><td>11 例</td><td>血中クレアチン増加</td><td>1 例</td></tr>
<tr><td>鼻咽頭炎</td><td>10 例</td><td>ヘモグロビン減少</td><td>1 例</td></tr>
<tr><td></td><td>等</td><td></td><td>等</td></tr>
</table>
</td></tr>
<tr><td>会社</td><td>ヤンセン ファーマ株式会社　製剤：製造</td></tr>
</table>

別紙

ウステキヌマブの重鎖（Heavy Chain）及び軽鎖（Light Chain）のアミノ酸配列

Heavy Chain

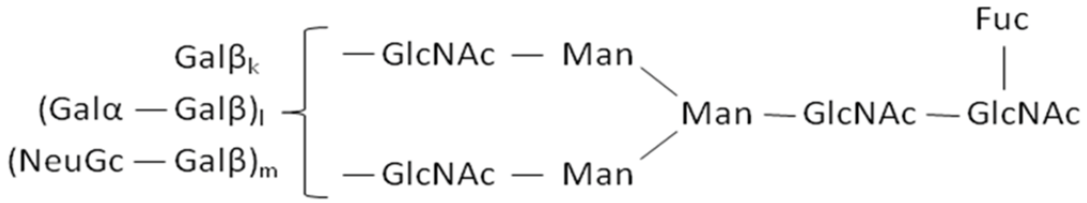
```
EVQLVQSGAE VKKPGESLKI SCKGSGYSFT TYWLGWVRQM PGKGLDWIGI MSPVDSDIRY   60
                          22-96
SPSFQGQVTM SVDKSITTAY LQWNSLKASD TAMYYCARRR PGQGYFDFWG QGTLVTVSSS  120
STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG  180
                     146-202
LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPELLGGP  240
                                  222  LC  228 HC  231 HC
SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS  300
                          263-323                          N-Glycan
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL  360
TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ  420
  369-427
QGNVFSCSVM HEALHNHYTQ KSLSLSPGK                                    449
```

Light Chain

```
DIQMTQSPSS LSASVGDRVT ITCRASQGIS SWLAWYQQKP EKAPKSLIYA ASSLQSGVPS   60
                          23-88
RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNIYPYTFGQ GTKLEIKRTV AAPSVFIFPP  120
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT  180
                 134-194
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC                              214
                                    HC
```

下線部：相補性決定部；H 鎖 K449：部分プロセシング

糖鎖構造



k, l, m = 0, 1, 2;　k + l + m = 0, 1, 2

【変更】

<table>
<tr><td>化学名・別名</td><td></td></tr>
<tr><td>構造式</td><td></td></tr>
<tr><td>効能・効果</td><td>中等症から重症の活動期クローン病の導入療法（既存治療で効果不十分な場合に限る）
中等症から重症の潰瘍性大腸炎の寛解導入療法（既存治療で効果不十分な場合に限る）
（下線部変更箇所）</td></tr>
<tr><td>用法・用量</td><td></td></tr>
<tr><td>劇薬等の指定</td><td></td></tr>
<tr><td>市販名及び有効成分・分量</td><td></td></tr>
<tr><td>毒性</td><td></td></tr>
<tr><td>副作用</td><td>クローン病
副作用発現率（臨床検査値異常変動を含む）　188／941 例＝20.0%
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<tr><td>嘔吐</td><td>11 例</td><td>血中クレアチン増加</td><td>1 例</td></tr>
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<tr><td></td><td>等</td><td></td><td>等</td></tr>
</table>

潰瘍性大腸炎
副作用発現率（臨床検査値異常変動を含む）　81／641 例＝12.6%
［国際共同第Ⅲ相試験（CNTO1275UCO3001 試験）］

<table>
<tr><th>副作用の種類</th><th>例数</th><th>臨床検査値異常の種類</th><th>例数</th></tr>
<tr><td>頭痛</td><td>10 例</td><td>リンパ球数減少</td><td>1 例</td></tr>
<tr><td>そう痒症</td><td>8 例</td><td>血中リン減少</td><td>1 例</td></tr>
<tr><td>疲労</td><td>7 例</td><td>好中球数減少</td><td>1 例</td></tr>
<tr><td>上気道感染</td><td>6 例</td><td>白血球数減少</td><td>1 例</td></tr>
<tr><td>リンパ球減少症</td><td>5 例</td><td></td><td></td></tr>
<tr><td></td><td>等</td><td></td><td></td></tr>
</table>

（下線部変更箇所）</td></tr>
<tr><td>会社</td><td></td></tr>
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1.10　毒薬・劇薬等の指定審査資料のまとめ

毒薬・劇薬等の指定審査に係る資料について，本申請に係る内容を次ページより示す。

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<tr><td>構造式</td><td>別紙</td></tr>
<tr><td>効能・効果</td><td>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
中等症から重症の活動期クローン病の維持療法（既存治療で効果不十分な場合に限る）</td></tr>
<tr><td>用法・用量</td><td>尋常性乾癬及び関節症性乾癬
通常，成人にはウステキヌマブ（遺伝子組換え）として 1 回 45mg を皮下投与する。初回投与及びその 4 週後に投与し，以降 12 週間隔で投与する。
ただし，効果不十分な場合には 1 回 90mg を投与することができる。
クローン病
ウステキヌマブ（遺伝子組換え）の点滴静注製剤を投与 8 週後に，通常，成人にはウステキヌマブ（遺伝子組換え）として 90mg を皮下投与し，以降は 12 週間隔で 90mg を皮下投与する。なお，効果が減弱した場合には，投与間隔を 8 週間に短縮できる。</td></tr>
<tr><td>劇薬等の指定</td><td></td></tr>
<tr><td>市販名及び有効成分・分量</td><td>市販名：ステラーラ皮下注 45mg シリンジ（1 シリンジ中 45mg 含有）
有効成分：ウステキヌマブ（遺伝子組換え）</td></tr>
<tr><td>毒性</td><td>単回投与毒性
<table><tr><td>動物種</td><td>投与経路</td><td>概略の致死量 1)
（mg/kg）</td></tr><tr><td>サ　ル</td><td>皮下</td><td>♂♀：>45</td></tr></table>1)：単回投与毒性試験を実施していないため，26 週間反復皮下投与毒性試験の初回投与時の結果から求めた。

反復投与毒性
<table><tr><td>動物種</td><td>投与期間
投与経路</td><td>性別</td><td>投与量 1)
（mg/kg）</td><td>無毒性量
（mg/kg）</td><td>主な所見</td></tr><tr><td>サ　ル</td><td>26 週間
皮下</td><td>♂♀</td><td>0, 22.5, 45</td><td>♂♀：45</td><td>特記すべき所見なし</td></tr></table>1)：週 2 回投与</td></tr>
<tr><td>副作用</td><td>乾癬
副作用発現率（臨床検査値異常変動を含む）　154／172 例＝89.5%
［国内第 I 相試験（JNS009-JPN-01 試験）及び国内第 II/III 相試験（JNS009-JPN-02 試験）］

副作用の種類　例数
鼻咽頭炎　77 例
アレルギー性鼻炎　14 例
湿疹　10 例
頭痛　9 例
高血圧　9 例
等

臨床検査値異常の種類　例数
肝機能検査異常　32 例
血中クレアチンホスホキナーゼ増加　24 例
血中トリグリセリド増加　23 例
リンパ球数減少　17 例
白血球数増加　12 例
等

クローン病
副作用発現率（臨床検査値異常変動を含む）　98／314 例＝31.2%
［国際共同第Ⅲ相試験（CNTO1275CRD3003 試験）］</td></tr>
</table>

	副作用の種類	例数	臨床検査値異常の種類	例数
	上気道感染	10 例	心拍数増加	2 例
	注射部位紅斑	10 例	肝機能検査異常	2 例
	頭痛	10 例		等
	発疹	8 例		
	鼻咽頭炎	7 例		
	悪心	7 例		
		等		
会社	ヤンセン ファーマ株式会社　製剤：製造			

別紙

ウステキヌマブの重鎖（Heavy Chain）及び軽鎖（Light Chain）のアミノ酸配列

Heavy Chain

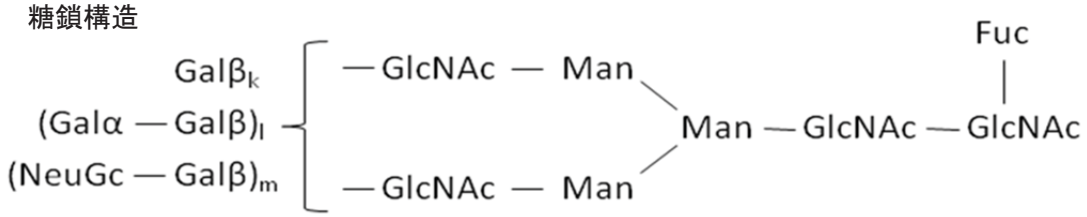
```
EVQLVQSGAE VKKPGESLKI SCKGSGYSFT TYWLGWVRQM PGKGLDWIGI MSPVDSDIRY   60
                          22-96
SPSFQGQVTM SVDKSITTAY LQWNSLKASD TAMYYCARRR PGQGYFDFWG QGTLVTVSSS  120
STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG  180
                     146-202
LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPELLGGP  240
                                  222  228  231
                                  LC   HC   HC   N-Glycan
SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS  300
                          263-323
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL  360
TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ  420
  369-427
QGNVFSCSVM HEALHNHYTQ KSLSLSPGK                                    449
```

Light Chain

```
DIQMTQSPSS LSASVGDRVT ITCRASQGIS SWLAWYQQKP EKAPKSLIYA ASSLQSGVPS   60
                     23-88
RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNIYPYTFGQ GTKLEIKRTV AAPSVFIFPP  120
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT  180
               134-194
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC                              214
                                    HC
```

下線部：相補性決定部；H 鎖 K449：部分プロセシング

糖鎖構造



k, l, m =0, 1, 2;　k + l + m =0, 1, 2

【変更】

<table>
<tr><td>化学名・別名</td><td></td></tr>
<tr><td>構造式</td><td></td></tr>
<tr><td>効能・効果</td><td>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
中等症から重症の活動期クローン病の維持療法（既存治療で効果不十分な場合に限る）
中等症から重症の潰瘍性大腸炎の維持療法（既存治療で効果不十分な場合に限る）

（下線部変更箇所）</td></tr>
<tr><td>用法・用量</td><td>尋常性乾癬及び関節症性乾癬
通常，成人にはウステキヌマブ（遺伝子組換え）として 1 回 45mg を皮下投与する。初回投与及びその 4 週後に投与し，以降 12 週間隔で投与する。
ただし，効果不十分な場合には 1 回 90mg を投与することができる。
クローン病/ 潰瘍性大腸炎
ウステキヌマブ（遺伝子組換え）の点滴静注製剤を投与 8 週後に，通常，成人にはウステキヌマブ（遺伝子組換え）として 90mg を皮下投与し，以降は 12 週間隔で 90mg を皮下投与する。なお，効果が減弱した場合には，投与間隔を 8 週間に短縮できる。

（下線部変更箇所）</td></tr>
<tr><td>劇薬等の指定</td><td></td></tr>
<tr><td>市販名及び有効成分・分量</td><td></td></tr>
<tr><td>毒性</td><td></td></tr>
<tr><td>副作用</td><td>乾癬
副作用発現率（臨床検査値異常変動を含む）　154／172 例＝89.5%
［国内第 I 相試験（JNS009-JPN-01 試験）及び国内第 II/III 相試験（JNS009-JPN-02 試験）］

<table>
<tr><th>副作用の種類</th><th>例数</th><th>臨床検査値異常の種類</th><th>例数</th></tr>
<tr><td>鼻咽頭炎</td><td>77 例</td><td>肝機能検査異常</td><td>32 例</td></tr>
<tr><td>アレルギー性鼻炎</td><td>14 例</td><td>血中クレアチンホスホキナーゼ増加</td><td>24 例</td></tr>
<tr><td>湿疹</td><td>10 例</td><td>血中トリグリセリド増加</td><td>23 例</td></tr>
<tr><td>頭痛</td><td>9 例</td><td>リンパ球数減少</td><td>17 例</td></tr>
<tr><td>高血圧</td><td>9 例</td><td>白血球数増加</td><td>12 例</td></tr>
<tr><td></td><td>等</td><td></td><td>等</td></tr>
</table>

クローン病
副作用発現率（臨床検査値異常変動を含む）　98／314 例＝31.2%
［国際共同第Ⅲ相試験（CNTO1275CRD3003 試験）］

<table>
<tr><th>副作用の種類</th><th>例数</th><th>臨床検査値異常の種類</th><th>例数</th></tr>
<tr><td>上気道感染</td><td>10 例</td><td>心拍数増加</td><td>2 例</td></tr>
<tr><td>注射部位紅斑</td><td>10 例</td><td>肝機能検査異常</td><td>2 例</td></tr>
<tr><td>頭痛</td><td>10 例</td><td></td><td>等</td></tr>
<tr><td>発疹</td><td>8 例</td><td></td><td></td></tr>
<tr><td>鼻咽頭炎</td><td>7 例</td><td></td><td></td></tr>
<tr><td>悪心</td><td>7 例</td><td></td><td></td></tr>
<tr><td></td><td>等</td><td></td><td></td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>潰瘍性大腸炎
副作用発現率（臨床検査値異常変動を含む）　76／348 例＝21.8%
［国際共同第Ⅲ相試験（CNTO1275UCO3001 試験）］

<table>
<tr><th>副作用の種類</th><th>例数</th><th>臨床検査値異常の種類</th><th>例数</th></tr>
<tr><td>上咽頭炎</td><td>11 例</td><td>肝機能検査異常</td><td>5 例</td></tr>
<tr><td>潰瘍性大腸炎</td><td>8 例</td><td>白血球数減少</td><td>2 例</td></tr>
<tr><td>上気道感染</td><td>7 例</td><td>ブドウ球菌検査陽性</td><td>1 例</td></tr>
<tr><td>発疹</td><td>7 例</td><td>リンパ球形態異常</td><td>1 例</td></tr>
<tr><td>頭痛</td><td>6 例</td><td>血中リン減少</td><td>1 例</td></tr>
<tr><td></td><td>等</td><td>好中球数減少</td><td>1 例</td></tr>
<tr><td></td><td></td><td>体重減少</td><td>1 例</td></tr>
</table>
（下線部変更箇所）</td></tr>
<tr><td>会社</td><td></td></tr>
</table>

添付資料番号	タイトル	掲載誌	評価資料 参考資料	申請電子データ有無
5.2 全臨床試験一覧表				
5.3 臨床試験報告書				
5.3.1 生物薬剤学試験報告書				
5.3.1.1 バイオアベイラビリティ（BA）試験報告書				
	該当資料なし			
5.3.1.2 比較BA試験及び生物学的同等性（BE）試験報告書				
	該当資料なし			
5.3.1.3 In Vitro－In Vivo の関連を検討した試験報告書				
	該当資料なし			
5.3.1.4 生物学的及び理化学的分析法検討報告書				
5.3.1.4.1	Validation of an Assay for the Quantification of CNTO 1275 in Human Serum Using the Meso Scale Discovery Platform	ヤンセンファーマ 社内資料 試験番号：CP[redacted]V-054	参考資料	無
5.3.1.4.2	Validation of an ECLIA Method to Detect Antibodies to Ustekinumab (CNTO 1275) in Human Serum Samples	ヤンセンファーマ 社内資料 試験番号：CP[redacted]V-035	参考資料	無
5.3.1.4.3	Validation of an Electrochemiluminescence-based Immunoassay to Detect Neutralizing Antibodies to Ustekinumab (CNTO1275) in Human Serum	ヤンセンファーマ 社内資料 試験番号：CP[redacted]V-050	参考資料	無
5.3.2 ヒト生体試料を用いた薬物動態関連の試験報告書				
5.3.2.1 血漿蛋白結合試験報告書				
	該当資料なし			
5.3.2.2 肝代謝及び薬物相互作用試験報告書				
	該当資料なし			
5.3.2.3 他のヒト生体試料を用いた試験報告書				
	該当資料なし			
5.3.3 臨床薬物動態（PK）試験報告書				
5.3.3.1 健康被験者におけるPK及び初期忍容性試験報告書				
	該当資料なし			
5.3.3.2 患者におけるPK及び初期忍容性試験報告書				
	該当資料なし			
5.3.3.3 内因性要因を検討したPK試験報告書				
	該当資料なし			
5.3.3.4 外因性要因を検討したPK試験報告書				
	該当資料なし			
5.3.3.5 ポピュレーションPK試験報告書				
5.3.3.5.1	Population Pharmacokinetic Analysis Report_ Treatment of Adult Patients With Moderately to Severely Active Ulcerative Colitis STELARA (ustekinumab)	ヤンセンファーマ 社内資料	評価資料	有
5.3.3.5.2	Exposure-Response Analysis Report_ Treatment of Adult Patients with Moderately to Severely Active Ulcerative Colitis STELARA® (ustekinumab)	ヤンセンファーマ 社内資料	評価資料	有
5.3.4 臨床薬力学（PD）試験報告書				
5.3.4.1 健康被験者におけるPD試験及びPK/PD試験報告書				
	該当資料なし			
5.3.4.2 患者におけるPD試験及びPK/PD試験報告書				
	該当資料なし			
5.3.5 有効性及び安全性試験報告書				
5.3.5.1 申請する適応症に関する比較対照試験報告書				
5.3.5.1.1-1	A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis_Induction	ヤンセンファーマ 社内資料 試験番号： CNTO1275UC03001	評価資料	有
5.3.5.1.1-2	A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis_Maintenance	ヤンセンファーマ 社内資料 試験番号： CNTO1275UC03001	評価資料	有
5.3.5.2 非対照試験報告書				
	該当資料なし			
5.3.5.3 複数の試験成績を併せて解析した報告書				
5.3.5.3.1	Integrated Summary of Safety	ヤンセンファーマ 社内資料	参考資料	有

添付資料番号	タイトル	掲載誌	評価資料 参考資料	申請電子データ有無
5.3.5.3.2	UC03001 CSR-TLF（全体集団）	ヤンセンファーマ社内資料	参考資料	無
5.3.5.3.3	追加解析帳票（日本人集団）	ヤンセンファーマ社内資料	参考資料	無
5.3.5.3.4	Clinical Relevance of Histologic and Mucosal Healing Endpoints in Ulcerative Colitis_Position Paper	ヤンセンファーマ社内資料	参考資料	無
5.3.5.3.5	Summary of Clinical Pharmacology and Clinical Efficacy	ヤンセンファーマ社内資料	参考資料	有
5.3.5.3.6	Integrated Summary of Safety Correction Report（日本人集団）	ヤンセンファーマ社内資料	参考資料	有
5.3.5.4 その他の試験報告書				
5.3.5.4.1	A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects with Moderately to Severely Active Crohn's Disease Who Have Failed or Are Intolerant to TNF Antagonist Therapy_UNITI-1	ヤンセンファーマ社内資料 試験番号：CNTO1275CRD3001	参考資料	無
5.3.5.4.2	A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects with Moderately to Severely Active Crohn's Disease_UNITI-2	ヤンセンファーマ社内資料 試験番号：CNTO1275CRD3002	参考資料	無
5.3.5.4.3	A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Subjects with Moderately to Severely Active Crohn's Disease_IM-UNITI	ヤンセンファーマ社内資料 試験番号：CNTO1275CRD3003	参考資料	無
5.3.5.4.4	Biomarker Technical Report_Protocol: CNTO1275UC03001	ヤンセンファーマ社内資料 試験番号：CNTO1275UC03001	参考資料	無
5.3.5.4.5	A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis_UNIFI	ヤンセンファーマ社内資料 試験番号：CNTO1275UC03001	参考資料	無
5.3.6 市販後の使用経験に関する報告書				
5.3.6.1	Periodic Benefit Risk Evaluation Report (01 Jan 2018 - 31 Dec 2018)	ヤンセンファーマ社内資料	参考資料	無
5.3.6.2	市販後に報告された重篤な有害事象一覧 (2008/12/31～2018/12/31)	ヤンセンファーマ社内資料	参考資料	無
5.3.7 患者データ一覧表及び症例記録				
5.3.7.1 用量設定の根拠となった主要な試験及び主要な有効性の検証試験の症例一覧表				
	該当資料なし			
5.3.7.2 実施された全ての臨床試験において副作用が観察された症例の一覧表				
5.3.7.2.1	5.3.5.1.1に関する患者データ一覧表及び症例記録 副作用が観察された症例の一覧表	ヤンセンファーマ社内資料	評価資料	無
5.3.7.3 実施された全ての臨床試験において重篤な有害事象が観察された症例の一覧表				
5.3.7.3.1	5.3.5.1.1に関する患者データ一覧表及び症例記録 重篤な有害事象が観察された症例の一覧表	ヤンセンファーマ社内資料	評価資料	無
5.3.7.4 実施された全ての臨床試験において臨床検査値異常変動が観察された症例の一覧表				
5.3.7.4.1	5.3.5.1.1に関する患者データ一覧表及び症例記録 臨床検査値異常変動が観察された症例の一覧表	ヤンセンファーマ社内資料	評価資料	無
5.3.7.5 実施された全ての臨床試験において観察された臨床検査値の変動を適切に示した図				
	該当資料なし			
5.4 参考文献				
5.4.1	参考文献	参考文献一覧表及び参考文献を添付	参考資料	