コセンティクス皮下注 150 mg シリンジ
コセンティクス皮下注 150 mg ペン
に関する資料

ノバルティス ファーマ株式会社

1.5 起源又は発見の経緯及び開発の経緯

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表 一 覧

略号一覧

略号	省略していない表現 (英)	省略していない表現 (日)
AIN457	Secukinumab	セクキヌマブ
AS	Ankylosing Spondylitis	強直性脊椎炎
ASAS	Assessment of SpondyloArthritis International Society	―
ASQoL	Ankylosing Spondylitis Quality of Life	―
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index	―
BASFI	Bath Ankylosing Spondylitis Functional Index	―
BASMI	Bath Ankylosing Spondylitis Metrology Index	―
CRP	C-reactive protein	C-反応性蛋白
DMARD	Disease modifying anti-rheumatic drug	疾患修飾性抗リウマチ薬
EMA	European Medicines Agency	欧州医薬品庁
FACIT-fatigue	Functional Assessment of Chronic Illness Therapy-fatigue	―
HLA-B27	human leukocyte antigen B-27	―
IL	interleukin	インターロイキン
IV	intravenous	静脈内
MRI	magnetic resonance imaging	磁気共鳴映像法
mSASSS	modified Stoke Ankylosing Spondylitis Spinal Score	―
NSAID	non-steroidal anti-inflammatory drug	非ステロイド性抗炎症薬
Pbo	placebo	プラセボ
PCS	physical component summary	身体的側面の QOL サマリースコア
PK	pharmacokinetics	薬物動態（学）
PoC	proof of concept	―
QoL	quality of life	生活の質
SC	subcutaneous	皮下
SF-36	Medical Outcome Short Form 36-Item Health Survey	―
TNF-α	tumor necrosis factor-α	腫瘍壊死因子-α

用語の定義一覧

用語	定義
試験の表記方法	治験実施計画書番号は，試験番号で示した。 例） CAIN457H1301 試験→H1301 試験 CAIN457F2310 試験→F2310 試験
投与群の表記方法	• F2310 試験及び H1301 試験の導入投与は皮下投与（SC 投与），F2305 試験の導入投与は静脈内投与（IV 投与）であることから，維持投与時の用量と併せて実薬群は以下のように表記した。 　• F2310 試験：SC-75 mg 群，SC-150 mg 群 　• H1301 試験：SC-150 mg 群 　• F2305 試験：IV-75 mg 群，IV-150 mg 群 • F2310 試験でセクキヌマブが投与された被験者を併合した。併合した集団を以下のように表記した。 　• Any セクキヌマブ群：セクキヌマブが一度でも投与された被験者集団 　• Any75 mg 群：セクキヌマブ 75 mg が一度でも投与された被験者集団 　• Any150 mg 群：セクキヌマブ 150 mg が一度でも投与された被験者集団

1 起源または発見の経緯

セクキヌマブ（開発コード：AIN457）は，ノバルティス社が創製したヒトインターロイキン-17A（IL-17A）に対する遺伝子組換えヒト型モノクローナル抗体であり，ヒト免疫グロブリン・レパートリーの一部を有する遺伝子改変マウス（HuMab®マウス，Medarex Inc.）からハイブリドーマ技術によって作成された。セクキヌマブは炎症性サイトカインである IL-17A に結合し，IL-17A の IL-17 受容体への結合を阻害することによりその活性を中和し，その結果，下流の炎症カスケードが無効となることで効果を発揮する。

ノバルティス社は20[redacted]年より自己免疫疾患の治療薬としてセクキヌマブの開発を進めている。国内では，「既存治療で効果不十分な尋常性乾癬及び関節症性乾癬」を適応として 2014 年 12 月に製造販売承認を取得し，2015 年 12 月に「膿疱性乾癬」の適応を追加した。外国では，2018 年 10 月現在，「乾癬」や「乾癬性関節炎」に加えて，本承認申請の適応症である「強直性脊椎炎」に対して欧米を含む 88 ヵ国で承認，発売されている。これらに加えて，「X 線上の所見を有さない体軸性脊椎関節炎」の適応取得を目的とした国際共同第 III 相試験を現在実施中である。

2 強直性脊椎炎について

2.1 定義，診断基準及び患者数

強直性脊椎炎（ankylosing spondylitis，AS）は，多くの場合 40 歳以下で発症し，脊椎や仙腸関節等の体軸や腱付着部に慢性炎症をきたす，体軸性脊椎関節炎に分類される慢性炎症性疾患である。AS の臨床的な特徴は炎症性の腰背部痛である。腱や付着部，さらに脊椎や関節に炎症がおこり，進行すると骨増殖が生じて骨棘が形成される。その結果，脊椎の構造的損傷が引き起こされ，体軸関節の可動域が制限され，日常動作が低下する原因となる。AS は疾患の進行が緩徐で，数十年という長い期間にわたる治療が必要とされるため，患者は身体的のみならず，心理的・社会的にも著しく生活の質（quality of life，QoL）が低下する。

AS の診断には国内外ともに改訂ニューヨーク基準（1984 年）（日本リウマチ学会 2010）が用いられており，臨床症状として（1）運動で改善するが，安静では改善しない腰背部の疼痛又はこわばりが 3 ヵ月以上持続，（2）腰椎の可動域制限，（3）胸郭の拡張制限のうち，1 つ以上の所見が認められ，かつ X 線で両側 2 度以上，または片側 3 度以上の仙腸関節炎が認められた場合に AS と確定診断される。

現在の日本の AS 患者数は約 4500 人と報告されており（厚生科学審議会 2015），男女比は約 3：1 と男性に多い（小竹 2013）。日本人の AS の有病率は 0.0065%（Hukuda et al. 2001）であり，欧米での有病率 0.03%～0.26%（Dean et al. 2014）と比較して極めて低い。AS の病因は特定されていないが，ヒト白血球抗原である HLA-B27 との強い関連性が認められており，AS 患者の HLA-B27 陽性率は 90%超と言われる（Bowness 2015）。HLA-B27 陽性率は地域や人種によって異なり，

一般的な欧米の白人では約 10%であるのに対し，日本人では 1%であり（Khan 1995），この差が AS の有病率の国内外での違いに反映されていると考えられている。

2.2 強直性脊椎炎に対する治療の現状

AS の根治療法はなく，治療の主な目的は，短期的には痛みやこわばりといった症状と炎症のコントロール，長期的には脊椎の構造的損傷の抑制，並びに身体機能と社会参加を維持又は正常化することにより，生活の質を高く維持することである。患者の臨床症状や疾患の進行度に応じて運動療法，理学療法，外科手術，薬物療法の中から，単独又は併用療法が選択される（van der Heijde et al. 2017，厚生科学審議会 2015）。

AS の薬物治療における第一選択薬は，非ステロイド性抗炎症薬（non-steroidal anti-inflammatory drug，NSAID）である。NSAID は炎症性関節炎による痛みを軽減するために用いられるが，長期投与に伴い，消化管障害や腎機能障害等の副作用により治療を中止せざるを得ない患者も多い（Boers et al. 2007，Straube et al. 2009，Dougados et al. 2011）。日本リウマチ学会は，「強直性脊椎炎（AS）に対する TNF 阻害療法施行ガイドライン」（2010 年 10 月改訂版）（日本リウマチ学会 2010）で NSAID に効果不十分，又は NSAID に対し忍容性不良な AS 患者に対して，抗腫瘍壊死因子（tumor necrosis factor，TNF）α 製剤による治療を推奨している。現在，国内ではアダリムマブとインフリキシマブの 2 剤が「既存治療で効果不十分な AS」を適応症に承認されているが，抗 TNF-α 製剤を投与しても十分な効果がみられない又は忍容性不良の患者が 20%～40%存在し（Dougados and Baeten 2011），中和抗体により効果が減弱する患者もいる。抗 TNF-α 製剤で効果不十分な場合，他の抗 TNF-α 製剤に変更しても，十分な効果が得られない場合もある（Lie et al. 2011）。上記の他に，末梢関節炎に対して修飾疾患性抗リウマチ薬（disease-modifying anti-rheumatic drug，DMARD）であるメトトレキサートやサラゾスルファピリジン，内服薬で効果不十分な場合は副腎皮質ステロイドの局所投与も行われるが，いずれも AS をはじめとする体軸性脊椎関節炎に対する有効性は確立されていない。

2.3 本剤の治療上の位置付け

前項で述べた通り，国内で主に使用されている AS 治療薬は NSAID 及び抗 TNF-α 製剤のみであり，治療の選択肢が少ない。そのため，NSAID で効果不十分な患者，忍容性不良により NSAID での治療が困難な患者，抗 TNF-α 製剤を用いても効果不十分又は忍容性不良な患者に対して，新規作用機序を持つ薬剤が求められている。

AS は免疫介在性炎症性疾患の一つであり（Dougados and Baeten 2011，Lories and McInnes 2012），その発症には IL-17A が関連するサイトカイン経路が寄与している（Gaffen et al 2014）。セクキヌマブは，ヒト IL-17A の生物活性を中和することにより，AS に対しても有効な治療薬になると期待される。

後述する国内外の臨床試験の結果から，セクキヌマブの投与により，NSAID で効果不十分若しくは忍容性不良な AS 患者の臨床症状・徴候，身体機能及び QoL がプラセボに比べて改善し，そ

の効果が長期にわたり持続し，忍容性も良好であることが明らかとなった。また，抗 TNF-α 製剤による治療で効果不十分な AS 患者でも，これらのベネフィットが得られることが確認された。以上より，セクキヌマブは，第一選択薬（NSAID）で効果不十分な患者に対する，新たな治療選択肢となり得る。

3 開発の経緯

AS の適応追加にあたり，新たな製剤の開発は行っていない。非臨床試験に関しては，ヒト線維芽細胞様滑膜細胞に対するマトリックスメタロプロテアーゼ-3 産生抑制作用を確認する試験を，セクキヌマブの薬効を裏付ける試験として新たに実施した以外に，先の承認申請時（尋常性乾癬，関節症性乾癬，膿疱性乾癬）に提出した資料に追加する試験はない。そのため，本項では臨床に関する開発の経緯のみを記す。

3.1 海外における開発

ノバルティス社は 2009 年より欧米を中心に AS に対する開発に着手し，中等症又は重症の外国人の活動性 AS 患者 30 名を対象とした proof-of-concept（PoC）試験（A2209 試験）を 2009 年 3 月～2011 年 5 月に実施した。A2209 試験の結果，AS 患者でもセクキヌマブの有効性が確認できたことから，第 III 相試験を計画した。第 III 相試験の用法用量は，主に活動性関節リウマチ患者を対象とした用量設定試験（F2201 試験）の結果，及び乾癬患者の薬物動態（pharmacokinetics，PK）データを用いた母集団 PK 解析の結果を参考に設定した。

第 III 相試験として実施した，導入投与及び維持投与の用法・用量が異なる 2 つの検証試験（F2305 試験，F2310 試験）の試験結果に基づき，F2310 試験の用法・用量を選択し，欧州では 2015 年 11 月，米国では 2016 年 1 月に以下の効能・効果及び用法・用量にて承認を取得した。なお，米国では，セクキヌマブ導入投与の有無を比較した海外第 III 相試験（F2320 試験）を 2015 年 5 月より実施し，導入投与なしで維持投与のみの用法・用量も承認されている。また，バイアル製剤を用いた IV 投与及びプレフィルドシリンジ製剤を用いた皮下（SC）投与時のデータを取得する目的で海外第 III 相試験（F2314 試験）も実施した。

欧州：

- 効能又は効果：既存治療で効果不十分な成人の活動性強直性脊椎炎
- 用法及び用量：導入投与としてセクキヌマブ 150 mg を初回，1 週後，2 週後，3 週後，4 週後に皮下投与，それ以降は維持投与としてセクキヌマブ 150 mg を 4 週間隔で皮下投与

米国：

- 効能又は効果：成人の活動性強直性脊椎炎
- 用法及び用量：

- 導入投与あり：導入投与としてセクキヌマブ 150 mg を初回，1 週後，2 週後，3 週後，4 週後に皮下投与，以降は維持投与としてセクキヌマブ 150 mg を 4 週間隔で皮下投与
- 導入投与なし：セクキヌマブ 150 mg を 4 週間隔で皮下投与

3.1.1 外国第 III 相検証試験（F2310 試験）成績（投与 156 週時）

F2310 試験は，多施設共同，ランダム化，二重盲検，並行群間比較試験である。本試験の主目的は，投与 16 週後の ASAS20 反応率を指標に，セクキヌマブ 75 mg 又は 150 mg の SC 投与時の有効性をプラセボと比較し，優越性を検証することである。試験期間は 5 年間で本承認申請時点も継続中であり，本申請資料では投与 156 週までのデータを評価した。用法・用量は，導入投与としてセクキヌマブ 75 mg，150 mg，又はプラセボをベースライン（Day 1），Week 1，2，3，4 に SC 投与し，それ以降，維持投与としてセクキヌマブ 75 mg，150 mg，又はプラセボを 4 週間隔で SC 投与した。

NSAID に対して効果不十分若しくは忍容性不良で，DMARD 又は抗 TNF-α 製剤の使用の有無を問わず中等症又は重症の活動性の AS 患者 253 名がスクリーニングされ，このうち 219 名が SC-75 mg 群（73 名），SC-150 mg 群（72 名），又はプラセボ群（74 名）にランダム化された。プラセボ群（74 名）のうち投与 16 週までに中止した 8 名を除く 66 名がセクキヌマブ 75 mg 群（以下，Pbo-75 mg 群，32 名）又は 150 mg 群（以下，Pbo-150 mg 群，34 名）に再ランダム化された。また，SC-75 mg 群 73 名のうち 2 名，Pbo-75 mg 群 32 名のうち 3 名が Week 52 以降 150 mg に増量した。Week 156 までに投与を中止した被験者の割合は，SC-75 mg 群（150 mg に増量した被験者も含む）が SC-150 mg 群に比べて高かった（SC-75 mg 群 31.5%，SC-150 mg 群 20.8%）。プラセボ群から再ランダム化された Pbo-75 mg 群（150 mg に増量した被験者も含む）及び Pbo-150 mg 群で，投与を中止した被験者の割合はそれぞれ 18.8%（6/32 名），14.7%（5/34 名）であり，投与群間で大きな違いはなかった。

有効性に関して，主要評価項目である投与 16 週の ASAS20 反応率は SC-75 mg 群で 41.1%，SC-150 mg 群で 61.1%，プラセボ群で 28.4%であった。ロジスティック回帰分析による群間比較の結果，SC-150 mg 群の ASAS 20 反応率はプラセボ群に比べて有意に高く（調整前 $p < 0.0001$，調整後 $p = 0.0001$），SC-150 mg 群の AS の臨床症状・徴候の改善効果はプラセボ群に比べて優れていることが示された。一方，SC-75 mg 群は，プラセボ群との有意差はみられなかった（調整前，調整後いずれも $p = 0.0967$）。SC-150 mg 群の ASAS 20 反応率はプラセボ群に比べて 30%以上高く，臨床的に意義のある改善（群間差 10%以上）が認められた。また，SC-150 mg 群は SC-75 mg 群に比べて 20%以上高く，用量の増加に伴い増加した [2.5-4 項]。

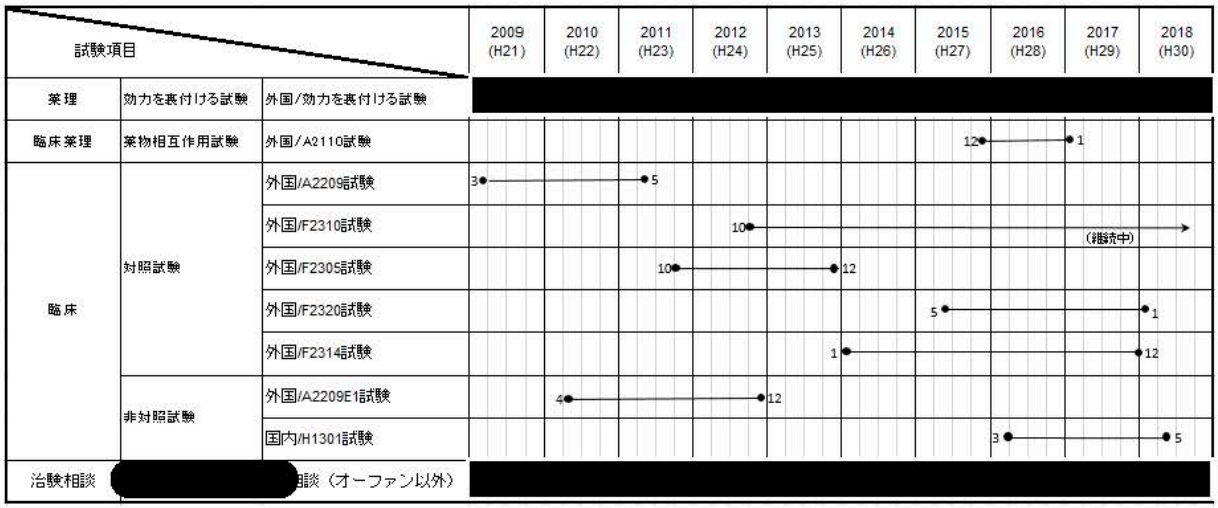
安全性に関して，SC-75 mg 群で 2 名（心筋梗塞，呼吸停止が各 1 名）及び SC-150 mg 群で 1 名（肺炎，心肥大，心拡張）の死亡が認められたが，死因はいずれも治験薬との関連を否定された。投与 156 週の中間解析データカットオフ時点での重篤な有害事象の発現率は，Any75 mg 群で 19.0%（20/105 名），Any150 mg 群で 13.5%（15/111 名）であり，治験薬との関連が否定されなか

った事象は，Any75 mg 群の薬効欠如及び強直性脊椎炎，虚血性大腸炎，クローン病，肺炎及び表在性血栓性静脈炎，術後創感染，ウイルス性髄膜炎，ネフローゼ症候群（各 1 名），Any150 mg 群の肝酵素上昇，熱性感染症（各 1 名）であった。これらのうち，ネフローゼ症候群以外は，薬物又は非薬物治療，治験薬の投与中止，又は休薬により消失した。投与 156 週の中間解析データカットオフ時点での有害事象発現率は，Any75 mg 群で 88.6%（93/105 名），Any150 mg 群で 84.7%（94/111 名）であり，有害事象発現率と用量に関連はみられなかった。Any セクキヌマブ群で最も多かった有害事象は鼻咽頭炎（24.6%，52/211 名）で，次いで上気道感染（11.4%），気管支炎及び下痢（各 10.9%）であった [2.5-5 項]。

3.2 国内における開発の経緯

上述した外国でのセクキヌマブの AS に対する開発経緯を踏まえ，日本での AS の適応に対する開発を計画・実施した。AS の適応追加に関わる開発の経緯図を Figure 3-1 に示す。

Figure 3-1 開発の経緯図



日本人と外国人で AS の有病率に違いはあるものの，発症機序，診断基準，及び標準治療に国内外で違いはない。また，日本人 AS 患者と外国人 AS 患者で全身曝露（PK）が大きく異なる可能性は少ないと考えられた [2.7.2-3.6.6 項]。そのため，外国検証試験で決定した推奨用法・用量を日本人 AS 患者に適用した場合，外国 AS 患者と同様の有効性が得られると考え，日本人 AS 患者におけるセクキヌマブの有効性及び安全性の確認を目的とする国内第 III 相臨床試験（H1301 試験）を計画した。

国内の AS 患者数が少なく，被験者数が限られるため，試験デザインは，多施設共同，非盲検，非対照試験とし，外国検証試験との結果の類似性を確認するために，対象患者，併用療法，有効性及び安全性評価変数は，F2310 試験及び F2305 試験と同じ項目を設定した。なお，20[redacted]年[redacted]月

に医薬品医療機器総合機構と[redacted]相談を実施し，[redacted]について合意を得た[1.13.2 治験相談記録 20[redacted]。

本邦における AS の承認申請を目的とした臨床データパッケージを Table 3-1 に示す。国内 H1301 試験，本承認申請の推奨用法により実施した外国 F2310 試験，及び H1301 試験の用法・用量の設定根拠の一つである外国 F2305 試験を評価資料とした。その他 2 つの外国検証試験（F2320, F2314 試験），PoC 及びその継続試験（A2209，A2209E1 試験）及び第 II 相試験終了後相談以降に外国で新たに実施した薬物相互作用試験（A2110 試験）を参考資料とした。国内 H1301 試験については，24 週投与時の総括報告書の補遺ならびに 52 週投与時の総括報告書を審査期間中に追加提出した。なお，臨床データパッケージに含まれる試験のうち F2310 試験のみ継続中である（2018 年 10 月時点）。。

Table 3-1　　臨床データパッケージ

対象患者	申請資料における試験の位置づけ	試験名	相	実施国	試験デザイン	試験期間	試験状況	資料区分
臨床薬理試験								
Pso	薬物相互作用	A2110	I	外国	非盲検，単群，上乗せ試験	40 週間 (24 週間*)	完了	参考
有効性及び安全性を評価した試験								
AS	日本人での有効性，安全性	H1301	III	日本	多施設共同，非盲検，非対照	1 年 (52 週**)	完了	評価
	プラセボに対する優越性の検証	F2310	III	外国	多施設共同，ランダム化，二重盲検，プラセボ対照	5 年 (156 週**)	継続中	評価
	IV 投与で導入投与した時の有効性，安全性	F2305	III	外国	多施設共同，ランダム化，二重盲検，プラセボ対照	2 年	完了	評価
	導入投与有無別の有効性，安全性	F2320	III	外国	多施設共同，ランダム化，二重盲検，プラセボ対照	2 年 (16 週**)	完了	参考
	高曝露投与時の有効性，安全性	F2314	III	外国	多施設共同，ランダム化，二重盲検，プラセボ対照	3 年 (52 週**)	完了	参考
	PoC 試験	A2209	II	外国	多施設共同，ランダム化，二重盲検，プラセボ対照	28 週間 (3 週間*)	完了	参考
	PoC 試験の継続試験	A2209E1	II	外国	多施設共同，非盲検，非対照，A2209 継続試験	64 週間 (52 週間*)	完了	参考

Pso：尋常性乾癬（plaque psoriasis）
*：投与期間
**：評価期間（直近の中間解析データカットオフ時点）

3.2.1　　国内非対照試験（H1301 試験）成績（投与 52 週時）

H1301 試験は，多施設共同，非盲検，非対照試験である。試験期間は 1 年で，投与 16 週後の ASAS20 反応率を指標に，日本人 AS 患者でのセクキヌマブの有効性及び安全性を確認することを主目的とした。用法用量は，F2310 試験と同じ，導入投与としてセクキヌマブ 150 mg をベース

ライン（Day 1），Week 1，2，3，4 に SC 投与し，それ以降，維持投与としてセクキヌマブ 150 mg を 4 週間隔で SC 投与した。

NSAID に対して効果不十分若しくは忍容性不良で，DMARD 又は抗 TNF-α 製剤の使用の有無を問わず中等症又は重症の活動性日本人 AS 患者 30 名が組入れられ，25 名が投与 52 週を完了した。有効性に関して，主要評価項目である投与 16 週の ASAS20 反応率は 70%（21/30）であり，F2310 試験の 150 mg 投与群の結果（61.1%）と大きな違いはなかった[2.5-4 項]。安全性に関して，H1301 試験における死亡の報告はなかった。投与 52 週のデータカットオフ時点での重篤な有害事象の発現率は 10%（3/30 名）で，内訳は薬疹，子宮頸部腺癌，冠動脈閉塞であり，いずれも投与 24 週のデータカットオフまでに発現した。薬疹及び子宮頸部腺癌は治験薬との関連を否定されなかったが，いずれも薬物又は非薬物治療で消失した。投与 52 週時点での有害事象発現率は 86.7%（26/30 名）で，最もよくみられた有害事象は，上咽頭炎が 50.0%（15/30 名），次いで口内炎が 23.3%（7/30 名），インフルエンザが 16.7%（5/30 名）であった。H1301 試験の安全性プロファイルは，外国試験でみられた安全性プロファイルと大きく異ならず，日本人 AS 患者で新たな安全性上の問題は認められなかった[2.5-5 項]。

4 特徴及び有用性

セクキヌマブは AS 患者の臨床症状・徴候を速やかかつ十分に改善する

AS の臨床症状・徴候（痛み，こわばり等）の速やかな改善は，患者のアドヒアランス向上につながる（Montgomery et al. 2012，Murphy and Bender 2009，Home et al. 2000）。

F2310 試験の SC-150 mg 群において，主要評価変数である ASAS20 反応率と，EMA ガイドラインで AS の臨床症状及び徴候に対する改善効果の主要評価変数とすることを推奨されている ASAS40 反応率は，投与開始 1 週後からプラセボ群に比べて臨床的に意義のある改善（10%以上）を示した。また，ASAS20 反応率は投与 3 週時，ASAS40 反応率は投与 4 週時で投与 16 週時と同程度まで上昇しており，投与開始直後から速やかな臨床症状・徴候の改善がみられた。

F2310 試験の SC-150 mg 群の投与 16 週時の ASAS 20 反応率はプラセボ群に比べて 30%以上，ASAS 40 反応率は 25%以上高く，それぞれ有意差がみられた。加えて，ASAS 20 反応率には含まれない客観的評価項目（CRP，BASMI）を含む ASAS 5/6 反応率，AS の臨床症状が軽微又は認められないことを示す ASAS 部分寛解率，AS の主要症状がベースラインに比べて 50%以上改善したことを示す BASDAI 50 反応率のいずれにおいても，SC-150 mg 群はプラセボ群に比べて 10%以上高く，有意差がみられ，プラセボ群に比べて優れた臨床症状・徴候の改善効果が認められた。

日本人 AS 患者を対象とした H1301 試験でも，投与 16 週時の ASAS20 反応率及び ASAS40 反応率，並びに投与開始から 16 週までの反応率の推移は，F2310 試験の SC-150 mg 群の結果と大きな違いはみられなかった [2.5-4.3.4.1 項]。

セクキヌマブは AS 患者の身体機能を改善する

F2310 試験の SC-150 mg 群において，健康関連の身体的 QoL 評価に幅広く使用されている SF-36 PCS スコアは，投与後ベースラインから上昇（改善）し，投与 4 週時から臨床的に意義のある変化（ベースラインに比べて 2.5 以上の上昇）がみられた。投与 16 週時ではプラセボ群に比べて有意に上昇（改善）した。また，AS の臨床症状に関連して患者が感じる日常動作の制限を評価した BASFI 及び治験担当医師が測定した体軸の可動域を評価した BASMI linear についても，F2310 試験の SC-150 mg 群はいずれもプラセボ群に比べて大きく改善した。日本人 AS 患者を対象とした H1301 試験でも，同様の結果が確認された [2.5-4.3.4.2 項]。

セクキヌマブは AS 患者の QoL を改善する

AS の進行は緩徐で，数十年という長い期間にわたる治療が必要とされるため，身体的のみならず，心理的・社会的にも患者の QoL は著しく低下する。F2310 試験の SC-150 mg 群において，AS 患者の疾患特異的な健康関連 QoL である ASQoL は，投与 4 週時点から臨床的に意義のある変化（ベースラインに比べ 1.8 以上の低下）がみられ，投与 16 週時のベースラインからの変化量はプラセボと比較して有意に低下（改善）した。また，慢性疾患患者における疲労による日常活動や機能への影響を評価する指標である FACIT-Fatigue についても，F2310 試験の SC-150 mg 群において，投与 16 週時にはベースラインから上昇（改善）し，ベースラインからの変化量はプラセボ群と比較して大きかった。日本人 AS 患者を対象とした H1301 試験でも，同様の結果が確認された [2.5-4.3.4.3 項]。

セクキヌマブの効果は長期にわたり持続する

AS は慢性炎症性疾患であり，長期にわたり治療効果を維持することは重要である。F2310 試験の SC-150 mg 群において，投与 16 週時点のセクキヌマブ投与による AS の臨床症状・徴候，身体機能及び体軸可動性，並びに QoL に対する改善効果が本承認申請時点で最長 3 年にわたり維持された [2.5-4.5 項]。

セクキヌマブは抗 TNF-α 製剤で治療しても効果不十分又は忍容性不良な患者の新たな治療選択肢となる

現在，国内で，既存治療で効果不十分な AS 患者に対する適応症を有している生物学的製剤は 2 つの抗 TNF-α 製剤（インフリキシマブ，アダリムマブ）のみであり，抗 TNF-α 製剤に効果不十分な患者に対する薬剤の提供は，AS 治療上のアンメットメディカルニーズの一つである。

セクキヌマブは，IL-17A の IL-17 受容体への結合を阻害することで IL-17A の生物活性を選択的に中和し効果を発揮する，新規作用機序の生物学的製剤である。F2310 試験の抗 TNF-α 製剤による治療で効果不十分又は忍容性不良な患者の部分集団データでも，抗 TNF-α 製剤で未治療の患者集団と同様に，セクキヌマブの投与により，臨床症状・徴候の短期的及び長期的な改善，身体機能の改善，並びに疾患関連の QoL の改善が示された。日本人 AS 患者を対象とした H1301 試験でも，同様の結果が確認された[2.5-4.4.2 項]。

セクキヌマブは AS に対しても，尋常性乾癬，関節症性乾癬，膿疱性乾癬と同様の管理で，安全に使用できる

F2310 試験及び H1301 試験の結果を中心に，その他外国試験（F2305 試験，F2320 試験，F2314 試験）及び市販後データを包括的に評価した結果，AS 患者にセクキヌマブ 150 mg を皮下投与した時の忍容性は良好であり [2.5-5.4 項]，既承認効能（尋常性乾癬，関節症性乾癬，膿疱性乾癬）でこれまでに特定されたセクキヌマブのリスクプロファイルに新たに追加又は変更すべきリスクはないことが確認された[2.5-6.2 項]。したがって，適応症を問わず同じ安全性管理方法で安全に使用できる。

セクキヌマブは，AS 患者の脊椎及び仙腸関節の炎症を改善する

AS 患者では，脊椎又は関節の炎症部位で骨増殖が起こり，進行すると脊椎の構造的損傷が引き起こされ，脊椎が強直する（Lories 2011）。骨の構造的損傷は不可逆であり，重症例では骨折による神経の損傷，正常な姿勢維持ができない等，著しく QoL を低下させる。F2305 試験に組入れられた被験者のうち，抗 TNF-α 製剤で未治療の AS 患者を対象に MRI を評価した結果，セクキヌマブによる仙腸関節及び脊椎の炎症が抑制されることが示された。F2305 試験の導入投与は IV 投与で行われており，F2310 試験及び H1301 試験の導入投与（SC 投与）と異なるが，F2305 試験でプラセボ群から投与 16 週以降に SC-150 mg が投与された被験者でも MRI のスコアが低下する傾向がみられていることから，導入投与の違いに依らず，セクキヌマブ SC-150 mg を投与することで，仙腸関節及び脊椎の炎症の抑制が期待できると考える。脊椎及び仙腸関節の炎症を抑制することで，脊椎の構造的損傷の抑制につながると考えられる。本承認申請時点でそれを示した臨床データはまだないものの，F2305 試験でセクキヌマブが投与された被験者の 80%で，投与 104 週時の mSASSS がベースラインから増加せず，X 線上での脊椎の構造的損傷の進行が認められなかった[2.5-4.3.4.4 項]。

5 まとめ

AS の治療の主な目的は，短期的には痛みやこわばりといった症状と炎症の改善，長期的には脊椎の構造的損傷の抑制，並びに身体機能と社会参加を維持又は正常化することにより，生活の質を高く維持することである。AS の根治療法は無く，国内で主に使用されている AS 治療薬（NSAID 及び抗 TNF-α 製剤）で効果不十分又は忍容性不良の患者に対して，新たな治療選択肢となる薬剤が求められている。

セクキヌマブは，AS の治療薬としては初の IL-17A を標的とする生物学的製剤である。F2310 試験及び H1301 試験の結果，NSAID で効果不十分若しくは忍容性不良な AS 患者に対し，セクキヌマブ SC-150 mg の臨床症状の改善効果が示された。セクキヌマブの臨床症状・徴候に対する改善効果の発現は投与開始 1 週後と速やかで，本承認申請時点で投与開始 3 年後まで効果が維持された。また，投与開始 4 週後から臨床的に意義のあるレベルまで身体機能及び疾患に関連する QoL を改善したことから，NSAID に続く治療選択肢として使用できると考えられた。また，抗

TNF-α 製剤による治療で効果不十分な患者に対しても，セクキヌマブ SC-150 mg の投与により，全体集団と同様のベネフィットが得られたことから，抗 TNF-α 製剤で効果不十分又は忍容性不良の患者に対しても使用できると考える。さらに，F2305 試験における MRI による脊椎及び仙腸関節の炎症の評価で，セクキヌマブによる炎症反応の改善が示唆された。

本剤の AS 患者における忍容性は良好であり，報告された有害事象は，本剤の既承認の適応症である乾癬，関節症性乾癬／乾癬性関節炎患者でみられた事象と同様で，新たなリスクは特定されなかった。重要なリスクは，既承認の適応症と同じ注意喚起をすることで，リスクを最小化することができると考える。

したがって，セクキヌマブの期待されるベネフィットは予測されるリスクに比べて高く，第一選択薬である NSAID による治療で効果不十分な AS 患者の薬物治療に使用可能な，臨床上意義の高い薬剤であると考え，以下のとおり承認事項一部変更承認申請を行うこととした。

【申請品目】

コセンティクス皮下注 150 mg シリンジ

コセンティクス皮下注 150 mg ペン

【効能又は効果（案）】

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

（下線部：追記箇所）

【用法及び用量（案）】

尋常性乾癬，関節症性乾癬，膿疱性乾癬

通常，成人にはセクキヌマブ（遺伝子組換え）として，1 回 300 mg を，初回，1 週後，2 週後，3 週後，4 週後に皮下投与し，以降，4 週間の間隔で皮下投与する。また，体重により，1 回 150 mg を投与することができる。

強直性脊椎炎

通常，成人にはセクキヌマブ（遺伝子組換え）として，1 回 150 mg を，初回，1 週後，2 週後，3 週後，4 週後に皮下投与し，以降，4 週間の間隔で皮下投与する。

（下線部：追記箇所）

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1.6 外国における使用状況等に関する資料

目　　次

表 一 覧

1 外国における使用状況等

2018 年 10 月現在，本剤は EU 及び米国をはじめ 88 ヶ国で承認されている。EU 及び米国での承認状況を，Table 1-1 に示す。

Table 1-1 EU 及び米国での承認状況

国名	承認年月日	効能・効果
EU（中央審査方式）	2015 年 1 月 15 日	全身療法の対象となる中等症から重症の成人の局面型皮疹を有する乾癬
	2015 年 11 月 19 日	疾患修飾性抗リウマチ薬で十分な効果が得られない成人の活動性乾癬性関節炎
	2015 年 11 月 19 日	既存治療では十分な効果が得られない成人の活動性強直性脊椎炎
米国	2015 年 1 月 21 日	全身療法又は光線療法の対象となる中等症から重症の成人の局面型皮疹を有する乾癬
	2016 年 1 月 15 日	成人の活動性乾癬性関節炎
	2016 年 1 月 15 日	成人の活動性強直性脊椎炎

2 外国の添付文書等の概要

米国の添付文書（2018 年 6 月改訂）及び EU 共通の添付文書（2018 年 10 月改訂）の和訳の概略をそれぞれ Table 2-1，Table 2-2 に示す。

Table 2-1 米国の添付文書の概略

販売名	コセンティクス ™（セクキヌマブ）注射液，皮下投与用 注射用コセンティクス ™（セクキヌマブ），皮下投与用
剤型・含量	注射液：使い捨て Sensoready®ペン*中 150 mg/mL 溶液 注射液：使い捨てプレフィルドシリンジ中 150 mg/mL 溶液 注射用：溶解用使い捨てバイアル入り 150 mg 凍結乾燥粉末（医療従事者のみが使用可能） * Sensoready®はプレフィルドペンの商標。原文は Sensoready®と記載されているが，ここではプレフィルドペンと記載する。
効能・効果	全身療法又は光線療法の対象となる中等症から重症の成人の局面型皮疹を有する乾癬 成人の活動性乾癬性関節炎 成人の活動性強直性脊椎炎
用法・用量	**局面型皮疹を有する乾癬** 300mg の皮下投与を初期投与として 0 週，1 週，2 週及び 3 週に実施し，4 週以降は毎月 300mg を維持投与することを推奨する。300mg を投与する場合，150mg の用量を 2 回皮下投与する。 一部の患者に対しては 150mg の投与も可とする。 **乾癬性関節炎** 中等症から重症の局面型皮疹を有する乾癬を併発する乾癬性関節炎患者に対しては，局面型皮疹を有する乾癬の推奨用量を用いる。 それ以外の乾癬性関節炎患者に対しては，以下の推奨用量でコセンティクスを投与する。 推奨用量： • 導入投与有りの場合，セクキヌマブ 150mg を初回，1 週後，2 週後，3 週後，4 週後に皮下投与し，以降は維持投与としてセクキヌマブ 150mg を 4 週間隔で皮下投与する。 • 導入投与無しの場合，セクキヌマブ 150mg を 4 週間隔で皮下投与する。

販売名	コセンティクス ™（セクキヌマブ）注射液，皮下投与用 注射用コセンティクス ™（セクキヌマブ），皮下投与用
	• 活動性の乾癬性関節炎の症状が継続する患者には，セクキヌマブ 300mg の投与を検討する コセンティクスはメトトレキサート使用の有無を問わず投与される。 **強直性脊椎炎** 以下の推奨用量でコセンティクスを投与する 推奨用量： • 導入投与有りの場合，セクキヌマブ 150mg を初回，1 週後，2 週後，3 週後，4 週後に皮下投与し，以降は維持投与としてセクキヌマブ 150mg を 4 週間隔で皮下投与する。 • 導入投与無しの場合，セクキヌマブ 150mg を 4 週間隔で皮下投与する。 **コセンティクス投与開始前の評価** コセンティクスの投与開始前に結核感染について確認すること。 **投与に関する重要な指示** コセンティクスの剤形は 3 種類ある（プレフィルドペン，プレフィルドシリンジ，溶解用バイアル入り凍結乾燥粉末）。コセンティクス各剤形の「使用に関する指示」には，コセンティクスの調製及び投与に関するより詳細な指示が記載されている。 コセンティクスは医師の助言及び監督下で使用する。プレフィルドペン又はプレフィルドシリンジを用いた皮下投与手技に関する適切な訓練を受け，医師が適切と判断した患者は自己投与してもよい。溶解用凍結乾燥粉末は医療従事者のみが使用できる。毎回，前回とは異なる解剖学的部位（上腕，大腿部，又は腹部の 4 つの区分のいずれか）に投与し，圧痛，打撲傷，紅斑，硬化が認められる又は乾癬の影響がある皮膚部位には投与しない。上腕外側への投与は介護者又は医療従事者が行う。 **コセンティクスプレフィルドペン及びプレフィルドシリンジ使用のための準備** 投与前に，コセンティクスプレフィルドペン又はコセンティクスプレフィルドシリンジを冷蔵庫から出し，針キャップを付けたままコセンティクスが室温になるまでおく（15～30 分）。 コセンティクスプレフィルドペン又はコセンティクスプレフィルドシリンジの取り外し可能なキャップには天然ゴムラテックスが含まれるため，ラテックスに感受性の高い者は取り扱ってはならない。 投与前に，粒子や変色がないか目視確認する，コセンティクス注射液は，澄明～わずかに混濁した，無色～微黄色の溶液である。肉眼で見える粒子が含まれているか，変色又は濁りがある場合は使用しない。コセンティクスには防腐剤は含まれていないため，プレフィルドペン又はプレフィルドシリンジは，冷蔵庫から出した後 1 時間以内に投与する。ペン又はシリンジに残った製剤は廃棄する。 **コセンティクス凍結乾燥粉末の溶解及び調製** コセンティクス凍結乾燥粉末は，訓練を受けた医療従事者が，無菌操作で中断せずに注射用滅菌水で調製及び溶解する。栓に穴を開けてから溶解が終わるまでの調製時間は平均 20 分であり，90 分を超えないこと。 a) コセンティクス凍結乾燥粉末のバイアルを冷蔵庫から出し，室温になるまで 15～30 分間おく。注射用滅菌水も室温にすること。 b) 注射用滅菌水 1mL を，コセンティクス凍結乾燥粉末バイアルにゆっくり注入する。このとき，注射用滅菌水を粉末上に直接滴下する。 c) バイアルを約 45 度傾け，約 1 分間ゆっくりと指先で回転させる。バイアルを振とうしたり反転させたりしてはならない。 d) バイアルを室温に約 10 分間おき，溶解させる。泡が生じる可能性があることに注意する。 e) バイアルを約 45 度傾け，約 1 分間ゆっくりと指先で回転させる。バイアルを振とうしたり反転させたりしてはならない。

販売名	コセンティクス ™（セクキヌマブ）注射液，皮下投与用 注射用コセンティクス ™（セクキヌマブ），皮下投与用
	f) バイアルをそのまま室温に約 5 分間おく。溶解したコセンティクス溶液は，本来肉眼で見える粒子がなく，澄明～わずかに混濁した，無色～微黄色の溶液である。凍結乾燥粉末の溶解が不完全，液体中に眼に見える粒子がある，又は液体に濁りや変色がある場合は使用しない。 g) 必要な数のバイアルを準備する（150mg 投与の場合 1 本，300mg 投与の場合 2 本）。 h) コセンティクス溶液 1mL 中にセクキヌマブは 150 mg 含まれている。溶解後は，直ちに使用するか，2°C～8°C（36°F～46°F）で冷蔵保存する（最長 24 時間）。冷凍はしない。 i) 2°C～8°C（36°F～46°F）で保存した場合，投与前に溶液が室温になるまでおく（15～30 分）。コセンティクスに防腐剤は含まれていないため，2°C～8°C（36°F～46°F）の保存場所から出した後は 1 時間以内に投与する。
使用上の注意	**禁忌** コセンティクスは，セクキヌマブ又は添加物のいずれかに対する重篤な過敏症反応の既往がある患者には禁忌とする。 **警告及び注意** <u>感染症</u> コセンティクスは感染のリスクを増大させる可能性がある。中等症から重症の局面型皮疹を有する乾癬患者を対象とした臨床試験において，プラセボ投与例に比べてコセンティクス投与例の方が感染症の発現率が高かった。プラセボ対照臨床試験において，一般的な感染症の発現率はコセンティクス投与例の方がプラセボ投与例に比べて高く，鼻咽頭炎は 11.4%対 8.6%，上気道感染は 2.5%対 0.7%，皮膚粘膜カンジダ症は 1.2%対 0.3%であった。乾癬性関節炎患者及び強直性脊椎炎患者を対象としたプラセボ対照試験において，感染症のリスクについて乾癬患者と同様の傾向が見られた。臨床試験において，一部の感染症の発現率は用量依存的であった。 慢性感染症を有する患者又は反復感染の既往がある患者にコセンティクスの使用を検討する際は注意すること。 感染を示唆する徴候や症状が生じた場合には医師の診察を受けるよう，患者に指導する。重篤な感染症を発現した患者については十分な観察を行い，感染症が消失するまでコセンティクスを投与しないこと。 <u>結核に関する投与前評価</u> コセンティクスの投与開始前に結核感染について患者を評価すること。活動性結核感染患者にコセンティクスを投与しないこと。コセンティクス投与前に潜在性結核の治療を開始すること。潜在性結核又は活動性結核の既往があり，十分な治療が確認できない患者にコセンティクスの投与を開始する前には，抗結核治療を検討すること。コセンティクスを投与する患者は，投与期間中及び投与後に，活動性結核の徴候及び症状を十分に観察すること。 <u>炎症性腸疾患</u> 炎症性腸疾患患者に対してコセンティクスを処方する際は注意すべきである。局面型皮疹を有する乾癬，乾癬性関節炎，及び強直性脊椎炎に対する臨床試験においてコセンティクスを投与された患者で，炎症性腸疾患の増悪が認められ，深刻な増悪が起こった事例や，新規の炎症性腸疾患の発現を認めた事例もあった。活動性クローン病の 59 名の患者を対象とした探索的試験において，プラセボ投与群と比較してコセンティクス投与群で，クローン病の疾患活動性増悪と有害事象の増加が見られた。コセンティクスを投与された患者の炎症性腸疾患の症状と徴候を観察すること。 <u>過敏症反応</u> 臨床試験において，コセンティクス投与患者でアナフィラキシー及び蕁麻疹が発現した。アナフィラキシー反応又はその他の重篤なアレルギー反応が生じた場合，直ちにコセンティクスの投与を中止し，適切な治療を開始すること。 <u>ラテックスに感受性のある者における過敏症のリスク</u>

販売名	コセンティクス ™（セクキヌマブ）注射液，皮下投与用 注射用コセンティクス ™（セクキヌマブ），皮下投与用
	コセンティクスプレフィルドペン及びコセンティクスプレフィルドシリンジの取り外し可能なキャップには天然ゴムラテックスが含まれる。これはラテックスに感受性のある者においてアレルギー反応をきたす可能性がある。ラテックスに感受性のある者におけるコセンティクスプレフィルドシリンジペン又はプレフィルドシリンジ使用の安全性は検討されていない。 ワクチン接種 コセンティクス投与開始前に，最新の予防接種ガイドラインに従って年齢に応じたすべての予防接種が完了しているかを検討する。コセンティクスを投与された患者に生ワクチンを投与してはならない。 コセンティクス投与期間中に非生ワクチンを接種した場合，疾患予防に十分な免疫反応が惹起されない可能性がある。 **副作用** 次の副作用については添付文書中に詳細に考察されている。 • 感染症 • 炎症性腸疾患 • 過敏症反応 臨床試験の経験 臨床試験は極めて多様な条件下で実施するため，ある薬剤の臨床試験における副作用の発現率を別の薬剤の臨床試験での発現率と直接比較することはできず，実地臨床での発現率を反映するわけでもない。 **局面型皮疹を有する乾癬** 対照及び非対照臨床試験において，計 3,430 例の局面型乾癬患者にコセンティクスを投与した。このうち 1,641 例が 1 年以上曝露された。 局面型乾癬患者を対象とした 4 件のプラセボ対照第 III 相試験を併合し，試験 1，2，3 及び 4 で投与開始 12 週間後までのコセンティクスの安全性をプラセボと比較評価した。計 2077 例について評価を行った（コセンティクス 300mg 群に 691 例，コセンティクス 150mg 群に 692 例，プラセボ群に 694 例）。 プラセボ対照試験の 12 週間プラセボ対照期間中の発現率が 1%以上及びコセンティクス群でプラセボ群よりも発現率が高い副作用を表 1 に要約する。 **表 1　試験 1，2，3 及び 4 の 12 週目までに局面型乾癬患者の 1%以上で報告された副作用**

副作用	コセンティクス		プラセボ (N=694) n (%)
	300mg (N=691) n (%)	150mg (N=692) n (%)	
鼻咽頭炎	79 (11.4)	85 (12.3)	60 (8.6)
下痢	28 (4.1)	18 (2.6)	10 (1.4)
上気道感染	17 (2.5)	22 (3.2)	5 (0.7)
鼻炎	10 (1.4)	10 (1.4)	5 (0.7)
口腔ヘルペス	9 (1.3)	1 (0.1)	2 (0.3)
咽頭炎	8 (1.2)	7 (1.0)	0 (0)
蕁麻疹	4 (0.6)	8 (1.2)	1 (0.1)
鼻漏	8 (1.2)	2 (0.3)	1 (0.1)

販売名	コセンティクス ™（セクキヌマブ）注射液，皮下投与用 注射用コセンティクス ™（セクキヌマブ），皮下投与用
	試験 1，2，3 及び 4 のプラセボ対照期間（12 週目まで）の発現率が 1%未満であった副作用は，副鼻腔炎，足部白癬，結膜炎，扁桃炎，口腔カンジダ症，膿痂疹，中耳炎，外耳炎，炎症性腸疾患，肝トランスアミナーゼ上昇及び好中球減少症であった。 *感染症* 局面型乾癬を対象とした臨床試験のプラセボ対照期間（コセンティクスを計 1,382 例に，プラセボを 694 例に最長 12 週間投与）において，感染症の発現率はプラセボ投与例では 18.9%であったのに対し，コセンティクス投与例で 28.7%であった。重篤な感染症の発現率は，プラセボ投与患者では 0.3%であったのに対し，コセンティクス投与患者では 0.14%であった。 投与期間全体（コセンティクスを計 3,430 例の局面型乾癬患者に投与，投与期間は患者の大半で最長 52 週間）では，コセンティクス投与患者の 47.5%で感染症が報告された（追跡調査期間の人年あたり 0.9）。重篤な感染症は，コセンティクス投与患者の 1.2%で報告された（追跡調査期間の人年あたり 0.015）。 第 III 相試験のデータによると，セクキヌマブの血清中濃度が増加すると一部の感染症が増加傾向を示した。セクキヌマブの血清中濃度が増加するとカンジダ感染，ヘルペスウイルス感染，ブドウ球菌皮膚感染及び治療を要する感染症が増加した。 臨床試験で好中球減少症が認められた。セクキヌマブに伴う好中球減少症の大部分は一過性かつ可逆的であった。好中球減少症に関連する重篤な感染症はなかった。 *炎症性腸疾患* コセンティクスの臨床試験において，重篤な事例も含む炎症性腸疾患の発現が認められた。投与期間全体（コセンティクスを計 3,430 例の局面型皮疹を有する患者に投与，投与期間は最長 52 週間，2, 725 人年）で，クローン病の悪化が 3 例（100 人年あたり 0.11），潰瘍性大腸炎の悪化が 2 例（100 人年あたり 0.08），新たな潰瘍性大腸炎の発生が 2 例（100 人年あたり 0.08）報告された。12 週のプラセボ対照期間中，プラセボ投与例（793 例，176 人年）ではこれらの有害事象は発現しなかった。 クローン病の増悪の 1 例は，局面型皮疹を有する乾癬を対象に実施中の長期臨床試験の非対照期間中に報告された。 *過敏症反応* 臨床試験において，コセンティクス投与患者でアナフィラキシー及び蕁麻疹が発現した。 **乾癬性関節炎** 乾癬性関節炎患者 1,003 例を対象とした 2 つのプラセボ対照試験が実施され，703 例にコセンティクスが，300 例にプラセボが投与された。コセンティクスが投与された 703 例のうち，299 例に対しては皮下投与による導入投与が，404 例に対しては静脈内投与による導入投与が行われ，導入投与後 4 週間ごとに皮下投与でコセンティクスが投与された。乾癬性関節炎患者に対する臨床試験の 16 週のプラセボ対照期間中，有害事象が見られた患者の全体的な割合は投与群間で同様で，コセンティクス投与群で 59%，プラセボ投与群で 58%であった。コセンティクス投与群でプラセボ投与群より 2%以上発現率が高かった有害事象は，鼻咽頭炎，上気道感染，頭痛，吐き気及び高コレステロール血症であった。コセンティクスを投与された乾癬性関節炎患者で見られた安全性プロファイルは，乾癬患者におけるコセンティクスの安全性プロファイルと同等であった。 感染症の患者の割合は，乾癬患者を対象とした臨床試験と同様で，コセンティクス投与群で（29%）でプラセボ投与群（26%）より高かった。 クローン病及び潰瘍性大腸炎の増悪若しくは新規発現が認められた事例もあった。炎症性腸疾患がコセンティクスを投与された 2 例及びプラセボを投与された 1 例の合計 3 例で見られた。 **強直性脊椎炎** 強直性脊椎炎患者590例を対象とした2つのプラセボ対照試験が実施され，394例にコセンティクスが，196例にプラセボが投与された。コセンティクスが投与された394例のうち，145例に対し

販売名	コセンティクス ™（セクキヌマブ）注射液，皮下投与用 注射用コセンティクス ™（セクキヌマブ），皮下投与用
	ては皮下投与による導入投与が，249例に対しては静脈内投与による導入投与が行われ，導入投与後4週間ごとに皮下投与でコセンティクスが投与された。強直性脊椎炎患者を対象とした臨床試験の16週のプラセボ対照期間中，有害事象が見られた患者の全体的な割合はプラセボ投与群（59%）と比較してコセンティクス投与群で高かった（66%）。コセンティクス投与群でプラセボ投与群より2%以上発現率が高かった有害事象は，鼻咽頭炎，吐き気及び上気道感染であった。コセンティクスを投与された強直性脊椎炎患者で見られた安全性プロファイルは乾癬患者におけるコセンティクスの安全性プロファイルと同等であった。 感染症の患者の割合は，乾癬患者を対象とした臨床試験と同様で，コセンティクス投与群で（31%）でプラセボ投与群（18%）より高かった。 強直性脊椎炎を対象とした臨床試験において，コセンティクスを曝露された571例中，全投与期間で8例の炎症性腸疾患（クローン病が5例（100人年あたり0.7），潰瘍性大腸炎が3例（100人年あたり0.4）が見られた。16週間のプラセボ対照期間中，コセンティクスが投与された患者で重篤な有害事象（クローン病の増悪が2例，潰瘍性大腸炎の新規発現が1例）が見られたが，プラセボが投与された患者では重篤な有害事象は見られなかった。臨床試験で全患者にコセンティクスが投与された期間中，クローン病の新規発現が1例，クローン病の増悪が2例，潰瘍性大腸炎の新規発現が1例，潰瘍性大腸炎の増悪が1例で見られた。 **免疫原性** すべての治療用蛋白質と同様，免疫原性の可能性がある。電気化学発光に基づくブリッジング免疫アッセイを用いてコセンティクスの免疫原性を評価した。コセンティクスを最長 52 週間投与された被験者のうち，セクキヌマブに対する抗体が生じた被験者は 1%未満であった。ただし，本アッセイではセクキヌマブ存在下での抗セクキヌマブ抗体の検出に限界があるため，抗体の発現率を正確に測定できなかった可能性がある。抗薬物抗体が発現した被験者のうち約半数では中和抗体に分類される抗体が認められた。中和抗体に伴う有効性の喪失はみられなかった。 抗体形成の検出は，アッセイの感度及び特異性に大きく依存している。さらに，アッセイにおける抗体（中和抗体を含む）陽性の発現率は，アッセイ方法，検体の取扱い，検体採取時期，併用療法及び基礎疾患などいくつかの要因による影響を受ける。以上の理由から，コセンティクスに対する抗体の発現率をほかの薬剤に対する抗体の発現率と比較すると誤解が生じる恐れがある。 **薬物間相互作用** コセンティクスの薬物間相互作用の試験は実施していない。 <u>生ワクチン</u> コセンティクス投与患者には生ワクチンを投与しない。 <u>非生ワクチン</u> コセンティクスを投与された患者に対して非生ワクチンを接種してもよい。米国で承認されていないグループ C 髄膜炎菌多糖共役ワクチン及び米国で承認されていない不活化季節性インフルエンザワクチンの接種 2 週間前にコセンティクス 150mg を単回投与された健康被験者の抗体応答は，ワクチン接種前にコセンティクスを投与されなかった被験者と同程度であった。コセンティクスを投与中の患者における髄膜炎菌ワクチン及びインフルエンザワクチンの臨床的有効性は評価されていない。 <u>CYP450 基質</u> 慢性炎症では、特定のサイトカイン（例、IL-1，IL-6，IL-10，TNFα，IFN）のレベルが増加すると CYP450 酵素の生成が変動する。 中等症から重症の局面型皮疹を有する乾癬患者における薬物相互作用試験の結果，セクキヌマブは CYP3A4 により代謝される薬剤の PK に臨床的に関連のある影響を及ぼさなかった。 CYP450 基質（特に治療域の狭いもの）を併用している患者にコセンティクスの投与を開始又は中止する際は，治療効果又は薬物濃度のモニタリング及び必要に応じた用量調整を検討する。

販売名	コセンティクス ™（セクキヌマブ）注射液，皮下投与用 注射用コセンティクス ™（セクキヌマブ），皮下投与用
	特殊な集団への使用 妊婦 *リスクの概要* 妊婦でのコセンティクスの使用経験は限られており，薬剤に関連した発達障害のリスクについての情報は十分には得られていない。妊娠サルを用いた胚・胎児発生試験において，最大推奨臨床用量の 30 倍のセクキヌマブを器官形成期に皮下投与した結果，催奇形性及び胚・胎児発生に影響は認められなかった。米国の通常の妊婦における先天性異常のリスクは 2-4%，流産のリスクは 15-20%であるが，コセンティクスを投与した妊婦における先天性異常及び流産のリスクは不明である。 *非臨床試験成績* セクキヌマブのカニクイザルを用いた胚・胎児発生毒性試験を実施した。妊娠サルを用いて，最大推奨臨床用量（体重換算で母動物への投与量は 150 mg/kg）の最大 30 倍のセクキヌマブを器官形成期に週 1 回皮下投与した結果，催奇形性及び胚・胎児発生に影響は認められなかった。 また，セクキヌマブのマウスサロゲート抗体を用いた出生前及び出生後の発生並びに母体機能に関する試験を実施した。マウスに 150 mg/kg/回までの用量で妊娠 6，11 及び 17 日並びに分娩後 4，10 及び 16 日に投与した結果，胎児の機能検査（成熟時の生殖機能，感覚機能及び運動機能），形態学的評価及び免疫原性評価に影響は認められなかった。 授乳婦 *リスクの概要* セクキヌマブのヒト乳汁中への移行，及び母乳を摂取後の乳児全身循環への授乳や母乳産生へのコセンティクスの影響に関するデータはない。授乳のベネフィットは，母親のコセンティクスの臨床的必要性，コセンティクスまたは授乳婦の状態が子供に与える潜在的な悪影響等をふまえて検討すべきである。 小児への使用 小児患者におけるコセンティクスの安全性及び有効性は評価されていない。 高齢者への使用 臨床試験でコセンティクスを曝露された局面型乾癬患者 3,430 例中，計 230 例が 65 歳以上であり，32 例が 75 歳以上であった。高齢被験者と若年被験者との間で安全性及び有効性に差は認められなかったが，65 歳以上の被験者の数は，若齢被験者との反応の差を判断するには不十分であった。 **過量投与** 臨床試験では 30 mg/kg（約 2000～3000 mg）までの用量を静脈内投与しても用量制限毒性はみられていない。過量投与の場合は，副作用の徴候及び症状について患者の観察を行い，速やかに適切な対症療法を行うことを推奨する。
承認年月日	2015 年 1 月 21 日

Table 2-2 EU 共通の添付文書の概略

販売名	コセンティクス注射溶液用 150 mg 凍結乾燥製剤 コセンティクスプレフィルドシリンジ入り 150 mg 注射溶液 コセンティクスプレフィルドペン入り 150 mg 注射溶液
剤型・含量	各バイアルは，セクキヌマブ*を 150 mg 含有する。溶解後，1 mL の溶液にセクキヌマブは 150 mg 含まれる。 各プレフィルドシリンジは 1 mL の溶液中セクキヌマブ*を 150 mg 含有する。

	各プレフィルドペンは 1 mL の溶液中セクキヌマブ*を 150 mg 含有する。 *セクキヌマブはインターロイキン 17A に選択的な組換え完全ヒトモノクローナル抗体である。セクキヌマブはチャイニーズハムスター卵巣（CHO）細胞から産生される IgG1/κ クラス抗体である。
効能・効果	局面型皮疹を有する乾癬 全身療法の対象となる中等症から重症の成人の局面型皮疹を有する乾癬患者 乾癬性関節炎 疾患修飾性抗リウマチ薬で十分な効果が得られない成人の活動性乾癬性関節炎患者に対し，単剤またはメトトレキサートと併用で使用する 強直性脊椎炎 既存治療では十分な効果が得られない成人の活動性強直性脊椎炎患者
用法・用量	コセンティクスは乾癬の診断及び治療の経験を有する医師の助言及び監督下で使用する。 用量 *局面型皮疹を有する乾癬* セクキヌマブ 300 mg の皮下投与を初期投与として 0 週，1 週，2 週，3 週に実施し，4 週以降は毎月維持投与することを推奨する。300 mg を投与する場合，150 mg の用量を 2 回皮下投与する。 *乾癬性関節炎* 中等症から重症の局面型皮疹を有する乾癬を併発する場合，又は抗-TNF で十分な効果が得られない患者に対しては，セクキヌマブ 300 mg の皮下投与を初期投与として 0 週，1 週，2 週， 3 週及び 4 週に実施し，以降は毎月維持投与することを推奨する。300 mg を投与する場合は，150 mg を 2 本皮下投与する。 それ以外の患者に対しては，セクキヌマブ 150 mg の皮下投与を初期投与として 0 週，1 週，2 週，3 週及び 4 週に実施し，以降は毎月維持投与することを推奨する。臨床症状に応じて，300 mg に増量できる。 *強直性脊椎炎* セクキヌマブ 150 mg の皮下投与を初期投与として 0 週，1 週，2 週， 3 週及び 4 週に実施し，以降は毎月維持投与することを推奨する。 上記のすべての適応症について，臨床データより，治療開始後 16 週以内に奏功が認められている。最長 16 週間投与しても奏効しない患者に対しては投与の中止を検討する。初期に部分奏効がみられた患者では，16 週間を超えて投与を継続すると改善する場合がある。 *高齢患者（65 歳以上）* 用量調整は必要ない。 *腎障害/肝障害* これらの患者集団に関するコセンティクスの試験は実施していない。用量の推奨はできない。 *小児* 18 歳未満の小児におけるコセンティクス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。 用法 コセンティクスは皮下投与する。可能であれば，乾癬を認める皮膚部位への投与は避ける。注射溶液用粉末は使用前に溶解すること。 皮下投与手技に関する適切な訓練を受け，医師が適切と判断した患者は自己投与してもよい。ただし，医師は継続的に患者のフォローアップを行うこと。患者用のパッケージリーフレットに従い，注射液全量が投与されるよう自己投与を行うこと。
使用上の注意	**禁忌**

	有効成分又は添加物のいずれかに対する重度の過敏症反応をきたす患者 臨床的に重要な活動性感染症（活動性結核等） **使用上の特別な警告・注意** 感染症 コセンティクスは感染症のリスクを増大させる可能性がある。市販後にコセンティクスを投与された患者において，重篤な感染症が認められている。慢性感染症を有する患者又は反復性感染の既往がある患者にコセンティクスの使用を検討する際は注意すること。 感染症を示唆する徴候や症状が生じた場合には医師の診察を受けるよう，患者に指導する。重篤な感染症を発現した患者については十分な観察を行い，感染症が消失するまでコセンティクスを投与しないこと。 臨床試験において，コセンティクス投与患者で感染症が認められている。これらの大部分は鼻咽頭炎等の軽度から中等度の上気道感染であり，投与を中止する必要はなかった。コセンティクスの作用機序に関連して，乾癬を対象とした臨床試験では，重篤でない粘膜皮膚カンジダ症の報告頻度はプラセボ群に比べてセクキヌマブ群の方が多かった（セクキヌマブ 300 mg 群では 100 人年あたり 3.55 であったのに対し，プラセボ群では 100 人年あたり 1.00）。 臨床試験では，結核に対する感受性の増加は報告されなかった。ただし，活動性結核の患者にコセンティクスを投与しないこと。潜伏結核患者については，コセンティクスの投与を開始する前に抗結核治療を検討する。 炎症性腸疾患 クローン病及び潰瘍性大腸炎の新規発症又は悪化の報告がある。クローン病及び潰瘍性大腸炎を含む炎症性腸疾患の患者にコセンティクスを投与する場合は注意し，投与後十分に経過観察すること。 過敏症反応 アナフィラキシー反応又はその他の重篤なアレルギー反応が生じた場合，直ちにコセンティクスの投与を中止し，適切な治療を開始すること。 ラテックスに感受性のある者における過敏症のリスク（プレフィルドペン及びプレフィルドシリンジのみ記載） コセンティクスプレフィルドペン及びコセンティクスプレフィルドシリンジの取り外し可能なキャップには天然ゴムラテックスが含まれる。これはラテックスに感受性のある者においてアレルギー反応をきたす可能性がある。ラテックスに感受性のある者におけるコセンティクスプレフィルドペン又はプレフィルドシリンジ使用の安全性は検討されていない。 ワクチン接種 生ワクチンをコセンティクスと同時に接種してはならない。 コセンティクスを投与する患者に不活化ワクチン又は非生ワクチンを同時に投与してもよい。ある試験において，髄膜炎菌ワクチン及び不活化インフルエンザワクチン接種の後，各ワクチンに対する抗体価が 4 倍以上増加する適切な免疫反応を獲得することができた健康被験者の割合は，セクキヌマブ 150 mg 投与例とプラセボ投与例とで同程度であった。このデータから，コセンティクスは髄膜炎菌ワクチンやインフルエンザワクチンに対する液性免疫反応を抑制しないことが示唆される。 免疫抑制療法の併用 乾癬の試験において，生物製剤を含む免疫抑制剤又は光療法と併用したときのコセンティクスの安全性及び有効性は評価していない。 **相互作用** 生ワクチンをコセンティクスと同時に接種してはならない。 局面型皮疹を有する乾癬患者を対象とした薬物相互作用試験において，セクキヌマブはミタゾラム（CYP3A4 基質）の PK に影響を及ぼさないことが示された。

	乾癬性関節炎患者及び強直性脊椎炎患者の臨床試験において，メトトレキサート又はコルチコステロイドとの併用により，コセンティクスの安全性に影響はみられなかった。 **受胎能，妊娠及び授乳** 妊娠可能な女性 妊娠可能な女性は，投与中及び投与後少なくとも 20 週間は有効な避妊法を用いること。 妊娠 妊婦へのセクキヌマブ使用に関する十分なデータはない。動物試験では，妊娠，胚/胎児発生，分娩又は出生後の発育において直接的又は間接的な毒性変化はみられていない。予防手段として，妊娠中はコセンティクスの使用を避けることが望ましい。 授乳 セクキヌマブのヒト乳汁中への移行は不明である。免疫グロブリンはヒト乳汁中に移行するものの，摂取後のセクキヌマブの全身吸収については不明である。乳児においてセクキヌマブによる副作用の可能性がある。このため，子どもにとっての授乳の有益性と母親にとってのコセンティクス投与の有益性を考慮した上で，投与中及び投与後少なくとも 20 週間は授乳を中止する，又はコセンティクスの投与を中止するとの判断を行う。 受胎能 セクキヌマブがヒト受胎能に及ぼす影響は評価されていない。動物試験では，受胎能に関して直接的又は間接的な毒性変化はみられていない。 **運転・機械操作への影響** コセンティクスが運転及び機械操作に及ぼす影響はない又は無視できる程度である。 **副作用** 安全性プロファイルの要約 さまざまな適応症（局面型皮疹を有する乾癬，乾癬性関節炎，強直性脊椎炎及びその他の自己免疫疾患）における盲検及び非盲検臨床試験で 11,900 例を超える患者にコセンティクスが投与され，曝露は 20,995 人年であった。このうち 7,100 例以上の患者は 1 年以上コセンティクスに曝露された。 局面型皮疹を有する乾癬における副作用 局面型皮疹を有する乾癬患者を対象とした 4 件のプラセボ対照第 III 相試験を併合し，投与開始 12 週間後までのコセンティクスの安全性をプラセボと比較評価した。計 2,076 例について評価を行った（150 mg 群 692 例，300 mg 群 690 例，プラセボ群 694 例）。 報告頻度の最も高い副作用は上気道感染（最も頻度の高い事象は鼻咽頭炎，鼻炎）であった。大部分の事象は軽度又は中等度であった。 乾癬性関節炎における副作用 コセンティクスの乾癬性関節炎患者を対象としたプラセボ対照試験における，計 2,754 例（コセンティクス群 1,871 例，プラセボ群 883 例）で，曝露は 4,478 人年であった。コセンティクスの乾癬性関節炎患者に対する安全性プロファイルは，局面型皮疹を有する乾癬患者と同様であった。 強直性脊椎炎における副作用 強直性脊椎炎患者を対象とした 2 つのプラセボ対照試験計 590 例（コセンティクス群 394 例，プラセボ群 196 例），755 人年（コセンティクス曝露期間の中央値はそれぞれの試験で 469 日及び 460 日）でコセンティクスの安全性が評価された。コセンティクスの強直性脊椎炎患者に対する安全性プロファイルは，局面型皮疹を有する乾癬患者と同様であった。 副作用の一覧表

局面型皮疹を有する乾癬，乾癬性関節炎，若しくは強直性脊椎炎を対象としたそれぞれの臨床試験並びに市販後に発現した副作用（表 1）を MedDRA 器官別大分類ごとに一覧で示す。それぞれの器官別大分類内で副作用を頻度の高い順に示している。各頻度グループ内で副作用を重症度の高い順に示す。また，各副作用の頻度カテゴリーは次のとおり慣行に従う：極めて高頻度（1/10 以上），高頻度（1/100 以上 1/10 未満），低頻度（1/1,000 以上 1/100 未満），まれ（1/10,000 以上 1/1,000 未満），極めてまれ（1/10,000 未満），頻度不明（利用可能なデータから推測不能）。

表 1　　臨床試験 [1)] 及び市販後における副作用の一覧表

SOC 分類	**頻度**	**副作用**
感染症および寄生虫症	極めて高頻度	上気道感染
	高頻度	口腔ヘルペス
	低頻度	口腔カンジダ症
		足部白癬
		外耳炎
	頻度不明	粘膜および皮膚カンジダ症（食道カンジダ症を含む）
血液およびリンパ系障害	低頻度	好中球減少症
免疫系障害	まれ	アナフィラキシー反応
眼障害	低頻度	結膜炎
呼吸器，胸郭および縦隔障害	高頻度	鼻漏
胃腸障害	高頻度	下痢
皮膚および皮下組織障害	低頻度	蕁麻疹

[1)] 局面型皮疹を有する乾癬，乾癬性関節炎，若しくは強直性脊椎炎患者を対象としたそれぞれのプラセボ対照第 III 相臨床試験で 300 mg，150 mg，75 mg 又はプラセボを 12 週間（局面型皮疹を有する乾癬）又は 16 週間（乾癬性関節炎，強直性脊椎炎）まで曝露した。

特定の副作用に関する記述

感染症

局面型乾癬を対象とした臨床試験のプラセボ対照期間（コセンティクスを計 1,382 例，プラセボを 694 例の患者に最長 12 週間投与）において，感染症の発現率は，プラセボ投与患者では 18.9%であったのに対し，コセンティクス投与患者では 28.7%であった。感染症の大部分は，重篤ではない鼻咽頭炎等の軽度又は中等度の上気道感染で，投与を中止する必要がなかった。作用機序に一致して粘膜又は皮膚のカンジダ症が増加したが，これらは軽度又は中等度であり，重篤ではなく，標準治療に反応し，投与を中止する必要がなかった。重篤な感染症の発現率は，プラセボ投与患者では 0.3%であったのに対し，コセンティクス投与患者では 0.14%であった。

投与期間全体（コセンティクスを計 3,430 例に投与，投与期間は患者の大半で最長 52 週間）では，コセンティクス投与患者の 47.5%で感染症が報告された（追跡調査期間の人年あたり 0.9）。重篤な感染症は，コセンティクス投与患者の 1.2%で報告された（追跡調査期間の人年あたり 0.015）。

乾癬性関節炎患者及び強直性脊椎炎患者をそれぞれ対象とした臨床試験での感染症の発現率は，局面型皮疹を有する乾癬患者を対象とした臨床試験での発現率と同様であった。

好中球減少症

	好中球減少症の頻度はプラセボに比べてセクキヌマブの方が高かったが，大部分は軽度で，一過性及び可逆的であった。1.0～0.5×10^9/L 未満（CTCAE グレード 3）の好中球減少症がセクキヌマブ投与患者 3,430 例中 18 例（0.5%）で報告され，18 例中 15 例は用量に依存せず感染症との時間的関連がなかった。より重度な好中球減少症の報告はなかった。残りの 3 例では，標準治療に通常の反応を示し，コセンティクスの投与を中止する必要がない，重篤でない感染症が報告された。 乾癬性関節炎患者及び強直性脊椎炎患者における好中球減少症の発現頻度は，局面型皮疹を有する乾癬患者と同様である。0.5×10^9/L 未満（CTCAE グレード 4）の好中球減少症がまれに報告された。 *過敏症反応* 臨床試験において，蕁麻疹，及びまれにコセンティクスに対するアナフィラキシー反応が認められた。 *免疫原性* コセンティクスを最長 52 週間投与された患者のうち，セクキヌマブに対する抗体が発現した患者は 1%未満であった。試験治療下で発現した抗薬物抗体の約半数が中和抗体であったが，有効性の喪失又は薬物動態の異常は伴わなかった。 <u>副作用の疑いの報告</u> 医薬品の認可後に，副作用の疑いを報告することは重要である。これにより，医薬品の有益性/危険性のバランスを継続的にモニタリングすることが可能となる。副作用の疑いがあれば，国の報告システムを介して報告するよう，医療従事者に依頼する。 **過量投与** 臨床試験において過量投与の事例は報告されていない。 臨床試験では 30 mg/kg（約 2,000～3,000 mg）までの用量を静脈内投与しても用量制限毒性はみられていない。過量投与の場合は，副作用の徴候及び症状について患者の観察を行い，速やかに適切な対症療法を行うことを推奨する。
承認年月日	2015 年 1 月 15 日

NOVARTIS

[redacted]

COSENTYX®/™ (secukinumab)

150 mg Powder for solution for injection
150 mg/mL Solution for injection in a pre-filled syringe or pre-filled pen

Core Data Sheet (CDS)

[redacted]

[redacted]

2-49頁削除

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

COSENTYX® (secukinumab) injection, for subcutaneous use

COSENTYX® (secukinumab) for injection, for subcutaneous use

Initial U.S. Approval: 2015

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

COSENTYX is a human interleukin-17A antagonist indicated for the treatment of:

- moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy (1.1)
- adults with active psoriatic arthritis (PsA) (1.2)
- adults with active ankylosing spondylitis (AS) (1.3)

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

Plaque Psoriasis

- Recommended dosage is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. For some patients, a dose of 150 mg may be acceptable. (2.1)

Psoriatic Arthritis

- For psoriatic arthritis patients with coexistent moderate to severe plaque psoriasis, use the dosage and administration for plaque psoriasis. (2.1)
- For other psoriatic arthritis patients administer with or without a loading dosage. The recommended dosage:
  - With a loading dosage is 150 mg at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter
  - Without a loading dosage is 150 mg every 4 weeks
  - If a patient continues to have active psoriatic arthritis, consider a dosage of 300 mg. (2.2)

Ankylosing Spondylitis

- Administer with or without a loading dosage. The recommended dosage:
  - With a loading dosage is 150 mg at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter
  - Without a loading dosage is 150 mg every 4 weeks (2.3)

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

- Injection: 150 mg/mL solution in a single-use Sensoready® pen (3)
- Injection: 150 mg/mL solution in a single-use prefilled syringe (3)
- For Injection: 150 mg, lyophilized powder in a single-use vial for reconstitution for healthcare professional use only (3)

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

Serious hypersensitivity reaction to secukinumab or to any of the excipients. (4)

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

- Infections: Serious infections have occurred. Caution should be exercised when considering the use of COSENTYX in patients with a chronic infection or a history of recurrent infection. If a serious infection develops, discontinue COSENTYX until the infection resolves. (5.1)
- Tuberculosis (TB): Prior to initiating treatment with COSENTYX, evaluate for TB. (5.2)
- Inflammatory Bowel Disease: Cases of inflammatory bowel disease were observed in clinical trials. Caution should be exercised when prescribing COSENTYX to patients with inflammatory bowel disease. (5.3)
- Hypersensitivity Reactions: If an anaphylactic reaction or other serious allergic reaction occurs, discontinue COSENTYX immediately and initiate appropriate therapy. (5.4)

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

Most common adverse reactions (greater than 1%) are nasopharyngitis, diarrhea, and upper respiratory tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Live Vaccines: Live vaccines should not be given with COSENTYX (5.6, 7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Plaque Psoriasis

COSENTYX® is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

1.2 Psoriatic Arthritis

COSENTYX is indicated for the treatment of adult patients with active psoriatic arthritis.

1.3 Ankylosing Spondylitis

COSENTYX is indicated for the treatment of adult patients with active ankylosing spondylitis.

2 DOSAGE AND ADMINISTRATION

2.1 Plaque Psoriasis

The recommended dosage is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. Each 300 mg dosage is given as 2 subcutaneous injections of 150 mg.

For some patients, a dosage of 150 mg may be acceptable.

2.2 Psoriatic Arthritis

For psoriatic arthritis patients with coexistent moderate to severe plaque psoriasis, use the dosing and administration recommendations for plaque psoriasis *[see Dosage and Administration (2.1)]*.

For other psoriatic arthritis patients, administer COSENTYX with or without a loading dosage by subcutaneous injection. The recommended dosage:

- With a loading dosage is 150 mg at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter
- Without a loading dosage is 150 mg every 4 weeks
- If a patient continues to have active psoriatic arthritis, consider a dosage of 300 mg.

COSENTYX may be administered with or without methotrexate.

2.3 Ankylosing Spondylitis

Administer COSENTYX with or without a loading dosage by subcutaneous injection. The recommended dosage:

- With a loading dosage is 150 mg at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter
- Without a loading dosage is 150 mg every 4 weeks.

2.4 Assessment Prior to Initiation of COSENTYX

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with COSENTYX *[see Warnings and Precautions (5.2)]*.

2.5 Important Administration Instructions

There are three presentations for COSENTYX (i.e., Sensoready pen, prefilled syringe, and lyophilized powder in vial for reconstitution). The COSENTYX “Instructions for Use” for each presentation contains more detailed instructions on the preparation and administration of COSENTYX *[see Instructions for Use]*.

COSENTYX is intended for use under the guidance and supervision of a physician. Patients may self-inject after proper training in subcutaneous injection technique using the Sensoready pen or prefilled syringe and when deemed appropriate. The lyophilized powder for reconstitution is for healthcare provider use only. Administer each injection at a different anatomic location (such as upper arms, thighs, or any quadrant of abdomen) than the previous injection, and not into areas where the skin is tender, bruised, erythematous, indurated, or affected by psoriasis. Administration of COSENTYX in the upper, outer arm may be performed by a caregiver or healthcare provider.

2.6 Preparation for Use of COSENTYX Sensoready® Pen and Prefilled Syringe

Before injection, remove COSENTYX Sensoready pen or COSENTYX prefilled syringe from the refrigerator and allow COSENTYX to reach room temperature (15 to 30 minutes) without removing the needle cap.

The removable cap of the COSENTYX Sensoready pen and the COSENTYX prefilled syringe contains natural rubber latex and should not be handled by latex-sensitive individuals *[see Warnings and Precautions (5.5)]*.

Inspect COSENTYX visually for particulate matter and discoloration prior to administration. COSENTYX injection is a clear to slightly opalescent, colorless to slightly yellow solution. Do not use if the liquid contains visible particles, is discolored or cloudy. COSENTYX does not contain preservatives; therefore, administer the Sensoready pen or prefilled syringe within 1 hour after removal from the refrigerator. Discard any unused product remaining in the Sensoready pen or prefilled syringe.

2.7 Reconstitution and Preparation of COSENTYX Lyophilized Powder

COSENTYX lyophilized powder should be prepared and reconstituted with Sterile Water for Injection by a trained healthcare provider using aseptic technique and without interruption. The preparation time from piercing the stopper until end of reconstitution on average takes 20 minutes and should not exceed 90 minutes.

a) Remove the vial of COSENTYX lyophilized powder from the refrigerator and allow to stand for 15 to 30 minutes to reach room temperature. Ensure the Sterile Water for Injection is at room temperature.

b) Slowly inject 1 mL of Sterile Water for Injection into the vial containing COSENTYX lyophilized powder and direct the stream of Sterile Water for Injection onto the lyophilized powder.

c) Tilt the vial at an angle of approximately 45 degrees and gently rotate between the fingertips for approximately 1 minute. Do not shake or invert the vial.

d) Allow the vial to stand for about 10 minutes at room temperature to allow for dissolution. Note that foaming may occur.

e) Tilt the vial at an angle of approximately 45 degrees and gently rotate between the fingertips for approximately 1 minute. Do not shake or invert the vial.

f) Allow the vial to stand undisturbed at room temperature for approximately 5 minutes. The reconstituted COSENTYX solution should be essentially free of visible particles, clear to opalescent, and colorless to slightly yellow. Do not use if the lyophilized powder has not fully dissolved or if the liquid contains visible particles, is cloudy or discolored.

g) Prepare the required number of vials (1 vial for the 150 mg dose or 2 vials for the 300 mg dose).

h) The COSENTYX reconstituted solution contains 150 mg of secukinumab in 1 mL of solution. After reconstitution, use the solution immediately or store in the refrigerator at 2ºC to 8ºC (36ºF to 46ºF) for up to 24 hours. Do not freeze.

i) If stored at 2ºC to 8ºC (36ºF to 46ºF), allow the reconstituted COSENTYX solution to reach room temperature (15 to 30 minutes) before administration. COSENTYX does not contain preservatives; therefore, administer within 1 hour after removal from 2ºC to 8ºC (36ºF to 46ºF) storage.

3 DOSAGE FORMS AND STRENGTHS

- Injection: 150 mg/mL solution in a single-use Sensoready pen
- Injection: 150 mg/mL solution in a single-use prefilled syringe
- For Injection: 150 mg, lyophilized powder in a single-use vial for reconstitution (for healthcare professional use only)

4 CONTRAINDICATIONS

COSENTYX is contraindicated in patients with a previous serious hypersensitivity reaction to secukinumab or to any of the excipients *[see Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

COSENTYX may increase the risk of infections. In clinical trials, a higher rate of infections was observed in COSENTYX treated subjects compared to placebo-treated subjects. In placebo-controlled clinical trials in patients with moderate to severe plaque psoriasis, higher rates of common infections such as nasopharyngitis (11.4% versus 8.6%), upper respiratory tract infection (2.5% versus 0.7%) and mucocutaneous infections with candida (1.2% versus 0.3%) were observed with COSENTYX compared with placebo. A similar increase in risk of infection was seen in placebo-controlled trials in patients with psoriatic arthritis and ankylosing spondylitis *[see Adverse Reactions (6.1)]*. The incidence of some types of infections appeared to be dose-dependent in clinical studies *[see Adverse Reactions (6.1)]*.

Exercise caution when considering the use of COSENTYX 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. If a patient develops a serious infection, the patient should be closely monitored and COSENTYX should be discontinued until the infection resolves.

5.2 Pre-treatment Evaluation for Tuberculosis

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with COSENTYX. Do not administer COSENTYX to patients with active TB infection. Initiate treatment of latent TB prior to administering COSENTYX. Consider anti-TB therapy prior to initiation of COSENTYX in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving COSENTYX should be monitored closely for signs and symptoms of active TB during and after treatment.

5.3 Inflammatory Bowel Disease

Caution should be used when prescribing COSENTYX to patients with inflammatory bowel disease. Exacerbations, in some cases serious, occurred in COSENTYX treated patients during clinical trials in plaque psoriasis, psoriatic arthritis and ankylosing spondylitis. In addition, new onset inflammatory bowel disease cases occurred in clinical trials with COSENTYX. In an exploratory study in 59 patients with active Crohn's disease, there were trends toward greater disease activity and increased adverse events in the secukinumab group as compared to the placebo group. Patients who are treated with COSENTYX should be monitored for signs and symptoms of inflammatory bowel disease *[see Adverse Reactions (6.1)]*.

5.4 Hypersensitivity Reactions

Anaphylaxis and cases of urticaria occurred in COSENTYX treated patients in clinical trials. If an anaphylactic or other serious allergic reaction occurs, administration of COSENTYX should be discontinued immediately and appropriate therapy initiated *[see Adverse Reactions (6.1)]*.

5.5 Risk of Hypersensitivity in Latex-sensitive Individuals

The removable cap of the COSENTYX Sensoready pen and the COSENTYX prefilled syringe contains natural rubber latex which may cause an allergic reaction in latex-sensitive individuals. The safe use of COSENTYX Sensoready pen or prefilled syringe in latex-sensitive individuals has not been studied.

5.6 Vaccinations

Prior to initiating therapy with COSENTYX, consider completion of all age appropriate immunizations according to current immunization guidelines. Patients treated with COSENTYX should not receive live vaccines.

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

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail elsewhere in the labeling:

- Infections *[see Warnings and Precautions (5.1)]*
- Inflammatory Bowel Disease *[see Warnings and Precautions (5.3)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.4)]*

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.

Plaque Psoriasis

A total of 3430 plaque psoriasis subjects were treated with COSENTYX in controlled and uncontrolled clinical trials. Of these, 1641 subjects were exposed for at least 1 year.

Four placebo-controlled phase 3 trials in plaque psoriasis subjects were pooled to evaluate the safety of COSENTYX in comparison to placebo up to 12 weeks after treatment initiation, in Trials 1, 2, 3, and 4. In total, 2077 subjects were

evaluated (691 to COSENTYX 300 mg group, 692 to COSENTYX 150 mg group, and 694 to placebo group) *[see Clinical Studies (14)]*.

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the COSENTYX groups than the placebo group during the 12-week placebo-controlled period of the placebo-controlled trials.

Table 1: Adverse Reactions Reported by Greater Than 1% of Subjects with Plaque Psoriasis Through Week 12 in Trials 1, 2, 3, and 4

Adverse Reactions	COSENTYX		Placebo (N = 694) n (%)
	300 mg (N = 691) n (%)	150 mg (N = 692) n (%)	
Nasopharyngitis	79 (11.4)	85 (12.3)	60 (8.6)
Diarrhea	28 (4.1)	18 (2.6)	10 (1.4)
Upper respiratory tract infection	17 (2.5)	22 (3.2)	5 (0.7)
Rhinitis	10 (1.4)	10 (1.4)	5 (0.7)
Oral herpes	9 (1.3)	1 (0.1)	2 (0.3)
Pharyngitis	8 (1.2)	7 (1.0)	0 (0)
Urticaria	4 (0.6)	8 (1.2)	1 (0.1)
Rhinorrhea	8 (1.2)	2 (0.3)	1 (0.1)

Adverse reactions that occurred at rates less than 1% in the placebo-controlled period of Trials 1, 2, 3, and 4 through Week 12 included: sinusitis, tinea pedis, conjunctivitis, tonsillitis, oral candidiasis, impetigo, otitis media, otitis externa, inflammatory bowel disease, increased liver transaminases, and neutropenia.

Infections

In the placebo-controlled period of the clinical trials in plaque psoriasis (a total of 1382 subjects treated with COSENTYX and 694 subjects treated with placebo up to 12 weeks), infections were reported in 28.7% of subjects treated with COSENTYX compared with 18.9% of subjects treated with placebo. Serious infections occurred in 0.14% of patients treated with COSENTYX and in 0.3% of patients treated with placebo *[see Warnings and Precautions (5.1)]*.

Over the entire treatment period (a total of 3430 plaque psoriasis subjects treated with COSENTYX for up to 52 weeks for the majority of subjects), infections were reported in 47.5% of subjects treated with COSENTYX (0.9 per patient-year of follow-up). Serious infections were reported in 1.2% of subjects treated with COSENTYX (0.015 per patient-year of follow-up).

Phase 3 data showed an increasing trend for some types of infection with increasing serum concentration of secukinumab. Candida infections, herpes viral infections, staphylococcal skin infections, and infections requiring treatment increased as serum concentration of secukinumab increased.

Neutropenia was observed in clinical trials. Most cases of secukinumab-associated neutropenia were transient and reversible. No serious infections were associated with cases of neutropenia.

Inflammatory Bowel Disease

Cases of inflammatory bowel disease, in some cases serious, were observed in clinical trials with COSENTYX. In the plaque psoriasis program, with 3430 patients exposed to COSENTYX over the entire treatment period for up to 52 weeks (2725 patient-years), there were 3 cases (0.11 per 100 patient-years) of exacerbation of Crohn’s disease, 2 cases (0.08 per 100 patient-years) of exacerbation of ulcerative colitis, and 2 cases (0.08 per 100 patient-years) of new onset ulcerative colitis. There were no cases in placebo patients (N = 793; 176 patient-years) during the 12 week placebo-controlled period.

One case of exacerbation of Crohn's disease was reported from long-term non-controlled portions of ongoing clinical trials in plaque psoriasis *[see Warnings and Precautions (5.3)]*.

Hypersensitivity Reactions

Anaphylaxis and cases of urticaria occurred in COSENTYX treated patients in clinical trials *[see Warnings and Precautions (5.4)]*.

Psoriatic Arthritis

COSENTYX was studied in two placebo-controlled psoriatic arthritis trials with 1003 patients (703 patients on COSENTYX and 300 patients on placebo). Of the 703 patients who received COSENTYX, 299 patients received a subcutaneous loading dose of COSENTYX (PsA1) and 404 patients received an intravenous loading dose of secukinumab (PsA2) followed by COSENTYX administered by subcutaneous injection every four weeks. During the 16-week placebo-controlled period of the trials in patients with psoriatic arthritis, the overall proportion of patients with adverse events was similar in the secukinumab and placebo-treatment groups (59% and 58%, respectively). The adverse events that occurred at a proportion of at least 2% and at a higher proportion in the COSENTYX groups than the placebo groups during the 16-week placebo-controlled period were nasopharyngitis, upper respiratory tract infection, headache, nausea, and hypercholesterolemia. The safety profile observed in patients with psoriatic arthritis treated with COSENTYX is consistent with the safety profile in psoriasis.

Similar to the clinical trials in patients with psoriasis, there was an increased proportion of patients with infections in the COSENTYX groups (29%) compared to placebo group (26%) *[see Warnings and Precautions (5.1)]*.

There were cases of Crohn's disease and ulcerative colitis that include patients who experienced either exacerbations or the development of new disease. There were three cases of inflammatory bowel disease, of which two patients received secukinumab and one received placebo *[see Warnings and Precautions (5.3)]*.

Ankylosing Spondylitis

COSENTYX was studied in two placebo controlled ankylosing spondylitis trials with 590 patients (394 patients on COSENTYX and 196 patients on placebo). Of the 394 patients who received COSENTYX, 145 patients received a subcutaneous load of COSENTYX (study AS1) and 249 received an intravenous loading dose of secukinumab (study AS2) followed by COSENTYX administered by subcutaneous injection every four weeks. During the 16-week placebo-controlled period of the trials in patients with ankylosing spondylitis, the overall proportion of patients with adverse events was higher in the secukinumab groups than the placebo-treatment groups (66% and 59%, respectively). The adverse events that occurred at a proportion of at least 2% and at a higher proportion in the COSENTYX groups than the placebo groups during the 16-week placebo-controlled period were nasopharyngitis, nausea, and upper respiratory tract infection. The safety profile observed in patients with ankylosing spondylitis treated with COSENTYX is consistent with the safety profile in psoriasis.

Similar to clinical trials in patients with psoriasis, there was an increased proportion of patients with infections in the COSENTYX groups (31%) compared to the placebo group (18%) *[see Warnings and Precautions (5.1)]*.

In the ankylosing spondylitis program, with 571 patients exposed to COSENTYX there were 8 cases of inflammatory bowel disease during the entire treatment period [5 Crohn's (0.7 per 100 patient-years) and 3 ulcerative colitis (0.4 per 100 patient-years)]. During the placebo-controlled 16-week period, there were 2 Crohn's disease exacerbations and 1 new onset ulcerative colitis case that was a serious adverse event in patients treated with COSENTYX compared to none of the patients treated with placebo. During the remainder of the study when all patients received COSENTYX, 1 patient developed Crohn's disease, 2 patients had Crohn's exacerbations, 1 patient developed ulcerative colitis, and 1 patient had an ulcerative colitis exacerbation *[see Warnings and Precautions (5.3)]*.

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The immunogenicity of COSENTYX was evaluated using an electrochemiluminescence-based bridging immunoassay. Less than 1% of subjects treated with COSENTYX developed antibodies to secukinumab in up to 52 weeks of treatment. However, this assay has limitations in detecting anti-secukinumab antibodies in the presence of secukinumab; therefore the incidence of antibody development might not have been reliably determined. Of the subjects who developed antidrug antibodies, approximately one-half had antibodies that were classified as neutralizing. Neutralizing antibodies were not associated with loss of efficacy.

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 incidence of antibodies to COSENTYX with the incidences of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

7.1 Live Vaccines

Patients treated with COSENTYX may not receive live vaccinations *[see Warnings and Precautions (5.6)]*.

7.2 Non-Live Vaccines

Patients treated with COSENTYX may receive non-live vaccinations. Healthy individuals who received a single 150 mg dose of COSENTYX 2 weeks prior to vaccination with a non-U.S. approved group C meningococcal polysaccharide conjugate vaccine and a non-U.S. approved inactivated seasonal influenza vaccine had similar antibody responses compared to individuals who did not receive COSENTYX prior to vaccination. The clinical effectiveness of meningococcal and influenza vaccines has not been assessed in patients undergoing treatment with COSENTYX *[see Warnings and Precautions (5.6)]*.

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.

Results from a drug-drug interaction study in subjects with moderate to severe psoriasis showed no clinically relevant interaction for drugs metabolized by CYP3A4.

Upon initiation or discontinuation of COSENTYX in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for therapeutic effect or drug concentration and consider dosage adjustment as needed *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available human data with COSENTYX use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. In an embryo-fetal development study, no adverse developmental effects were observed in infants born to pregnant monkeys after subcutaneous administration of secukinumab during organogenesis at doses up to 30 times the maximum recommended human dose (MRHD) *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the background risk in the U.S. general population of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data

Animal Data

An embryo-fetal development study was performed in cynomolgus monkeys with secukinumab. No malformations or embryo-fetal toxicity were observed in fetuses from pregnant monkeys that were administered secukinumab weekly by the subcutaneous route during the period of organogenesis at doses up to 30 times the MRHD (on a mg/kg basis at a maternal dose of 150 mg/kg).

A pre- and post-natal development toxicity study was performed in mice with a murine analog of secukinumab. No treatment related effects on functional, morphological or immunological development were observed in fetuses from pregnant mice that were administered the murine analog of secukinumab on gestation days 6, 11, and 17 and on postpartum days 4, 10, and 16 at doses up to 150 mg/kg/dose.

8.2 Lactation

Risk Summary

It is not known whether secukinumab is excreted in human milk or absorbed systemically after ingestion. There are no data on the effects of COSENTYX on the breastfed child or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for COSENTYX and any potential adverse effects on the breastfed child from COSENTYX or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of COSENTYX in pediatric patients have not been evaluated.

8.5 Geriatric Use

Of the 3430 plaque psoriasis subjects exposed to COSENTYX in clinical trials, a total of 230 were 65 years or older, and 32 subjects were 75 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 years and older was not sufficient to determine whether they responded differently from younger subjects.

10 OVERDOSAGE

Doses up to 30 mg/kg intravenously have been administered in clinical trials without dose-limiting toxicity. In the event of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

11 DESCRIPTION

Secukinumab is a recombinant human monoclonal IgG1/κ antibody that binds specifically to IL-17A. It is expressed in a recombinant Chinese Hamster Ovary (CHO) cell line. Secukinumab has a molecular mass of approximately 151 kDa; both heavy chains of secukinumab contain oligosaccharide chains.

COSENTYX Injection

COSENTYX injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution. COSENTYX is supplied in a single-use Sensoready pen with a 27-gauge fixed ½-inch needle, or a single-use prefilled syringe with a 27-gauge fixed ½-inch needle. The removable cap of the COSENTYX Sensoready pen or prefilled syringe contains natural rubber latex.

Each COSENTYX Sensoready pen or prefilled syringe contains 150 mg of secukinumab formulated in: L-histidine/histidine hydrochloride monohydrate (3.103 mg), L-methionine (0.746 mg), polysorbate 80 (0.2 mg), trehalose dihydrate (75.67 mg), and Sterile Water for Injection, USP, at pH of 5.8.

COSENTYX for Injection

COSENTYX for injection is supplied as a sterile, preservative free, white to slightly yellow, lyophilized powder in single-use vials. Each COSENTYX vial contains 150 mg of secukinumab formulated in L-histidine/histidine hydrochloride monohydrate (4.656 mg), polysorbate 80 (0.6 mg), and sucrose (92.43 mg). Following reconstitution with 1 mL Sterile Water for Injection, USP, the resulting pH is approximately 5.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Secukinumab is a human IgG1 monoclonal antibody that selectively binds to the interleukin-17A (IL-17A) cytokine and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Secukinumab inhibits the release of proinflammatory cytokines and chemokines.

12.2 Pharmacodynamics

Elevated levels of IL-17A are found in psoriatic plaques. Treatment with COSENTYX may reduce epidermal neutrophils and IL-17A levels in psoriatic plaques. Serum levels of total IL-17A (free and secukinumab-bound IL-17A) measured at Week 4 and Week 12 were increased following secukinumab treatment. These pharmacodynamic activities are based on small exploratory studies. The relationship between these pharmacodynamic activities and the mechanism(s) by which secukinumab exerts its clinical effects is unknown.

Increased numbers of IL-17A producing lymphocytes and innate immune cells and increased levels of IL-17A have been found in the blood of patients with psoriatic arthritis and ankylosing spondylitis.

12.3 Pharmacokinetics

The PK properties of secukinumab observed in psoriatic arthritis and ankylosing spondylitis patients were similar to the PK properties displayed in plaque psoriasis patients.

Absorption

Following a single subcutaneous dose of either 150 mg (one-half the recommended dose) or 300 mg in plaque psoriasis patients, secukinumab reached peak mean (± SD) serum concentrations (C_{max}) of 13.7 ± 4.8 mcg/mL and 27.3 ± 9.5 mcg/mL, respectively, by approximately 6 days post dose.

Following multiple subcutaneous doses of secukinumab, the mean (± SD) serum trough concentrations of secukinumab ranged from 22.8 ± 10.2 mcg/mL (150 mg) to 45.4 ± 21.2 mcg/mL (300 mg) at Week 12. At the 300 mg dose at Week 4 and Week 12, the mean trough concentrations resulted from the Sensoready pen were 23% to 30% higher than those from the lyophilized powder and 23% to 26% higher than those from the prefilled syringe based on cross-study comparisons.

Steady-state concentrations of secukinumab were achieved by Week 24 following the every 4 week dosing regimens. The mean (± SD) steady-state trough concentrations ranged from 16.7 ± 8.2 mcg/mL (150 mg) to 34.4 ± 16.6 mcg/mL (300 mg).

In healthy subjects and subjects with plaque psoriasis, secukinumab bioavailability ranged from 55% to 77% following subcutaneous dose of 150 mg (one-half the recommended dose) or 300 mg.

Distribution

The mean volume of distribution during the terminal phase (Vz) following a single intravenous administration ranged from 7.10 to 8.60 L in plaque psoriasis patients. Intravenous use is not recommended *[see Dosage and Administration (2)]*.

Secukinumab concentrations in interstitial fluid in lesional and non-lesional skin of plaque psoriasis patients ranged from 27% to 40% of those in serum at 1 and 2 weeks after a single subcutaneous dose of secukinumab 300 mg.

Elimination

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

The mean systemic clearance (CL) ranged from 0.14 L/day to 0.22 L/day and the mean half-life ranged from 22 to 31 days in plaque psoriasis subjects following intravenous and subcutaneous administration across all psoriasis trials. Intravenous use is not recommended *[see Dosage and Administration (2)]*.

Dose Linearity

Secukinumab exhibited dose-proportional pharmacokinetics in subjects with psoriasis over a dose range from 25 mg (approximately 0.083 times the recommended dose) to 300 mg following subcutaneous administrations.

Weight

Secukinumab clearance and volume of distribution increase as body weight increases.

Specific Populations

Hepatic or Renal Impairment:

No formal trial of the effect of hepatic or renal impairment on the pharmacokinetics of secukinumab was conducted.

Age: Geriatric Population:

Population pharmacokinetic analysis indicated that the clearance of secukinumab was not significantly influenced by age in adult subjects with plaque psoriasis, psoriatic arthritis and ankylosing spondylitis. Subjects who are 65 years or older had apparent clearance of secukinumab similar to subjects less than 65 years old.

Drug Interactions

Cytochrome P450 Substrates

In subjects with plaque psoriasis, midazolam (CYP3A4 substrate) pharmacokinetics was similar when administered alone, or when administered following either a single or five weekly subcutaneous administrations of 300 mg secukinumab *[see Drug interactions (7.3)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of COSENTYX. Some published literature suggests that IL-17A directly promotes cancer cell invasion in vitro, whereas other reports indicate IL-17A promotes T-cell mediated tumor rejection. Depletion of IL-17A with a neutralizing antibody inhibited tumor development in mice. The relevance of experimental findings in mouse models for malignancy risk in humans is unknown.

No effects on fertility were observed in male and female mice that were administered a murine analog of secukinumab at subcutaneous doses up to 150 mg/kg once weekly prior to and during the mating period.

14 CLINICAL STUDIES

14.1 Plaque Psoriasis

Four multicenter, randomized, double-blind, placebo-controlled trials (Trials 1, 2, 3, and 4) enrolled 2403 subjects (691 randomized to COSENTYX 300 mg, 692 to COSENTYX 150 mg, 694 to placebo, and 323 to a biologic active control) 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 greater than or equal to 12, and who were candidates for phototherapy or systemic therapy.

- Trial 1 enrolled 738 subjects (245 randomized to COSENTYX 300 mg, 245 to COSENTYX 150 mg, and 248 to placebo). Subjects received subcutaneous treatment at Weeks 0, 1, 2, 3, and 4 followed by dosing every 4 weeks. Subjects randomized to COSENTYX received 300 mg or 150 mg doses at Weeks 0, 1, 2, 3, and 4 followed by the same dose every 4 weeks. Subjects randomized to receive placebo that were non-responders at Week 12 were then crossed over to receive COSENTYX (either 300 mg or 150 mg) at Weeks 12, 13, 14, 15, and 16 followed by the same dose every 4 weeks. All subjects were followed for up to 52 weeks following first administration of study treatment.
- Trial 2 enrolled 1306 subjects (327 randomized to COSENTYX 300 mg, 327 to COSENTYX 150 mg, 326 to placebo, and 323 to a biologic active control). COSENTYX and placebo data are described. Subjects received subcutaneous treatment at Weeks 0, 1, 2, 3, and 4 followed by dosing every 4 weeks. Subjects randomized to COSENTYX received 300 mg or 150 mg doses at Weeks 0, 1, 2, 3, and 4 followed by the same dose every 4 weeks. Subjects randomized to receive placebo that were non-responders at Week 12 then crossed over to receive COSENTYX (either 300 mg or 150 mg) at Weeks 12, 13, 14, 15, and 16 followed by the same dose every 4 weeks. All subjects were followed for up to 52 weeks following first administration of study treatment.
- Trial 3 enrolled 177 subjects (59 randomized to COSENTYX 300 mg, 59 to COSENTYX 150 mg, and 59 to placebo) and assessed safety, tolerability, and usability of COSENTYX self-administration via prefilled syringe for 12 weeks. Subjects received subcutaneous treatment at Weeks 0, 1, 2, 3, and 4, followed by the same dose every 4 weeks for up to 12 weeks total.
- Trial 4 enrolled 182 subjects (60 randomized to COSENTYX 300 mg, 61 to COSENTYX 150 mg, and 61 to placebo) and assessed safety, tolerability, and usability of COSENTYX self-administration via Sensoready pen for 12 weeks. Subjects received subcutaneous treatment at Weeks 0, 1, 2, 3, and 4, followed by the same dose every 4 weeks for up to 12 weeks total.

Endpoints

In all trials, the endpoints were the proportion of subjects who achieved a reduction in PASI score of at least 75% (PASI 75) from baseline to Week 12 and treatment success (clear or almost clear) on the Investigator's Global Assessment modified 2011 (IGA). Other evaluated outcomes included the proportion of subjects who achieved a reduction in PASI score of at least 90% (PASI 90) from baseline at Week 12, maintenance of efficacy to Week 52, and improvements in itching, pain, and scaling at Week 12 based on the Psoriasis Symptom Diary©.

The PASI is a composite score that takes into consideration both the percentage of body surface area affected and the nature and severity of psoriatic changes within the affected regions (induration, erythema and scaling). The IGA is a 5-category scale including "0 = clear", "1 = almost clear", "2 = mild", "3 = moderate" or "4 = severe" indicating the physician's overall assessment of the psoriasis severity focusing on induration, erythema and scaling. Treatment success of "clear" or "almost clear" consisted of no signs of psoriasis or normal to pink coloration of lesions, no thickening of the plaque, and none to minimal focal scaling.

Baseline Characteristics

Across all treatment groups the baseline PASI score ranged from 11 to 72 with a median of 20 and the baseline IGA score ranged from “moderate” (62%) to “severe” (38%). Of the 2077 plaque psoriasis subjects who were included in the placebo-controlled trials, 79% were biologic-naïve (have never received a prior treatment with biologics) and 45% were non-biologic failures (failed to respond to a prior treatment with non-biologics therapies). Of the patients who received a prior treatment with biologics, over one-third were biologic failures. Approximately 15% to 25% of trial subjects had a history of psoriatic arthritis.

Clinical Response

The results of Trials 1 and 2 are presented in Table 2.

Table 2: Clinical Outcomes at Week 12 in Adults with Plaque Psoriasis in Trials 1 and 2

	Trial 1			**Trial 2**		
	COSENTYX 300 mg (N = 245) n (%)	**COSENTYX 150 mg (N = 245) n (%)**	**Placebo (N = 248) n (%)**	**COSENTYX 300 mg (N = 327) n (%)**	**COSENTYX 150 mg (N = 327) n (%)**	**Placebo (N = 326) n (%)**
PASI 75 response	200 (82)	174 (71)	11 (4)	249 (76)	219 (67)	16 (5)
IGA of clear or almost clear	160 (65)	125 (51)	6 (2)	202 (62)	167 (51)	9 (3)

The results of Trials 3 and 4 are presented in Table 3.

Table 3: Clinical Outcomes at Week 12 in Adults with Plaque Psoriasis in Trials 3 and 4

	Trial 3			**Trial 4**		
	COSENTYX 300 mg (N = 59) n (%)	**COSENTYX 150 mg (N = 59) n (%)**	**Placebo (N = 59) n (%)**	**COSENTYX 300 mg (N = 60) n (%)**	**COSENTYX 150 mg (N = 61) n (%)**	**Placebo (N = 61) n (%)**
PASI 75 response	44 (75)	41 (69)	0 (0)	52 (87)	43 (70)	2 (3)
IGA of clear or almost clear	40 (68)	31 (53)	0 (0)	44 (73)	32 (52)	0 (0)

Examination of age, gender, and race subgroups did not identify differences in response to COSENTYX among these subgroups. Based on post-hoc sub-group analyses in patients with moderate to severe psoriasis, patients with lower body weight and lower disease severity may achieve an acceptable response with COSENTYX 150 mg.

PASI 90 response at Week 12 was achieved with COSENTYX 300 mg and 150 mg compared to placebo in 59% (145/245) and 39% (95/245) versus 1% (3/248) of subjects, respectively (Trial 1) and 54% (175/327) and 42% (137/327) versus 2% (5/326) of subjects, respectively (Trial 2). Similar results were seen in Trials 3 and 4.

With continued treatment over 52 weeks, subjects in Trial 1 who were PASI 75 responders at Week 12 maintained their responses in 81% (161/200) of the subjects treated with COSENTYX 300 mg and in 72% (126/174) of subjects treated with COSENTYX 150 mg. Trial 1 subjects who were clear or almost clear on the IGA at Week 12 also maintained their responses in 74% (119/160) of subjects treated with COSENTYX 300 mg and in 59% (74/125) of subjects treated with COSENTYX 150 mg. Similarly in Trial 2, PASI 75 responders maintained their responses in 84% (210/249) of subjects treated with COSENTYX 300 mg and in 82% (180/219) of subjects treated with COSENTYX 150 mg. Trial 2 subjects who were clear or almost clear on the IGA also maintained their responses in 80% (161/202) of subjects treated with COSENTYX 300 mg and in 68% (113/167) of subjects treated with COSENTYX 150 mg.

Among the subjects who chose to participate (39%) in assessments of patient reported outcomes, improvements in signs and symptoms related to itching, pain, and scaling, at Week 12 compared to placebo (Trials 1 and 2) were observed using the Psoriasis Symptom Diary©.

Psoriasis Lesions of Scalp

A randomized, placebo-controlled study enrolled 102 subjects with moderate to severe psoriasis lesions of scalp, defined as having a Psoriasis Scalp Severity Index (PSSI) score of greater than or equal to 12, an IGA scalp only score of 3 or greater, and at least 30% of the scalp affected. In this study, 62% of subjects had at least 50% of scalp surface area affected. The proportions of subjects achieving an IGA scalp only score of *0* or *1* (clear or almost clear) were 56.9% and 5.9% for the COSENTYX 300 mg and the placebo groups, respectively.

14.2 Psoriatic Arthritis

The safety and efficacy of COSENTYX were assessed in 1999 patients, in 3 randomized, double-blind, placebo-controlled studies (PsA1, PsA2 and PsA3) in adult patients, age 18 years and older with active psoriatic arthritis (greater than or equal to 3 swollen and greater than or equal to 3 tender joints) despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or disease modifying anti-rheumatic drug (DMARD) therapy. Patients in these studies had a diagnosis of PsA of at least 5 years across all studies. At baseline, over 61% and 42% of the patients had enthesitis and dactylitis, respectively. Overall, 31% of patients discontinued previous treatment with anti-TNFα agents due to either lack of efficacy or intolerance. In addition, approximately 53% of patients from both studies had concomitant methotrexate (MTX) use. Patients with different subtypes of PsA were enrolled including polyarticular arthritis with no evidence of rheumatoid nodules (80%), asymmetric peripheral arthritis (63%), distal interphalangeal involvement (58%), spondylitis with peripheral arthritis (20%) and arthritis mutilans (7%).

PsA1 Study (NCT 01752634) evaluated 397 patients, who were treated with COSENTYX 75 mg, 150 mg or 300 mg subcutaneous treatment at Weeks 0, 1, 2, 3 and 4, followed by the same dose every 4 weeks. Patients receiving placebo were re-randomized to receive COSENTYX (either 150 mg or 300 mg every 4 weeks) at Week 16 or Week 24 based on responder status. The primary endpoint was the percentage of patients achieving an ACR20 response at Week 24.

PsA2 Study (NCT 01392326) evaluated 606 patients, who were treated with secukinumab 10 mg/kg, intravenous treatment (or placebo) at Weeks 0, 2, and 4, followed by either 75 mg or 150 mg subcutaneous COSENTYX treatment (or placebo) every 4 weeks. Patients receiving placebo were re-randomized to receive COSENTYX (either 75 mg or 150 mg every 4 weeks) at Week 16 or Week 24 based on responder status.

PsA3 Study (NCT 02404350) evaluated 996 patients, who were treated with COSENTYX 150 mg or 300 mg subcutaneous treatment at Weeks 0, 1, 2, 3 and 4 followed by the same dose every 4 weeks, or once every 4 weeks of COSENTYX 150 mg. Patients treated with placebo received COSENTYX, either 150 mg or 300 mg, s.c., per baseline randomization, at Week 16 or Week 24 based upon responder status. The primary endpoint was ACR20 response at Week 16 with the key secondary endpoint the change from baseline in modified Total Sharp Score (mTSS) at Week 24.

Clinical Response

In PsA1, patients treated with 150 mg or 300 mg COSENTYX demonstrated a greater clinical response including ACR20, ACR50, and ACR70 compared to placebo at Week 24 (Table 4). Responses were similar in patients regardless of concomitant methotrexate treatment. Responses were seen regardless of prior anti-TNFα exposure.

In patients with coexistent plaque psoriasis receiving COSENTYX (n = 99), the skin lesions of psoriasis improved with treatment, relative to placebo, as measured by the Psoriasis Area Severity Index (PASI).

Table 4: Responses[a] in PsA1 Study at Week 16 and Week 24

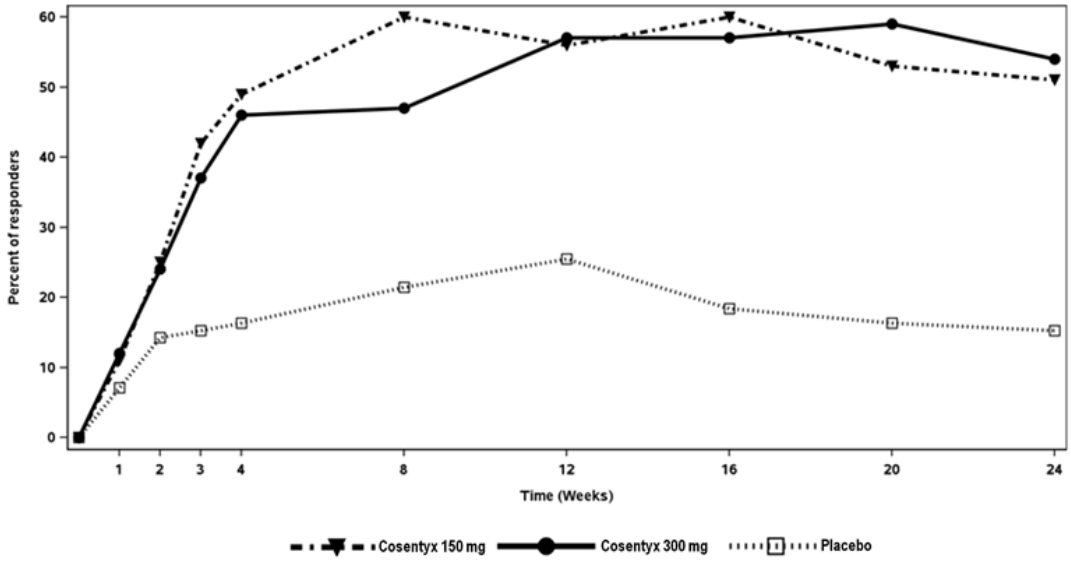
	COSENTYX 150 mg (N = 100)	**COSENTYX 300 mg (N = 100)**	**Placebo (N = 98)**	**Difference from placebo (95% CI)**	
				COSENTYX 150 mg	**COSENTYX 300 mg**
ACR20 response					
Week 16 (%)	60	57	18	42 (30, 54)	38 (26, 51)
Week 24 (%)	51	54	15	36 (24, 48)	39 (27, 51)
ACR50 response					
Week 16 (%)	37	35	6	31 (21, 42)	28 (18, 39)
Week 24 (%)	35	35	7	28	28

				(18, 38)	(17, 38)
ACR70 response					
Week 16 (%)	17	15	2	15 (7, 23)	13 (5, 20)
Week 24 (%)	21	20	1	20 (12, 28)	19 (11, 27)

[a]Patients who met escape criteria (less than 20% improvement in tender or swollen joint counts) at Week 16 were considered non-responders

The percentage of patients achieving ACR20 response by visit is shown in Figure 1. Patients on placebo who received COSENTYX without a loading regimen achieved similar ACR20 responses over time (data not shown).

Figure 1: Percent of Patients Achieving ACR 20 Response[a] in PsA1 Study Through Week 24



[a]Patients who met escape criteria (less than 20% improvement in tender or swollen joint counts) at Week 16 were considered non-responders

The improvements in the components of the ACR response criteria are shown in Table 5.

Table 5: Mean Change from Baseline in ACR Components at Week 16[a] (PsA1 Study)

	COSENTYX 150 mg (N = 100)	**COSENTYX 300 mg** (N = 100)	**Placebo** (N = 98)
No. of Swollen Joints			
Baseline	12.0	11.2	12.1
Mean change at Week 16	-4.86	-5.83	-3.22
Number of Tender Joints			
Baseline	24.1	20.2	23.5
Mean change at Week 16	-10.70	-10.01	-1.77
Patient's assessment of Pain			
Baseline	58.9	57.7	55.4
Mean change at Week 16	-22.91	-23.97	-7.98
Patient Global Assessment			
Baseline	62.0	60.7	57.6
Mean change at Week 16	-25.47	-25.40	-8.25
Physician Global Assessment			
Baseline	56.7	55.0	55.0
Mean change at Week 16	-29.24	-34.71	-14.95
Disability Index (HAQ)			
Baseline	1.2200	1.2828	1.1684

Mean change at Week 16	-0.45	-0.55	-0.23
CRP (mg/L)			
Baseline	14.15	10.88	7.87
Mean Change at Week 16[b]	-8.41	-7.21	0.79

[a]Week 16 rather than Week 24 data are displayed to provide comparison between arms prior to placebo escape to COSENTYX.
[b]Mean Change based upon observed data

Improvements in enthesitis and dactylitis scores were observed in each COSENTYX group compared to placebo at Week 24.

Radiographic Response

In PsA3 Study, inhibition of progression of structural damage was assessed radiographically and expressed by the modified mTSS and its components, the Erosion Score (ES) and Joint Space Narrowing Score (JSN), at Week 24 compared to baseline. Radiographs of hands, wrists, and feet were obtained at baseline, Week 16 and/or Week 24 and scored independently by at least two readers who were blinded to treatment group and visit number. COSENTYX 150 mg without load, 150 mg with load and 300 mg with load treatment significantly inhibited progression of peripheral joint damage compared with placebo treatment as measured by change from baseline in mTSS at Week 24. The percentage of patients with no disease progression (defined as a change from baseline in mTSS of less than or equal to 0.0) from randomization to Week 24 was 75.7%, 70.9%, and 76.5% for COSENTYX 150 mg without load, 150 mg, 300 mg, respectively versus 68.2% for placebo.

Table 6: Rate of Change per 24 Weeks in Modified Total Sharp Score

Treatment	N	Rate of Change per 24 weeks	Difference from Placebo (95% CI)
COSENTYX 150 mg without load	210	-0.10	-0.61 (-0.95, -0.26)
COSENTYX 150 mg with load	213	0.14	-0.37 (-0.71, -0.03)
COSENTYX 300 mg with load	217	0.03	-0.48 (-0.82, -0.14)
Placebo	296	0.51	--

Results from a linear mixed effects model that excluded data after escape for placebo subjects who received escape therapy at week 16. The model assumes approximately linear progression over time and estimates a difference in rates (slopes) of progression over 24 weeks to compare treatment arms.

Physical Function

Improvement in physical function as assessed by Health Assessment Questionnaire-Disability Index (HAQ-DI) demonstrated that the proportion of patients who achieved at least -0.3 improvement in HAQ-DI score from baseline was greater in the COSENTYX 150 mg and 300 mg groups compared to placebo at Week 16 and 24. At Week 16 in PsA1 study, estimated mean change from baseline was -0.23 in the placebo group compared with -0.45 in the COSENTYX 150 mg group and -0.55 in the COSENTYX 300 mg group.

14.3 Ankylosing Spondylitis

The safety and efficacy of COSENTYX were assessed in 590 patients in two randomized, double-blind, placebo-controlled studies (AS1 and AS2) in adult patients 18 years of age and older with active ankylosing spondylitis. Patients had active disease as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) greater or equal to 4 despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or disease modifying anti-rheumatic drug (DMARD) therapy. At baseline, approximately 14% and 26% used concomitant methotrexate or sulfasalazine, respectively. Overall, 33% of patients discontinued previous treatment with anti-TNFα agents due to either lack of efficacy or intolerance.

AS1 Study evaluated 219 patients, who were treated with COSENTYX 75 mg or 150 mg subcutaneous treatment at Weeks 0, 1, 2, 3 and 4, followed by the same dose every 4 weeks. At Week 16, patients receiving placebo were re-randomized to either COSENTYX 75 mg or 150 mg every 4 weeks. The primary endpoint was the percentage of patients achieving an ASAS20 response at Week 16.

AS2 Study evaluated 371 patients, who were treated with secukinumab 10 mg/kg intravenous treatment at Weeks 0, 2, and 4 (for both treatment arms) or placebo, followed by either 75 mg or 150 mg subcutaneous COSENTYX treatment every 4 weeks or placebo. Patients receiving placebo were re-randomized to receive COSENTYX (either 75 mg or 150 mg every 4 weeks) at Week 16 or Week 24 based on responder status.

Clinical Response

In AS1, patients treated with 150 mg COSENTYX demonstrated greater improvements in ASAS20 and ASAS40 responses compared to placebo at Week 16 (Table 7). Responses were similar in patients regardless of concomitant therapies.

Table 7: ASAS20 and ASAS40 Responses in All AS Patients at Week 16 in Study AS1

	COSENTYX 150 mg (n = 72)	**Placebo (n = 74)**	**Difference from placebo (95% CI)**
ASAS20 response, %	61	28	33 (18, 48)
ASAS40 response, %	36	11	25 (12, 38)

The improvements in the main components of the ASAS20 response criteria and other measures of disease activity are shown in Table 8.

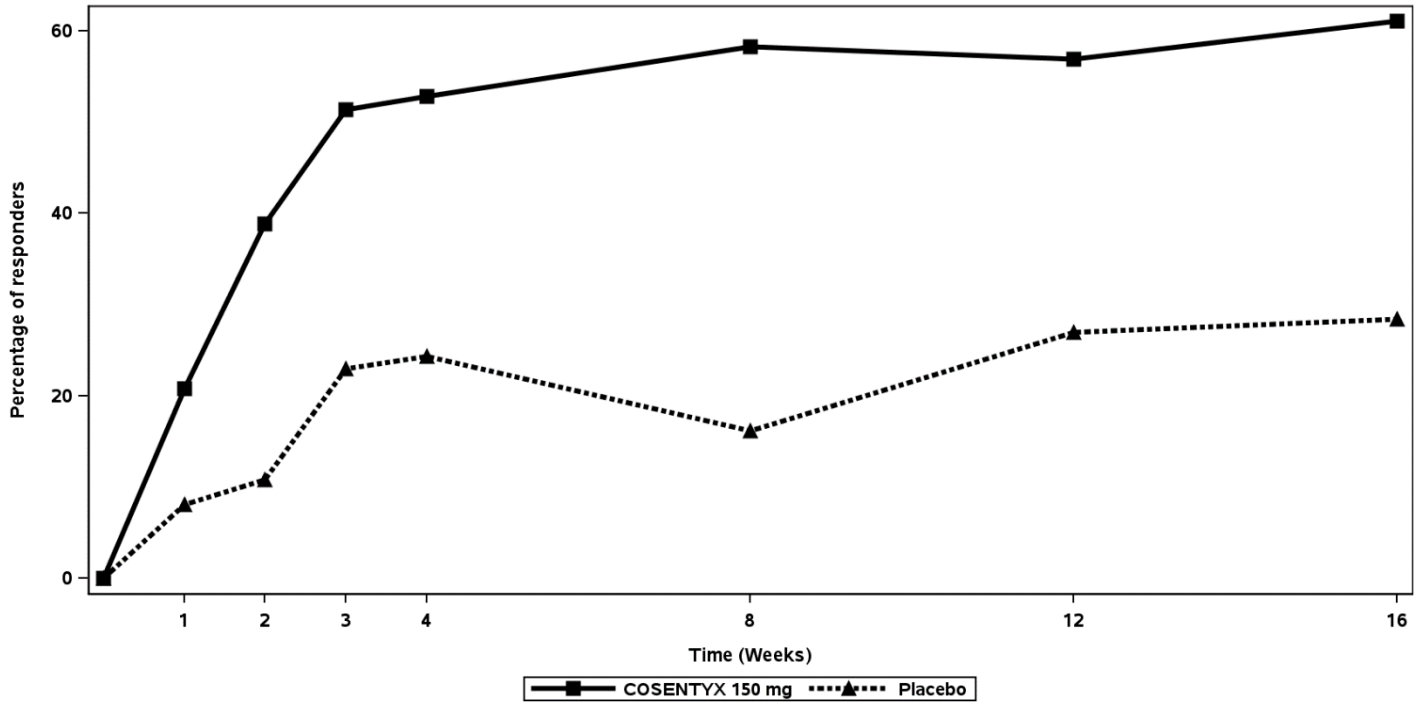
Table 8: ASAS20 Components and Other Measures of Disease Activity at Week 16 (AS1 Study)

	COSENTYX 150 mg (N = 72)		**Placebo (N = 74)**	
	Baseline	Week 16 change from baseline	Baseline	Week 16 change from baseline
ASAS20 Response criteria				
-Patient Global Assessment of Disease Activity (0-100 mm)[1]	67.5	-27.7	70.5	-12.9
-Total spinal pain (0-100 mm)	66.2	-28.5	69.2	-10.9
-BASFI (0-10)[2]	6.2	-2.2	6.1	-0.7
-Inflammation (0-10)[3]	6.5	-2.5	6.5	-0.8
BASDAI Score[4]	6.6	-2.2	6.8	-0.9
BASMI[5]	3.6	-0.51	3.9	-0.22
hsCRP[6] (mg/L) Mean Change at Week 16	27.0	-17.2	15.9	0.8

1. Percent of subjects with at least a 20% and 10 unit improvement measured on a Visual Analog Scale (VAS) with 0= none, 100= severe
2. Bath Ankylosing Spondylitis Functional Index
3. Inflammation is the mean of two patient-reported stiffness self-assessment in BASDAI
4. Bath Ankylosing Spondylitis Disease Activity Index
5. Bath Ankylosing Spondylitis Metrology Index
6. High sensitivity C-reactive protein / mean change based upon observed data

The percent of patients achieving ASAS20 responses by visit is shown in Figure 2. Patients on placebo who received COSENTYX without a loading regimen achieved similar ASAS20 responses over time (data not shown).

Figure 2: ASAS20 Responses in all AS1 Study Patients Over Time Up to Week 16



COSENTYX treated patients showed improvement compared to placebo-treated patients in health-related quality of life as assessed by ASQoL at Week 16.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

COSENTYX Sensoready pen:

• NDC 0078-0639-41: Carton of two 150 mg/mL (300 mg dose) Sensoready pens (injection)

• NDC 0078-0639-68: Carton of one 150 mg/mL single-use Sensoready pen (injection)

COSENTYX prefilled syringe:

• NDC 0078-0639-98: Carton of two 150 mg/mL (300 mg dose) single-use prefilled syringes (injection)

• NDC 0078-0639-97: Carton of one 150 mg/mL single-use prefilled syringe (injection)

The removable cap of the COSENTYX Sensoready pen and prefilled syringe contains natural rubber latex. Each Sensoready pen and prefilled syringe is equipped with a needle safety guard.

COSENTYX vial (for healthcare professional use only):

• NDC 0078-0657-61: Carton of one 150 mg lyophilized powder in a single-use vial (for injection)

16.2 Storage and Handling

COSENTYX Sensoready pens, prefilled syringes and vials must be refrigerated at 2ºC to 8ºC (36ºF to 46ºF). Keep the product in the original carton to protect from light until the time of use. Do not freeze. To avoid foaming do not shake. COSENTYX does not contain a preservative; discard any unused portion.

17 PATIENT COUNSELING INFORMATION

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

Patient Counseling

Instruct patients to read the Medication Guide before starting COSENTYX therapy and to re-read the Medication Guide each time the prescription is renewed.

Advise patients of the potential benefits and risks of COSENTYX.

Infections

Inform patients that COSENTYX may lower the ability of their immune system to fight infections. Instruct patients of the importance of communicating any history of infections to the doctor and contacting their doctor if they develop any symptoms of infection *[see Warnings and Precautions (5.1)]*.

Hypersensitivity

Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions *[see Warnings and Precautions (5.4)]*.

Instruction on Injection Technique

Perform the first self-injection under the supervision of a qualified healthcare professional. If a patient or caregiver is to administer COSENTYX, instruct him/her in injection techniques and assess their ability to inject subcutaneously to ensure the proper administration of COSENTYX *[see Medication Guide and Instructions for Use]*.

Instruct patients or caregivers in the technique of proper syringe and needle disposal, and advise them not to reuse these items. Instruct patients to inject the full amount of COSENTYX (1 or 2 subcutaneous injections of 150 mg) according to the directions provided in the Medication Guide and Instructions for Use. Dispose of needles, syringes and pens in a puncture-resistant container.

Manufactured by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

US License No. 1244

T2018-93

MEDICATION GUIDE

COSENTYX® (koe-sen-tix)
(secukinumab) Injection

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

COSENTYX is a medicine that affects your immune system. COSENTYX may increase your risk of having serious side effects such as:

Infections. COSENTYX may lower the ability of your immune system to fight infections and may increase your risk of infections.

- Your healthcare provider should check you for tuberculosis (TB) before starting treatment with COSENTYX.
- If your healthcare provider feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with COSENTYX and during treatment with COSENTYX.
- Your healthcare provider should watch you closely for signs and symptoms of TB during treatment with COSENTYX. **Do not take COSENTYX if you have an active TB infection.**

Before starting COSENTYX, tell your healthcare provider if you:

- are being treated for an infection
- have an infection that does not go away or that keeps coming back
- have TB or have been in close contact with someone with TB
- think you have an infection or have symptoms of an infection such as:
  - fever, sweats, or chills
  - muscle aches
  - cough
  - shortness of breath
  - blood in your 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

After starting COSENTYX, call your healthcare provider right away if you have any of the signs of infection listed above. Do not use COSENTYX if you have any signs of infection unless you are instructed to by your healthcare provider.

See **"What are the possible side effects of COSENTYX?"** for more information about side effects.

What is COSENTYX?

COSENTYX is a prescription medicine used to treat adults:

- with moderate to severe plaque psoriasis that involves large areas or many areas of the body, and who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet or UV light alone or with systemic therapy)
- with active psoriatic arthritis
- with active ankylosing spondylitis

COSENTYX may improve your psoriasis, psoriatic arthritis and ankylosing spondylitis but it may also lower the ability of your immune system to fight infections.

It is not known if COSENTYX is safe and effective in children.

Do not take COSENTYX:

Do not use COSENTYX if you have had a severe allergic reaction to secukinumab or any of the other ingredients in COSENTYX. See the end of this Medication Guide for a complete list of ingredients in COSENTYX.

Before taking COSENTYX, tell your healthcare provider 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 COSENTYX?"**

- have inflammatory bowel disease (Crohn's disease or ulcerative colitis)
- are allergic to latex. The needle cap on the COSENTYX Sensoready® pen and prefilled syringe contains latex.
- have recently received or are scheduled to receive an immunization (vaccine). People who take COSENTYX **should not** receive live vaccines.
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if COSENTYX can harm your unborn baby. You and your healthcare provider should decide if you will use COSENTYX.
- are breastfeeding or plan to breastfeed. It is not known if COSENTYX passes into your breast milk.

Tell your healthcare provider 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 your medicines to show your healthcare provider and pharmacist when you get a new medicine.

How should I use COSENTYX?

See the detailed "Instructions for Use" that comes with your COSENTYX for information on how to prepare and inject a dose of COSENTYX, and how to properly throw away (dispose of) used COSENTYX Sensoready pens and prefilled syringes.

- Use COSENTYX exactly as prescribed by your healthcare provider.
- If your healthcare provider decides that you or a caregiver may give your injections of COSENTYX at home, you should receive training on the right way to prepare and inject COSENTYX. Do not try to inject COSENTYX yourself, until you or your caregiver has been shown how to inject COSENTYX by your healthcare provider.
- COSENTYX comes in a Sensoready pen or prefilled syringe that you or your caregiver may use at home to give injections. Your healthcare provider will decide which type of COSENTYX is best for you to use at home.
- Your healthcare provider will prescribe the dose of COSENTYX that is right for you.
  - If your prescribed dose of COSENTYX is **150 mg**, you must give **1 injection** of COSENTYX for each dose.
  - If your prescribed dose of COSENTYX is **300 mg**, you must give **2 injections** for each dose.
- COSENTYX is given as an injection under your skin (subcutaneous injection), in your upper legs (thighs) or stomach-area (abdomen) by you or a caregiver. A caregiver may also give you an injection of COSENTYX in your upper outer arm.
- **Do not** give an injection in an area of the skin that is tender, bruised, red or hard, or in an area of skin that is affected by psoriasis.
- Each injection should be given at a different site. **Do not** use the 2-inch area around your navel (belly button).
- If you inject more COSENTYX than prescribed, call your healthcare provider or go to the nearest emergency room right away.

What are the possible side effects of COSENTYX?

See **"What is the most important information I should know about COSENTYX?"**

- **Inflammatory bowel disease.** New cases of inflammatory bowel disease or "flare-ups" can happen with COSENTYX, and can sometimes be serious. If you have inflammatory bowel disease (ulcerative colitis or Crohn's disease), tell your healthcare provider if you have worsening disease symptoms during treatment with COSENTYX or develop new symptoms of stomach pain or diarrhea.
- **Serious allergic reactions.** Get emergency medical help right away if you get any of the following symptoms of a serious allergic reaction:
  - feel faint
  - swelling of your face, eyelids, lips, mouth, tongue, or throat
  - trouble breathing or throat tightness
  - chest tightness
  - skin rash

If you have a severe allergic reaction, do not give another injection of COSENTYX.

The most common side effects of COSENTYX include:

- cold symptoms
- diarrhea
- upper respiratory infections

These are not all of the possible side effects of COSENTYX.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store COSENTYX?

- Store COSENTYX in a refrigerator, between 36°F to 46°F (2°C to 8°C).
- Keep COSENTYX in the original carton until ready for use to protect from light.
- Do not freeze COSENTYX.
- Do not shake COSENTYX.

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

General information about the safe and effective use of COSENTYX.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use COSENTYX for a condition for which it was not prescribed. Do not give COSENTYX to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about COSENTYX that is written for health professionals.

What are the ingredients in COSENTYX?

Active ingredient: secukinumab

Inactive ingredients: Sensoready pen and prefilled syringe: L-histidine/histidine hydrochloride monohydrate, L-methionine, polysorbate 80, trehalose dihydrate, and sterile water for injection.

Vial: L-histidine/histidine hydrochloride monohydrate, polysorbate 80, and sucrose.

Manufactured by: Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936

T2018-06

For more information, call 1-888-669-6682 or go to www.COSENTYX.com

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

Revised: January 2018

INSTRUCTIONS FOR USE

COSENTYX® (koe-sen-tix)

(secukinumab)

For Injection

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

IMPORTANT:

- The single-use vial contains 150 mg of COSENTYX for reconstitution with Sterile Water for Injection (SWFI). Do not use the vial after the expiry date shown on the outer box or vial. If it has expired, return the entire pack to the pharmacy.
- The preparation of the solution for subcutaneous injection shall be done without interruption ensuring that aseptic technique is used. The preparation time from piercing the stopper until end of reconstitution on average takes 20 minutes and should not exceed 90 minutes.
- Throw away (dispose of) the used syringe right away after use. Do not re-use a syringe. See **"How should I dispose of a used syringe?"** at the end of this Instructions for Use.

How should I store COSENTYX?

- Store the vial of COSENTYX in the refrigerator between 2°C to 8°C (36°F to 46°F).

To prepare COSENTYX 150 mg for injection, please adhere to the following instructions:

Instructions for reconstitution of COSENTYX 150 mg for injection:

Step 1. Remove the vial of COSENTYX 150 mg for injection from the refrigerator and allow to stand for 15 to 30 minutes to reach room temperature. Ensure the Sterile Water for Injection (SWFI) is at room temperature.

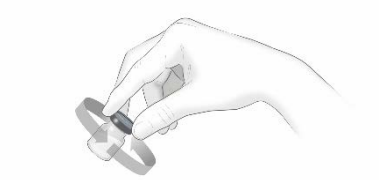
Step 2. Reconstitute the lyophilized powder by slowly injecting 1 mL of Sterile Water for Injection (SWFI) into the vial. Direct the stream of SWFI onto the lyophilized powder (**See Figure A**).

Figure A

Step 3. Tilt the vial to an angle of approximately 45 degrees and gently rotate between the fingertips for approximately 1 minute. Do not shake or invert the vial (**See Figure B**).

Step 4. Keep the vial standing at room temperature for a minimum of 10 minutes to allow for dissolution. Note that foaming of the solution may occur.

Figure B



Step 5. Tilt the vial to an angle of approximately 45 degrees and gently rotate between the fingertips for approximately 1 minute. Do not shake or invert the vial (**See Figure B**).

Step 6. Allow the vial to stand undisturbed at room temperature for approximately 5 minutes. The resulting solution should be clear. Its color may vary from colorless to slightly yellow. Do not use if the lyophilized powder has not fully dissolved or if the liquid contains visible particles, is cloudy or is discolored.

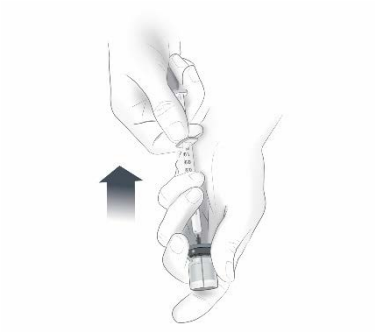
Step 7. Prepare the required number of vials (1 vial for the 150 mg dose or 2 vials for the 300 mg dose).

After preparation, use the solution for subcutaneous injection immediately or store at 2°C to 8 °C (36°F to 46°F) for up to 24 hours. Do not freeze. After storage at 2°C to 8°C (36°F to 46°F), allow the reconstituted solution to come to room temperature (15 to 30 minutes) before administration. Administer the solution within 1 hour after removal from the 2°C to 8°C (36°F to 46°F) storage.

Instructions for administration of COSENTYX solution:

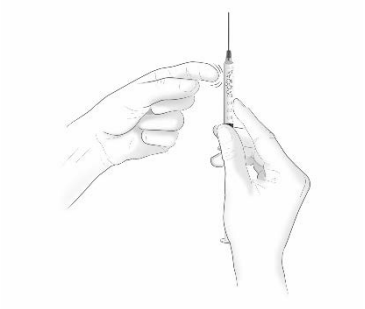
Step 1. Tilt the vial to an angle of approximately 45 degrees and position the needle tip at the very bottom of the solution in the vial when drawing the solution into the syringe. DO NOT invert the vial.

Figure C



Step 2. Carefully withdraw slightly more than 1 mL of the solution for subcutaneous injection from the vial into a 1 mL graduated disposable syringe using a suitable needle (e.g., 21G x 2") **(See Figure C).** This needle will only be used for withdrawing COSENTYX into the disposable syringe. Prepare the required number of syringes (1 syringe for the 150 mg dose or 2 syringes for the 300 mg dose).

Figure D



Step 3. With the needle pointing upward, gently tap the syringe to move any air bubbles to the top **(See Figure D).**

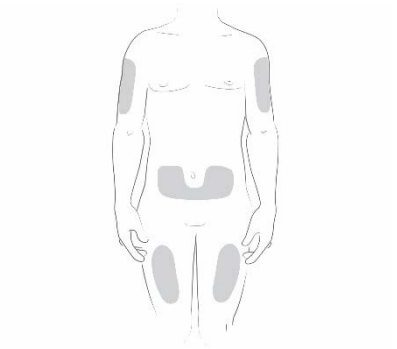
Figure E

Step 4. Replace the attached needle with a 27G x ½" needle **(See Figure E).**

Step 5. Expel the air bubbles and advance the plunger to the 1 mL mark.

Step 6. Clean the injection site with an alcohol wipe.

Figure F



Step 7. Inject the COSENTYX solution subcutaneously into the front of thighs, lower abdomen [but not the area 2 inches around the navel (belly button)] or outer upper arms **(See Figure F).** Choose a different site each time an injection is administered. Do not inject into areas where the skin is tender, bruised, red, scaly or hard, or in an area of skin that is affected by psoriasis. Avoid areas with scars or stretch marks.

How should I dispose of a used syringe?

Any remaining solution in the vial must not be used and must be discarded in accordance with local requirements. Vials are for single use only.

Put the used syringes and needles in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of)** the syringes and needles in your household trash.

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

1. made of a heavy-duty plastic,
2. can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
3. upright and stable during use,
4. leak-resistant, and
5. 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 state or local laws about how you should throw away used needles and syringes. 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.

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

Manufactured by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
US License Number 1244

Revised: January 2018

T2018-07

INSTRUCTIONS FOR USE
COSENTYX® (koe-sen-tix)
(secukinumab)
Injection
Prefilled Syringe

Be sure that you read, understand, and follow this Instructions for Use before injecting COSENTYX. Your healthcare provider should show you how to prepare and inject COSENTYX properly using the prefilled syringe before you use it for the first time. Talk to your healthcare provider if you have any questions.

Important:

- **Do not use** the COSENTYX prefilled syringe if either the seal on the outside carton or the seal of the blister are broken. Keep the COSENTYX prefilled syringe in the sealed carton until you are ready to use it.
- Inject COSENTYX **within 1 hour** after taking it out of the refrigerator.
- **Do not shake** the COSENTYX prefilled syringe.
- **The needle caps of the prefilled syringes contain latex. Do not handle the prefilled syringes if you are sensitive to latex.**
- The prefilled syringe has a needle guard that will be activated to cover the needle after the injection is finished. The needle guard will help to prevent needle stick injuries to anyone who handles the prefilled syringe.
- Do not remove the needle cap until just before you give the injection.
- Avoid touching the syringe guard wings before use. Touching them may cause the syringe guard to be activated too early.
- Throw away (dispose of) the used COSENTYX prefilled syringe right away after use. **Do not re-use a COSENTYX prefilled syringe.** See **"How should I dispose of used COSENTYX prefilled syringes?"** at the end of this Instructions for Use.

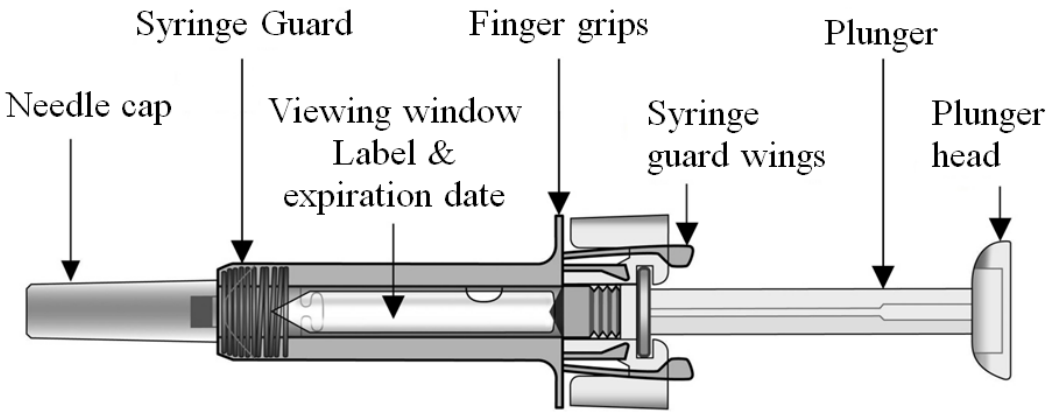
How should I store COSENTYX?

- Store your carton of COSENTYX prefilled syringes in a refrigerator, between 36°F to 46°F (2°C to 8°C).
- Keep COSENTYX prefilled syringes in the original carton until ready to use to protect from light.
- Do not freeze COSENTYX prefilled syringes.

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

COSENTYX prefilled syringe parts (see Figure A):

Figure A



What you need for your injection:

Included in the carton:
A new COSENTYX prefilled syringe.
Each COSENTYX prefilled syringe contains **150 mg** of COSENTYX.

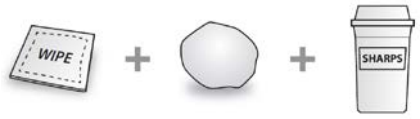
- If your **prescribed dose** of COSENTYX is **150 mg**, you must give **1 injection**.
- If your **prescribed dose** of COSENTYX is **300 mg**, you must give **2 injections**.

Not included in the carton **(see Figure B)**:

- 1 Alcohol wipe
- 1 Cotton ball or gauze
- Sharps disposal container

Figure B

See "**How should I dispose of used COSENTYX prefilled syringes**?" at the end of this Instructions for Use.



Prepare the COSENTYX prefilled syringe

Step 1. Find a clean, well-lit, flat work surface.

Step 2. Take the carton containing the COSENTYX prefilled syringe out of the refrigerator and leave it **unopened** on your work surface for about 15 to 30 minutes so that it reaches room temperature.

Step 3. Wash your hands well with soap and water.

Step 4. Remove the COSENTYX prefilled syringe from the outer carton and take it out of the blister.

Step 5. Look through the viewing window on the COSENTYX prefilled syringe. The liquid inside should be clear. The color may be colorless to slightly yellow. You may see a small air bubble in the liquid. This is normal. **Do not use** the prefilled syringe if the liquid contains visible particles, or if the liquid is cloudy or discolored.

Step 6. **Do not use** the COSENTYX prefilled syringe if it is broken. Return the prefilled syringe and the package it came in to the pharmacy.

Step 7. Do not use the COSENTYX prefilled syringe if the expiration date has passed.

Choose and clean the injection site

- Areas of your body that you may use as injection sites include:
  - the front of your thighs **(see Figure C)**
  - the lower stomach-area (abdomen), but **not** the area 2 inches around your navel (belly button) **(see Figure C)**
  - your upper outer arms, if a caregiver is giving you the injection **(see Figure D)**
- Choose a different site for each injection of COSENTYX.
- **Do not** inject into areas where the skin is tender, bruised, red, scaly, or hard, or in an area of skin that is affected by psoriasis. Avoid areas with scars or stretch marks.

Figure C

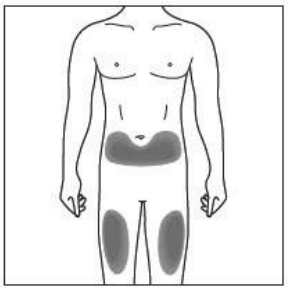
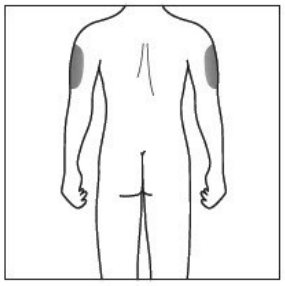


Figure D

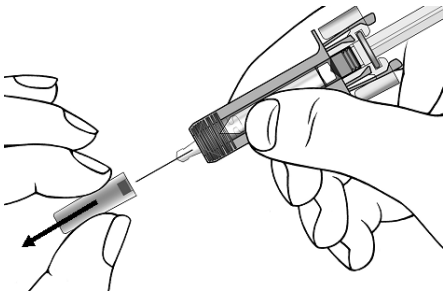


Step 8. Using a circular motion, clean the injection site with the alcohol wipe. Leave it to dry before injecting. Do not touch the cleaned area again before injecting.

Giving your injection

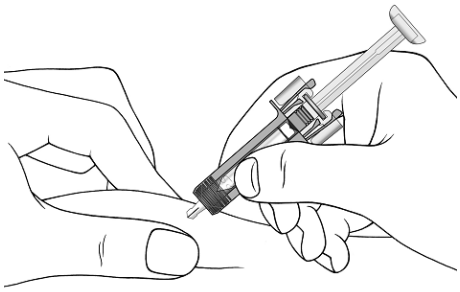
Step 9. Carefully remove the needle cap from the COSENTYX prefilled syringe **(see Figure E).** Throw away the needle cap. You may see a drop of liquid at the end of the needle. This is normal.

Figure E



Step 10. With one hand gently pinch the skin at the injection site. With your other hand insert the needle into your skin as shown **(see Figure F).** Push the needle all the way in to make sure that you inject your full dose.

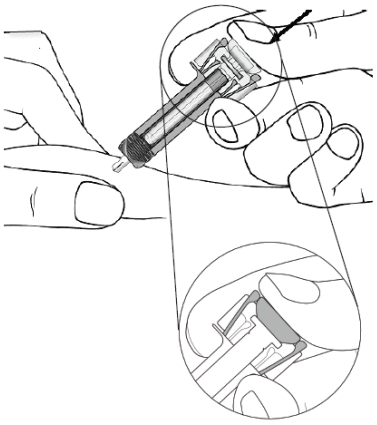
Figure F



Step 11. Hold the COSENTYX prefilled syringe finger grips as shown (**see Figure G**). Slowly press down on the plunger as far as it will go, so that the plunger head is completely between the syringe guard wings.

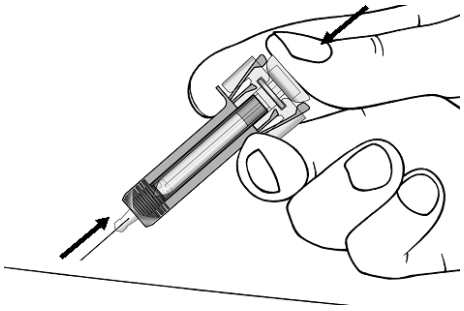
Step 12. Continue to press fully on the plunger for an additional 5 seconds. Hold the syringe in place for the full 5 seconds.

Figure G



Step 13. Keep the plunger fully depressed while you carefully pull the needle straight out from the injection site **(see Figure H).**

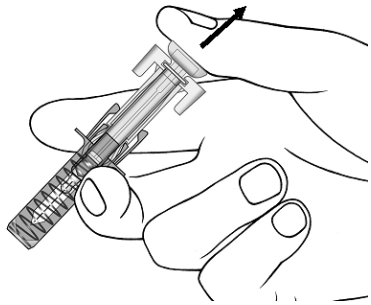
Figure H



Step 14. Slowly release the plunger and allow the syringe guard to automatically cover the exposed needle **(see Figure I).**

Step 15. There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 10 seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

Figure I

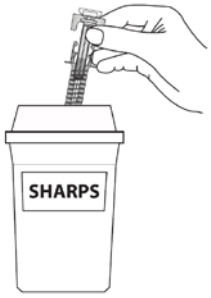


If your prescribed dose of COSENTYX is 300 mg, repeat steps 4 through 15 with a new COSENTYX prefilled syringe.

How should I dispose of used COSENTYX prefilled syringes?

Step 16. Put your used prefilled syringes in a FDA-cleared sharps disposal container right away after use **(see Figure J). Do not throw away (dispose of)** prefilled syringes in your household trash.

Figure J



If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a 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 state or local laws about how you should throw away used needles, syringes and prefilled syringes. 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.

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

Manufactured by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
US License Number 1244

Revised: January 2018

T2018-08

INSTRUCTIONS FOR USE
COSENTYX® (koe-sen-tix)
(secukinumab)
Injection
Sensoready® Pen

Be sure that you read, understand, and follow this Instructions for Use before injecting COSENTYX. Your healthcare provider should show you how to prepare and inject COSENTYX properly using the Sensoready Pen before you use it for the first time. Talk to your healthcare provider if you have any questions.

Important:

- **Do not use** the COSENTYX Sensoready Pen if either the seal on the outer carton or the seal on the pen is broken. Keep the COSENTYX Sensoready Pen in the sealed outer carton until you are ready to use it.
- Inject COSENTYX **within 1 hour** after taking it out of the refrigerator.
- **Do not shake** the COSENTYX Sensoready Pen.
- The caps of the Sensoready Pens contain latex. **Do not handle the Sensoready Pens if you are sensitive to latex.**
- If you drop your COSENTYX Sensoready Pen, **do not use** it if the Sensoready Pen looks damaged, or if you dropped it with the cap removed.
- Throw away (dispose of) the used COSENTYX Sensoready Pen right away after use. **Do not re-use a COSENTYX Sensoready Pen.** See "How should I dispose of used COSENTYX Sensoready Pens?" at the end of this Instructions for Use.

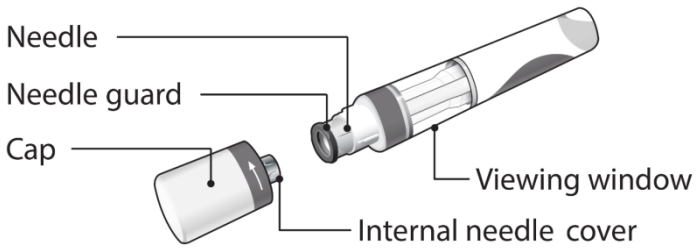
How should I store COSENTYX?

- Store your carton of COSENTYX Sensoready Pen in a refrigerator, between 36°F to 46°F (2°C to 8°C).
- Keep COSENTYX Sensoready Pen in the original carton until ready to use to protect from light.
- Do not freeze COSENTYX Sensoready Pen.

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

COSENTYX Sensoready Pen parts (see Figure A):

Figure A



The COSENTYX Sensoready Pen is shown above with the cap removed. **Do not** remove the cap until you are ready to inject.

What you need for your injection:

Included in the carton:

A new COSENTYX Sensoready Pen (**see Figure B**).

Figure B

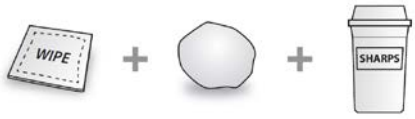
Each COSENTYX Sensoready Pen contains 150 mg of COSENTYX.

- If your **prescribed dose** of COSENTYX is **150 mg**, you must give **1 injection.**
- If your **prescribed dose** of COSENTYX is **300 mg**, you must give **2 injections**.

Not included in the carton **(see Figure C)**:

- 1 Alcohol wipe
- 1 Cotton ball or gauze
- Sharps disposal container.

Figure C



See "**How should I dispose of used COSENTYX Sensoready Pen**?" at the end of this Instructions for Use.

Before your injection:

Take the COSENTYX Sensoready Pen out of the refrigerator **15 to 30 minutes before injecting** to allow it to reach room temperature.

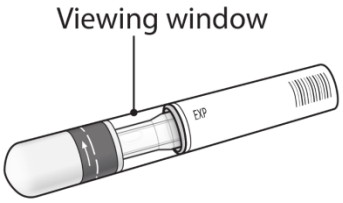
Step 1. Important safety checks before you inject (see Figure D):

Figure D

- Look through the viewing window. The liquid should be clear. Its color may vary from colorless to slightly yellow.

  Do not use if the liquid contains visible particles, is cloudy or is discolored. You may see a small air bubble, which is normal.

- Look at the **expiration date (EXP)** on your Sensoready Pen. **Do not use** your COSENTYX Sensoready Pen if the expiration date has passed.



Contact your pharmacist if the COSENTYX Sensoready Pen fails any of these checks.

Step 2. Choose your injection site:

Figure E

- The recommended site is the front of the thighs. You may also use the lower abdomen, but **not** the area 2 inches around your navel (belly button) **(see Figure E).**
- Choose a different site each time you give yourself an injection.
- Do not inject into areas where the skin is tender, bruised, red, scaly or hard, or in an area of skin that is affected by psoriasis. Avoid areas with scars or stretch marks.

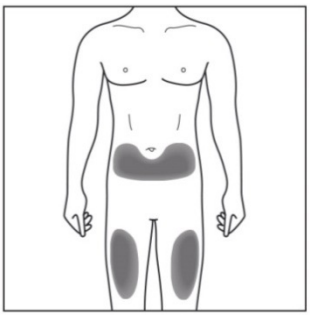
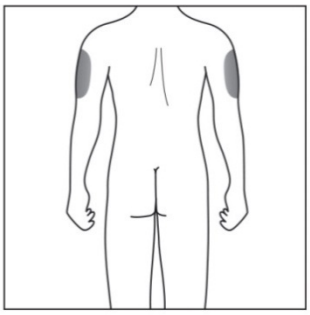


Figure F

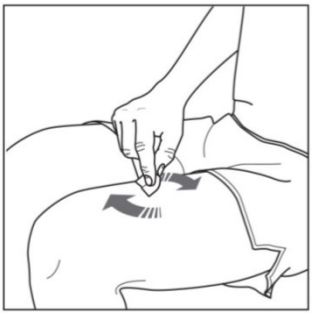
- If a **caregiver** or **healthcare provider** is giving you your injection, they may also inject into your outer upper arm **(see Figure F).**



Step 3. Cleaning your injection site:

- Wash your hands well with soap and water.
- Using a circular motion, clean the injection site with the alcohol wipe. Leave it to dry before injecting **(see Figure G).**
- Do not touch the cleaned area again before injecting.

Figure G

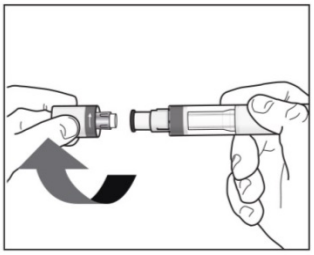


Your injection:

Step 4. Removing the cap:

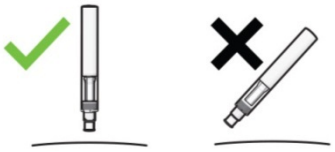
- Only remove the cap when you are ready to use the COSENTYX Sensoready Pen.
- Twist off the cap in the direction of the arrow **(see Figure H)**.
- Throw away the cap. **Do not try to re-attach the cap.**
- Use the COSENTYX Sensoready Pen within 5 minutes of removing the cap.

Figure H



Step 5. Holding your COSENTYX Sensoready Pen:

- Hold the COSENTYX Sensoready Pen at 90 degrees to the cleaned injection site **(see Figure I).**



Correct **Incorrect**

Figure I

Important: During the injection you will hear **2 loud clicks**:

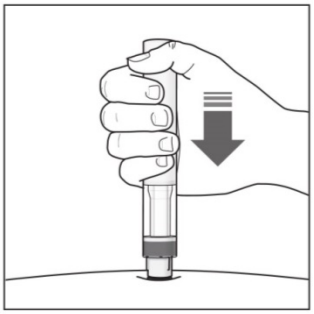
- The **1st click** indicates that **the injection has started**.
- Several seconds later a **2nd click** will indicate that **the injection is almost finished**.

You must keep holding the COSENTYX Sensoready Pen firmly against your skin until you see a **green indicator** fill the window and stop moving.

Step 6. Starting your injection:

- Press the COSENTYX Sensoready Pen firmly against the skin to start the injection **(see Figure J).**
- The **1st click** indicates the injection has started.
- **Keep holding** the COSENTYX Sensoready Pen firmly against your skin.
- The **green indicator** shows the progress of the injection.

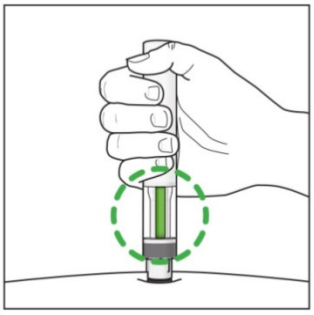
Figure J



Step 7. Completing your injection:

- Listen for the **2nd click**. This indicates the injection is **almost** complete.
- Check the **green indicator** fills the window and has stopped moving **(see Figure K).**
- The COSENTYX Sensoready Pen can now be removed.

Figure K

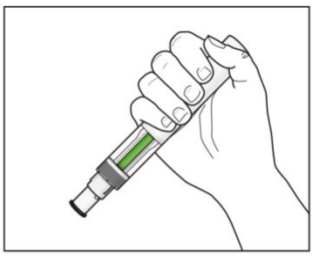


After your injection:

Step 8. Check the green indicator fills the window (see Figure L):

- This means the medicine has been delivered. Contact your healthcare provider if the green indicator is not visible.
- There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 10 seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

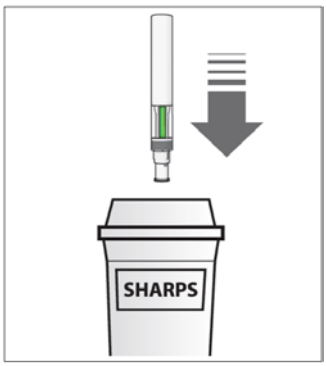
Figure L



If your prescribed dose of COSENTYX is 300 mg, repeat steps 1 through 8 with a new COSENTYX Sensoready Pen.

How should I dispose of used COSENTYX Sensoready Pens?

Figure M



Step 9. Put your used Sensoready Pens in a FDA-cleared sharps disposal container right away after use **(see Figure M). Do not throw away (dispose of)** Sensoready Pens in your household trash.

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a 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 state or local laws about how you should throw away used needles, syringes, and Sensoready Pens. 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.

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

Manufactured by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
US License Number 1244

Revised: January 2018

T2018-09

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Cosentyx 150 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains 150 mg secukinumab*. After reconstitution, 1 ml of solution contains 150 mg secukinumab.

*Secukinumab is a recombinant fully human monoclonal antibody selective for interleukin-17A. Secukinumab is of the IgG1/κ-class produced in Chinese Hamster Ovary (CHO) cells.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection

The powder is a white solid lyophilisate.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Plaque psoriasis

Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Psoriatic arthritis

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

Ankylosing spondylitis

Cosentyx is indicated for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

4.2 Posology and method of administration

Cosentyx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Cosentyx is indicated.

Posology

Plaque psoriasis
The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Each 300 mg dose is given as two subcutaneous injections of 150 mg.

Psoriatic arthritis
For patients with concomitant moderate to severe plaque psoriasis or who are anti-TNFα inadequate responders (IR), the recommended dose is 300 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Each 300 mg dose is given as two subcutaneous injections of 150 mg.

For other patients, the recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Based on clinical response, the dose can be increased to 300 mg.

Ankylosing spondylitis
The recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing.

For all of the above indications, available data suggest that a clinical response is usually achieved within 16 weeks of treatment. Consideration should be given to discontinuing treatment in patients who have shown no response by 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks.

Special populations

Elderly patients (aged 65 years and over)
No dose adjustment is required (see section 5.2).

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

Paediatric population
The safety and efficacy of Cosentyx in children below the age of 18 years have not yet been established. No data are available.

Method of administration

Cosentyx is to be administered by subcutaneous injection. If possible, areas of the skin that show psoriasis should be avoided as injection sites. The powder for solution for injection must be reconstituted before use. For instructions on reconstitution of the medicinal product before administration, see section 6.6 and the Instructions for Use in the package leaflet.

4.3 Contraindications

Severe hypersensitivity reactions 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

Infections

Cosentyx has the potential to increase the risk of infections. Serious infections have been observed in patients receiving Cosentyx in the post-marketing setting. Caution should be exercised when considering the use of Cosentyx in patients with a chronic infection or a history of recurrent infection.

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 Cosentyx should not be administered until the infection resolves.

In clinical studies, infections have been observed in patients receiving Cosentyx (see section 4.8). Most of these were mild or moderate upper respiratory tract infections such as nasopharyngitis and did not require treatment discontinuation.

Related to the mechanism of action of Cosentyx, non-serious mucocutaneous candida infections were more frequently reported for secukinumab than placebo in the psoriasis clinical studies (3.55 per 100 patient years for secukinumab 300 mg versus 1.00 per 100 patient years for placebo) (see section 4.8).

No increased susceptibility to tuberculosis was reported from clinical studies. However, Cosentyx should not be given to patients with active tuberculosis. Anti-tuberculosis therapy should be considered prior to initiation of Cosentyx in patients with latent tuberculosis.

Inflammatory bowel disease

Cases of new or exacerbations of Crohn's disease and ulcerative colitis have been reported. Caution should be exercised when prescribing Cosentyx to patients with inflammatory bowel disease, including Crohn's disease and ulcerative colitis. Patients should be closely monitored.

Hypersensitivity reactions

In clinical studies, rare cases of anaphylactic reactions have been observed in patients receiving Cosentyx. If an anaphylactic or other serious allergic reactions occur, administration of Cosentyx should be discontinued immediately and appropriate therapy initiated.

Vaccinations

Live vaccines should not be given concurrently with Cosentyx.

Patients receiving Cosentyx may receive concurrent inactivated or non-live vaccinations. In a study, after *meningococcal* and inactivated *influenza* vaccinations, a similar proportion of healthy volunteers treated with 150 mg of secukinumab and those treated with placebo were able to mount an adequate immune response of at least a 4-fold increase in antibody titres to *meningococcal* and *influenza* vaccines. The data suggest that Cosentyx does not suppress the humoral immune response to the *meningococcal* or *influenza* vaccines.

Concomitant immunosuppressive therapy

In psoriasis studies, the safety and efficacy of Cosentyx in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated (see also section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

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

In a study in subjects with plaque psoriasis, no interaction was observed between secukinumab and midazolam (CYP3A4 substrate).

No interaction was seen when Cosentyx was administered concomitantly with methotrexate (MTX) and/or corticosteroids in arthritis studies (including in patients with psoriatic arthritis and ankylosing spondylitis).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use an effective method of contraception during treatment and for at least 20 weeks after treatment.

Pregnancy

There are no adequate data from the use of secukinumab 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 Cosentyx in pregnancy.

Breast-feeding

It is not known whether secukinumab is excreted in human milk. Immunoglobulins are excreted in human milk and it is not known if secukinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from secukinumab, a decision on whether to discontinue breast-feeding during treatment and up to 20 weeks after treatment or to discontinue therapy with Cosentyx must be made taking into account the benefit of breast-feeding to the child and the benefit of Cosentyx therapy to the woman.

Fertility

The effect of secukinumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Over 11,900 patients have been treated with Cosentyx in blinded and open-label clinical studies in various indications (plaque psoriasis, psoriatic arthritis, ankylosing spondylitis and other autoimmune conditions), representing 20,995 patient years of exposure. Of these, over 7,100 patients were exposed to Cosentyx for at least one year.

Adverse reactions in plaque psoriasis

Four placebo-controlled phase III studies in plaque psoriasis were pooled to evaluate the safety of Cosentyx in comparison to placebo up to 12 weeks after treatment initiation. In total, 2,076 patients were evaluated (692 patients on 150 mg, 690 patients on 300 mg and 694 patients on placebo).

The most frequently reported adverse drug reactions (ADRs) were upper respiratory tract infections (most frequently nasopharyngitis, rhinitis). Most of the reactions were mild or moderate in severity.

Adverse reactions in psoriatic arthritis

In Cosentyx placebo-controlled psoriatic arthritis studies, there were 2,754 patients (1,871 patients on Cosentyx and 883 patients on placebo) with a total exposure of 4,478 patient-years of study exposure on Cosentyx. The safety profile observed in patients with psoriatic arthritis treated with Cosentyx is consistent with the safety profile in psoriasis.

Adverse reactions in ankylosing spondylitis

Cosentyx was studied in two placebo-controlled ankylosing spondylitis studies with 590 patients (394 patients on Cosentyx and 196 patients on placebo) for a total of 755 patient-years of study exposure (median duration of exposure for secukinumab-treated patients: 469 days in AS Study 1 and 460 days in AS Study 2). The safety profile observed in patients with ankylosing spondylitis treated with Cosentyx is consistent with the safety profile in psoriasis.

Tabulated list of adverse reactions

ADRs from psoriasis, psoriatic arthritis and ankylosing spondylitis clinical studies as well as from post-marketing experience (Table 1) are listed by MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available data).

Table 1 List of adverse reactions in clinical studies[1)] and post-marketing experience

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Very common	Upper respiratory tract infections
	Common	Oral herpes
	Uncommon	Oral candidiasis
		Tinea pedis
		Otitis externa
	Not known	Mucosal and cutaneous candidiasis (including oesophageal candidiasis)
Blood and lymphatic system disorders	Uncommon	Neutropenia
Immune system disorders	Rare	Anaphylactic reactions
Eye disorders	Uncommon	Conjunctivitis
Respiratory, thoracic and mediastinal disorders	Common	Rhinorrhoea
Gastrointestinal disorders	Common	Diarrhoea
Skin and subcutaneous disorders	Uncommon	Urticaria
[1)] Placebo-controlled clinical studies (phase III) in plaque psoriasis, PsA and AS patients exposed to 300 mg, 150 mg, 75 mg or placebo up to 12 weeks (psoriasis) or 16 weeks (PsA and AS) treatment duration		

Description of selected adverse reactions

Infections

In the placebo-controlled period of clinical studies in plaque psoriasis (a total of 1,382 patients treated with Cosentyx and 694 patients treated with placebo for up to 12 weeks), infections were reported in 28.7% of patients treated with Cosentyx compared with 18.9% of patients treated with placebo. The majority of infections consisted of non-serious and mild to moderate upper respiratory tract infections, such as nasopharyngitis, which did not necessitate treatment discontinuation. There was an increase in mucosal or cutaneous candidiasis, consistent with the mechanism of action, but the cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in 0.14% of patients treated with Cosentyx and in 0.3% of patients treated with placebo (see section 4.4).

Over the entire treatment period (a total of 3,430 patients treated with Cosentyx for up to 52 weeks for the majority of patients), infections were reported in 47.5% of patients treated with Cosentyx (0.9 per patient-year of follow-up). Serious infections were reported in 1.2% of patients treated with Cosentyx (0.015 per patient-year of follow-up).

Infection rates observed in psoriatic arthritis and ankylosing spondylitis clinical studies were similar to those observed in the psoriasis studies.

Neutropenia

In psoriasis phase 3 clinical studies, neutropenia was more frequently observed with secukinumab than with placebo, but most cases were mild, transient and reversible. Neutropenia <1.0-0.5x10^9/l (CTCAE Grade 3) was reported in 18 out of 3,430 (0.5%) patients on secukinumab, with no dose dependence and no temporal relationship to infections in 15 out of 18 cases. There were no reported cases of more severe neutropenia. Non-serious infections with usual response to standard care and not requiring discontinuation of Cosentyx were reported in the remaining 3 cases.

The frequency of neutropenia in psoriatic arthritis and ankylosing spondylitis is similar to psoriasis.

Rare cases of neutropenia <0.5x10^9/l (CTCAE Grade 4) were reported.

Hypersensitivity reactions

In clinical studies, urticaria and rare cases of anaphylactic reaction to Cosentyx were observed (see also section 4.4).

Immunogenicity

In psoriasis, psoriatic arthritis and ankylosing spondylitis clinical studies, less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. About half of the treatment-emergent anti-drug antibodies were neutralising, but this was not associated with loss of efficacy or pharmacokinetic abnormalities.

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

No cases of overdose have been reported in clinical studies.

Doses up to 30 mg/kg (approximately 2000 to 3000 mg) have been administered intravenously in clinical studies without dose-limiting toxicity. In the event 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: L04AC10

Mechanism of action

Secukinumab is a fully human IgG1/κ monoclonal antibody that selectively binds to and neutralises the proinflammatory cytokine interleukin-17A (IL-17A). Secukinumab works by targeting IL-17A and inhibiting its interaction with the IL-17 receptor, which is expressed on various cell types including keratinocytes. As a result, secukinumab inhibits the release of proinflammatory cytokines, chemokines and mediators of tissue damage and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases. Clinically relevant levels of secukinumab reach the skin and reduce local inflammatory markers. As a direct consequence treatment with secukinumab reduces erythema, induration and desquamation present in plaque psoriasis lesions.

IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. IL-17A plays a key role in the pathogenesis of plaque psoriasis, psoriatic arthritis and ankylosing spondylitis and is up-regulated in lesional skin in contrast to non-lesional skin of plaque psoriasis patients and in synovial tissue of psoriatic arthritis patients. The frequency of IL-17-producing cells was also significantly higher in the subchondral bone marrow of facet joints from patients with ankylosing spondylitis.

Pharmacodynamic effects

Serum levels of total IL-17A (free and secukinumab-bound IL-17A) are initially increased in patients receiving secukinumab. This is followed by a slow decrease due to reduced clearance of secukinumab-bound IL-17A, indicating that secukinumab selectively captures free IL-17A, which plays a key role in the pathogenesis of plaque psoriasis.

In a study with secukinumab, infiltrating epidermal neutrophils and various neutrophil-associated markers that are increased in lesional skin of plaque psoriasis patients were significantly reduced after one to two weeks of treatment.

Secukinumab has been shown to lower (within 1 to 2 weeks of treatment) levels of C-reactive protein, which is a marker of inflammation.

Clinical efficacy and safety

Plaque psoriasis
The safety and efficacy of Cosentyx were assessed in four randomised, double-blind, placebo-controlled phase III studies in patients with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy [ERASURE, FIXTURE, FEATURE, JUNCTURE]. The efficacy and safety of Cosentyx 150 mg and 300 mg were evaluated versus either placebo or etanercept. In addition, one study assessed a chronic treatment regimen versus a "retreatment as needed" regimen [SCULPTURE].

Of the 2,403 patients who were included in the placebo-controlled studies, 79% were biologic-naive, 45% were non-biologic failures and 8% were biologic failures (6% were anti-TNF failures, and 2% were anti-p40 failures). Approximately 15 to 25% of patients in phase III studies had psoriatic arthritis (PsA) at baseline.

Psoriasis Study 1 (ERASURE) evaluated 738 patients. Patients randomised to Cosentyx received 150 mg or 300 mg doses at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month. Psoriasis Study 2 (FIXTURE) evaluated 1,306 patients. Patients randomised to Cosentyx received 150 mg or 300 mg doses at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month. Patients randomised to etanercept received 50 mg doses twice per week for 12 weeks followed by 50 mg every week. In both Study 1 and Study 2, patients randomised to receive placebo who were non-responders at Week 12 then crossed over to receive Cosentyx (either 150 mg or 300 mg) at Weeks 12, 13, 14, and 15, followed by the same dose every month starting at Week 16. All patients were followed for up to 52 weeks following first administration of study treatment.

Psoriasis Study 3 (FEATURE) evaluated 177 patients using a pre-filled syringe compared with placebo after 12 weeks of treatment to assess the safety, tolerability, and usability of Cosentyx self-administration via the pre-filled syringe. Psoriasis Study 4 (JUNCTURE) evaluated 182 patients using a pre-filled pen compared with placebo after 12 weeks of treatment to assess the safety, tolerability, and usability of Cosentyx self-administration via the pre-filled pen. In both Study 3 and Study 4, patients randomised to Cosentyx received 150 mg or 300 mg doses at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month. Patients were also randomised to receive placebo at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month.

Psoriasis Study 5 (SCULPTURE) evaluated 966 patients. All patients received Cosentyx 150 mg or 300 mg doses at Weeks 0, 1, 2, 3, 4, 8 and 12 and then were randomised to receive either a maintenance regimen of the same dose every month starting at Week 12 or a "retreatment as needed" regimen of the same dose. Patients randomised to "retreatment as needed" did not achieve adequate maintenance of response and therefore a fixed monthly maintenance regimen is recommended.

The co-primary endpoints in the placebo and active-controlled studies were the proportion of patients who achieved a PASI 75 response and IGA mod 2011 "clear" or "almost clear" response versus placebo at Week 12 (see Tables 2 and 3). The 300 mg dose provided improved skin clearance particularly for "clear" or "almost clear" skin across the efficacy endpoints of PASI 90, PASI 100, and IGA mod 2011 0 or 1 response across all studies with peak effects seen at Week 16, therefore this dose is recommended.

Table 2 Summary of PASI 50/75/90/100 & IGA* mod 2011 "clear" or "almost clear" clinical response in Psoriasis Studies 1, 3 and 4 (ERASURE, FEATURE and JUNCTURE)

		Week 12		Week 16		Week 52	
	Placebo	**150 mg**	**300 mg**	**150 mg**	**300 mg**	**150 mg**	**300 mg**
Study 1							
Number of patients	246	244	245	244	245	244	245
PASI 50 response n (%)	22 (8.9%)	203 (83.5%)	222 (90.6%)	212 (87.2%)	224 (91.4%)	187 (77%)	207 (84.5%)
PASI 75 response n (%)	11 (4.5%)	174 (71.6%)**	200 (81.6%)**	188 (77.4%)	211 (86.1%)	146 (60.1%)	182 (74.3%)
PASI 90 response n (%)	3 (1.2%)	95 (39.1%)**	145 (59.2%)**	130 (53.5%)	171 (69.8%)	88 (36.2%)	147 (60.0%)
PASI 100 response n (%)	2 (0.8%)	31 (12.8%)	70 (28.6%)	51 (21.0%)	102 (41.6%)	49 (20.2%)	96 (39.2%)
IGA mod 2011 "clear" or "almost clear" response n (%)	6 (2.40%)	125 (51.2%)**	160 (65.3%)**	142 (58.2%)	180 (73.5%)	101 (41.4%)	148 (60.4%)
Study 3							
Number of patients	59	59	58	-	-	-	-
PASI 50 response n (%)	3 (5.1%)	51 (86.4%)	51 (87.9%)	-	-	-	-
PASI 75 response n (%)	0 (0.0%)	41 (69.5%)**	44 (75.9%)**	-	-	-	-
PASI 90 response n (%)	0 (0.0%)	27 (45.8%)	35 (60.3%)	-	-	-	-
PASI 100 response n (%)	0 (0.0%)	5 (8.5%)	25 (43.1%)	-	-	-	-
IGA mod 2011 "clear" or "almost clear" response n (%)	0 (0.0%)	31 (52.5%)**	40 (69.0%)**	-	-	-	-
Study 4							
Number of patients	61	60	60	-	-	-	-
PASI 50 response n (%)	5 (8.2%)	48 (80.0%)	58 (96.7%)	-	-	-	-
PASI 75 response n (%)	2 (3.3%)	43 (71.7%)**	52 (86.7%)**	-	-	-	-
PASI 90 response n (%)	0 (0.0%)	24 (40.0%)	33 (55.0%)	-	-	-	-
PASI 100 response n(%)	0 (0.0%)	10 (16.7%)	16 (26.7%)	-	-	-	-
IGA mod 2011 "clear" or "almost clear" response n (%)	0 (0.0%)	32 (53.3%)**	44 (73.3%)**	-	-	-	-

* The IGA mod 2011 is a 5-category scale including "0 = clear", "1 = almost clear", "2 = mild", "3 = moderate" or "4 = severe", indicating the physician's overall assessment of the psoriasis severity focusing on induration, erythema and scaling. Treatment success of "clear" or "almost clear" consisted of no signs of psoriasis or normal to pink colouration of lesions, no thickening of the plaque and none to minimal focal scaling.

** p values versus placebo and adjusted for multiplicity: $p<0.0001$.

Table 3 Summary of clinical response on Psoriasis Study 2 (FIXTURE)

	Week 12				Week 16			Week 52		
	Placebo	**150 mg**	**300 mg**	**Etanercept**	**150 mg**	**300 mg**	**Etanercept**	**150 mg**	**300 mg**	**Etanercept**
Number of patients	324	327	323	323	327	323	323	327	323	323
PASI 50 response n (%)	49 (15.1%)	266 (81.3%)	296 (91.6%)	226 (70.0%)	290 (88.7%)	302 (93.5%)	257 (79.6%)	249 (76.1%)	274 (84.8%)	234 (72.4%)
PASI 75 response n (%)	16 (4.9%)	219 (67.0%) **	249 (77.1%) **	142 (44.0%)	247 (75.5%)	280 (86.7%)	189 (58.5%)	215 (65.7%)	254 (78.6%)	179 (55.4%)
PASI 90 response n (%)	5 (1.5%)	137 (41.9%)	175 (54.2%)	67 (20.7%)	176 (53.8%)	234 (72.4%)	101 (31.3%)	147 (45.0%)	210 (65.0%)	108 (33.4%)
PASI 100 response n (%)	0 (0%)	47 (14.4%)	78 (24.1%)	14 (4.3%)	84 (25.7%)	119 (36.8%)	24 (7.4%)	65 (19.9%)	117 (36.2%)	32 (9.9%)
IGA mod 2011 “clear” or “almost clear” response n (%)	9 (2.8%)	167 (51.1%) **	202 (62.5%) **	88 (27.2%)	200 (61.2%)	244 (75.5%)	127 (39.3%)	168 (51.4%)	219 (67.8%)	120 (37.2%)

** p values versus etanercept: p=0.0250

In an additional psoriasis study (CLEAR) 676 patients were evaluated. Secukinumab 300 mg met the primary and secondary endpoints by showing superiority to ustekinumab based on PASI 90 response at Week 16 (primary endpoint), speed of onset of PASI 75 response at Week 4, and long-term PASI 90 response at Week 52. Greater efficacy of secukinumab compared to ustekinumab for the endpoints PASI 75/90/100 and IGA mod 2011 0 or 1 response (“clear” or “almost clear”) was observed early and continued through to Week 52.

Table 4 Summary of clinical response on CLEAR Study

	Week 4		Week 16		Week 52	
	Secukinumab 300 mg	**Ustekinumab***	**Secukinumab 300 mg**	**Ustekinumab***	**Secukinumab 300 mg**	**Ustekinumab***
Number of patients	334	335	334	335	334	335
PASI 75 response n (%)	166 (49.7%)**	69 (20.6%)	311 (93.1%)	276 (82.4%)	306 (91.6%)	262 (78.2%)
PASI 90 response n (%)	70 (21.0%)	18 (5.4%)	264 (79.0%)**	192 (57.3%)	250 (74.9%)***	203 (60.6%)
PASI 100 response n (%)	14 (4.2%)	3 (0.9%)	148 (44.3%)	95 (28.4%)	150 (44.9%)	123 (36.7%)
IGA mod 2011 “clear” or “almost clear” response n (%)	128 (38.3%)	41 (12.2%)	278 (83.2%)	226 (67.5%)	261 (78.1%)	213 (63.6%)

* Patients treated with secukinumab received 300 mg doses at Weeks 0, 1, 2, 3 and 4, followed by the same dose every 4 weeks until Week 52. Patients treated with ustekinumab received 45 mg or 90 mg at Weeks 0 and 4, then every 12 weeks until Week 52 (dosed by weight as per approved posology)

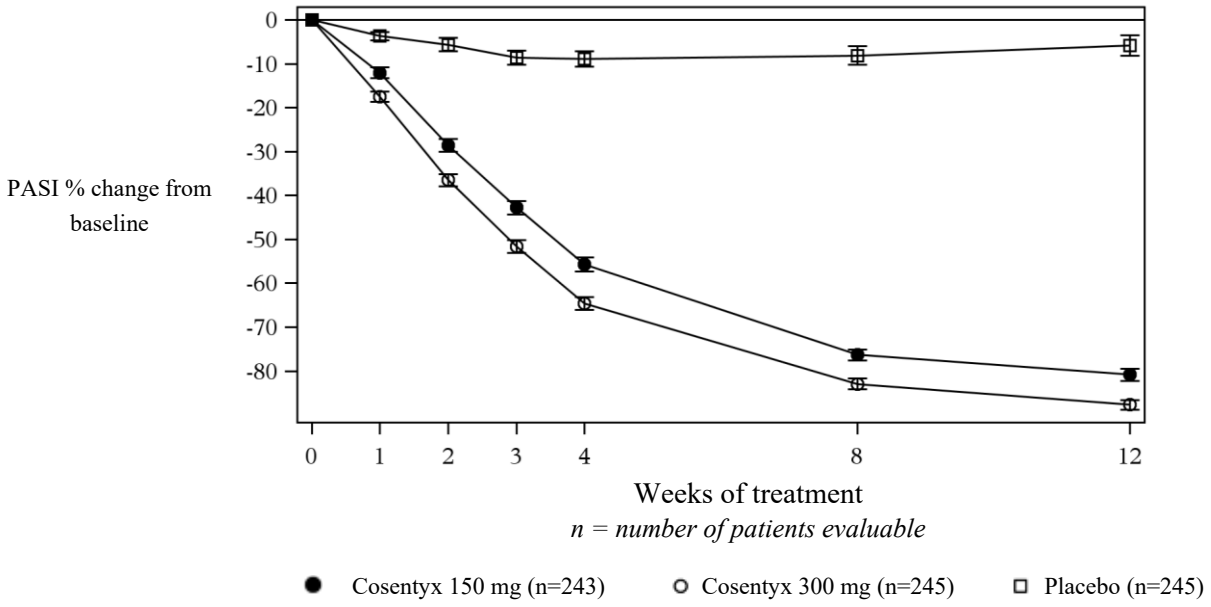
** p values versus ustekinumab: p<0.0001 for primary endpoint of PASI 90 at Week 16 and secondary endpoint of PASI 75 at Week 4

*** p values versus ustekinumab: p=0.0001 for secondary endpoint of PASI 90 at Week 52

Cosentyx was efficacious in systemic treatment-naive, biologic-naive, biologic/anti-TNF-exposed and biologic/anti-TNF-failure patients. Improvements in PASI 75 in patients with concurrent psoriatic arthritis at baseline were similar to those in the overall plaque psoriasis population.

Cosentyx was associated with a fast onset of efficacy with a 50% reduction in mean PASI by Week 3 for the 300 mg dose.

Figure 1 Time course of percentage change from baseline of mean PASI score in Study 1 (ERASURE)



Specific locations/forms of plaque psoriasis
In two additional placebo-controlled studies, improvement was seen in both nail psoriasis (TRANSFIGURE, 198 patients) and palmoplantar plaque psoriasis (GESTURE, 205 patients). In the TRANSFIGURE Study, secukinumab was superior to placebo at Week 16 (46.1% for 300 mg, 38.4% for 150 mg and 11.7% for placebo) as assessed by significant improvement from baseline in the Nail Psoriasis Severity Index (NAPSI %) for patients with moderate to severe plaque psoriasis with nail involvement. In the GESTURE Study, secukinumab was superior to placebo at Week 16 (33.3% for 300 mg, 22.1% for 150 mg, and 1.5% for placebo) as assessed by significant improvement of ppIGA 0 or 1 response ("clear" or "almost clear") for patients with moderate to severe palmoplantar plaque psoriasis.

A placebo-controlled study evaluated 102 patients with moderate to severe scalp psoriasis, defined as having a Psoriasis Scalp Severity Index (PSSI) score of ≥12, an IGA mod 2011 scalp only score of 3 or greater and at least 30% of the scalp surface area affected. Secukinumab 300 mg was superior to placebo at Week 12 as assessed by significant improvement from baseline in both the PSSI 90 response (52.9% versus 2.0%) and IGA mod 2011 0 or 1 scalp only response (56.9% versus 5.9%). Improvement in both endpoints was sustained for secukinumab patients who continued treatment through to Week 24.

Quality of life/patient-reported outcomes
Statistically significant improvements at Week 12 (Studies 1-4) from baseline compared to placebo were demonstrated in the DLQI (Dermatology Life Quality Index). Mean decreases (improvements) in DLQI from baseline ranged from -10.4 to -11.6 with secukinumab 300 mg, from -7.7 to -10.1 with secukinumab 150 mg, versus -1.1 to -1.9 for placebo at Week 12. These improvements were maintained for 52 weeks (Studies 1 and 2).

Forty percent of the participants in Studies 1 and 2 completed the Psoriasis Symptom Diary©. For the participants completing the diary in each of these studies, statistically significant improvements at Week 12 from baseline compared to placebo in patient-reported signs and symptoms of itching, pain and scaling were demonstrated.

Statistically significant improvements at Week 4 from baseline in patients treated with secukinumab compared to patients treated with ustekinumab (CLEAR) were demonstrated in the DLQI and these improvements were maintained for up to 52 weeks.

Statistically significant improvements in patient-reported signs and symptoms of itching, pain and scaling at Week 16 and Week 52 (CLEAR) were demonstrated in the Psoriasis Symptom Diary© in patients treated with secukinumab compared to patients treated with ustekinumab.

Statistically significant improvements (decreases) at Week 12 from baseline in the scalp psoriasis study were demonstrated in patient reported signs and symptoms of scalp itching, pain and scaling compared to placebo.

Psoriatic arthritis
The safety and efficacy of Cosentyx were assessed in 1,999 patients in three randomised, double-blind, placebo-controlled phase III studies in patients with active psoriatic arthritis (≥3 swollen and ≥3 tender joints) despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or disease-modifying anti-rheumatic drug (DMARD) therapy. Patients with each subtype of PsA were enrolled in these studies, including polyarticular arthritis with no evidence of rheumatoid nodules, spondylitis with peripheral arthritis, asymmetric peripheral arthritis, distal interphalangeal involvement and arthritis mutilans. Patients in these studies had a diagnosis of PsA of at least five years. The majority of patients also had active psoriasis skin lesions or a documented history of psoriasis. Over 61% and 42% of the PsA patients had enthesitis and dactylitis at baseline, respectively. For all studies, the primary endpoint was American College of Rheumatology (ACR) 20 response. For Psoriatic Arthritis Study 1 (PsA Study 1) and Psoriatic Arthritis Study 2 (PsA Study 2), the primary endpoint was at Week 24. For Psoriatic Arthritis Study 3 (PsA Study 3), the primary endpoint was at Week 16 with the key secondary endpoint, the change from baseline in modified Total Sharp Score (mTSS), at Week 24.

In PsA Study 1, PsA Study 2 and PsA Study 3, 29%, 35% and 30% of patients, respectively, were previously treated with an anti-TNFα agent and discontinued the anti-TNFα agent for either lack of efficacy or intolerance (anti-TNFα-IR patients).

PsA Study 1 (FUTURE 1) evaluated 606 patients, of whom 60.7% had concomitant MTX. Patients randomised to Cosentyx received 10 mg/kg intravenously at Weeks 0, 2, and 4, followed by either 75 mg or 150 mg subcutaneously every month starting at Week 8. Patients randomised to placebo who were non-responders at Week 16 (early rescue) and other placebo patients at Week 24 were crossed over to receive Cosentyx (either 75 mg or 150 mg subcutaneously) followed by the same dose every month.

PsA Study 2 (FUTURE 2) evaluated 397 patients, of whom 46.6% had concomitant MTX. Patients randomised to Cosentyx received 75 mg, 150 mg or 300 mg subcutaneously at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month. Patients randomised to receive placebo who were non-responders at Week 16 (early rescue) were crossed over to receive Cosentyx (either 150 mg or 300 mg subcutaneously) at Week 16 followed by the same dose every month. Patients randomised to receive placebo who were responders at Week 16 were crossed over to receive Cosentyx (either 150 mg or 300 mg subcutaneously) at Week 24 followed by the same dose every month.

PsA Study 3 (FUTURE 5) evaluated 996 patients, of whom 50.1% had concomitant MTX. Patients were randomised to receive Cosentyx 150 mg, 300 mg or placebo subcutaneously at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month, or a once monthly injection of Cosentyx 150 mg (without loading). Patients randomised to receive placebo who were non-responders at Week 16 (early rescue) were then crossed over to receive Cosentyx (either 150 mg or 300 mg subcutaneously) at Week 16 followed by the same dose every month. Patients randomised to receive placebo who were responders at Week 16 were crossed over to receive Cosentyx (either 150 mg or 300 mg subcutaneously) at Week 24 followed by the same dose every month.

Signs and symptoms
Treatment with Cosentyx resulted in significant improvement in measures of disease activity compared to placebo at Weeks 16 and 24 (see Table 5).

Table 5 Clinical response in PsA Study 2 and PsA Study 3 at Week 16 and Week 24

	PsA Study 2			PsA Study 3		
	Placebo	150 mg[1]	300 mg[1]	Placebo	150 mg[1]	300 mg[1]
Number of patients randomised	98	100	100	332	220	222
ACR20 response n (%)						
Week 16	18 (18.4%)	60 (60.0%***)	57 (57.0%***)	91◊ (27.4%)	122◊ (55.5%***)	139◊ (62.6%***)
Week 24	15◊ (15.3%)	51◊ (51.0%***)	54◊ (54.0%***)	78 (23.5%)	117 (53.2%***)	141 (63.5%***)
ACR50 response n (%)						
Week 16	6 (6.1%)	37 (37.0%***)	35 (35.0%***)	27 (8.1%)	79 (35.9%*)	88 (39.6%*)
Week 24	7 (7.1%)	35 (35.0%)	35 (35.0%**)	29 (8.7%)	86 (39.1%***)	97 (43.7%***)
ACR70 response n (%)						
Week 16	2 (2.0%)	17 (17.0%**)	15 (15.0%**)	14 (4.2%)	40 (18.2%***)	45 (20.3%***)
Week 24	1 (1.0%)	21 (21.0%**)	20 (20.0%**)	13 (3.9%)	53 (24.1%***)	57 (25.7%***)
DAS28-CRP						
Week 16	-0.50	-1.45***	-1.51***	-0.63	-1.29*	-1.49*
Week 24	-0.96	-1.58**	-1.61**	-0.84	-1.57***	-1.68***
Number of patients with ≥3% BSA psoriasis skin involvement at baseline	43 (43.9%)	58 (58.0%)	41 (41.0%)	162 (48.8%)	125 (56.8%)	110 (49.5%)
PASI 75 response n (%)						
Week 16	3 (7.0%)	33 (56.9%***)	27 (65.9%***)	20 (12.3%)	75 (60.0%*)	77 (70.0%*)
Week 24	7 (16.3%)	28 (48.3%**)	26 (63.4%***)	29 (17.9%)	80 (64.0%***)	78 (70.9%***)
PASI 90 response n (%)						
Week 16	3 (7.0%)	22 (37.9%***)	18 (43.9%***)	15 (9.3%)	46 (36.8%*)	59 (53.6%*)
Week 24	4 (9.3%)	19 (32.8%**)	20 (48.8%***)	19 (11.7%)	51 (40.8%***)	60 (54.5%***)
Dactylitis resolution n (%) †						
Week 16	10 (37%)	21 (65.6%*)	26 (56.5%)	40 (32.3%)	46 (57.5%*)	54 (65.9%*)
Week 24	4 (14.8%)	16 (50.0%**)	26 (56.5%**)	42 (33.9%)	51 (63.8%***)	52 (63.4%***)

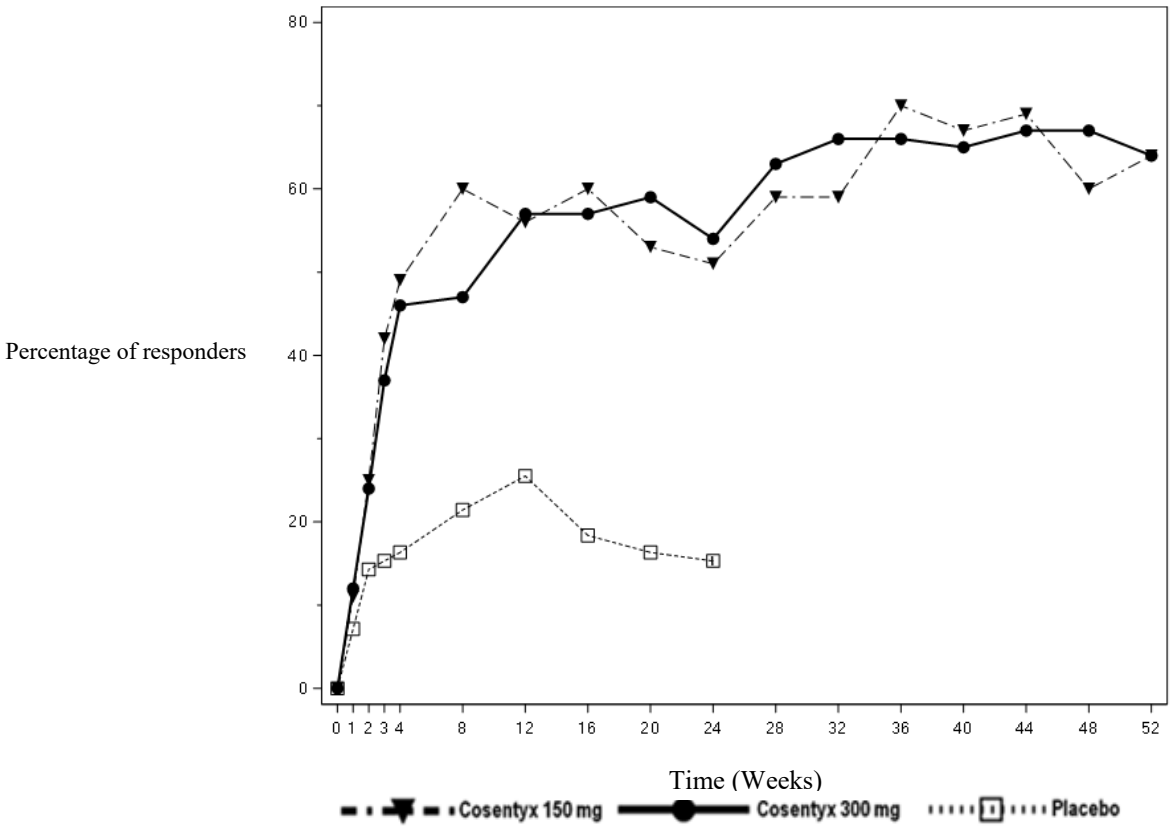
Enthesitis resolution n (%) ‡						
Week 16	17 (26.2%)	32 (50.0%**)	32 (57.1%***)	68 (35.4%)	77 (54.6%*)	78 (55.7%*)
Week 24	14 (21.5%)	27 (42.2%*)	27 (48.2%**)	66 (34.4%)	77 (54.6%***)	86 (61.4%***)

* p<0.05, ** p<0.01, *** p<0.001; versus placebo
All p-values are adjusted for multiplicity of testing based on pre-defined hierarchy at Week 24 for PsA Study 2, except for ACR70, Dactylitis and Enthesitis, which were exploratory endpoints and all endpoints at Week 16.
All p-values are adjusted for multiplicity of testing based on pre-defined hierarchy at Week 16 for PsA Study 3, except for ACR70 which was an exploratory endpoint and all endpoints at Week 24.
Non-responder imputation used for missing binary endpoint.
ACR: American College of Rheumatology; PASI: Psoriasis Area and Severity Index; DAS: Disease Activity Score; BSA: Body Surface Area
◊Primary Endpoint
[1]Cosentyx 150 mg or 300 mg s.c. at Weeks 0, 1, 2, 3, and 4 followed by the same dose every month
†In patients with dactylitis at baseline (n=27, 32, 46, respectively for PsA Study 2 and n=124, 80, 82, respectively for PsA Study 3)
‡In patients with enthesitis at baseline (n=65, 64, 56, respectively for PsA Study 2 and n=192, 141, 140, respectively for PsA Study 3)

The onset of action of Cosentyx occurred as early as Week 2. Statistically significant difference in ACR 20 versus placebo was reached at Week 3.

The percentage of patients achieving ACR 20 response by visit is shown in Figure 2.

Figure 2 ACR20 response in PsA Study 2 over time up to Week 52



Similar responses for primary and key secondary endpoints were seen in PsA patients regardless of whether they were on concomitant MTX treatment or not. In PsA Study 2, at Week 24, Cosentyx-treated patients with concomitant MTX use had a higher ACR 20 response (47.7% and 54.4% for 150 mg and 300 mg, respectively, compared to placebo 20.0%) and ACR 50 response (31.8% and 38.6% for 150 mg and 300 mg, respectively, compared to placebo 8.0%). Cosentyx-treated patients without concomitant MTX use had a higher ACR 20 response (53.6% and 53.6% for 150 mg and 300 mg, respectively, compared to placebo 10.4%) and ACR 50 response (37.5% and 32.1% for 150 mg and 300 mg, respectively, compared to placebo 6.3%).

In PsA Study 2, both anti-TNFα-naive and anti-TNFα-IR Cosentyx-treated patients had a significantly higher ACR 20 response compared to placebo at Week 24, with a slightly higher response in the anti-TNFα-naive group (anti-TNFα-naive: 64% and 58% for 150 mg and 300 mg, respectively, compared to placebo 15.9%; anti-TNFα-IR: 30% and 46% for 150 mg and 300 mg, respectively, compared to placebo 14.3%). In the anti-TNFα-IR patients subgroup, only the 300 mg dose showed significantly higher response rate for ACR 20 compared to placebo ($p<0.05$) and demonstrated clinical meaningful benefit over 150 mg on multiple secondary endpoints. Improvements in the PASI 75 response were seen in both subgroups and the 300 mg dose showed statistically significant benefit in the anti-TNFα-IR patients.

The number of PsA patients with axial involvement was too small to allow meaningful assessment.

Improvements were shown in all components of the ACR scores, including patient assessment of pain. In PsA Study 2, the proportion of patients achieving a modified PsA Response Criteria (PsARC) response was greater in the Cosentyx-treated patients (59.0% and 61.0% for 150 mg and 300 mg, respectively) compared to placebo (26.5%) at Week 24.

In PsA Study 1 and PsA Study 2, efficacy was maintained up to Week 104. In PsA Study 2, among 200 patients initially randomised to Cosentyx 150 mg and 300 mg, 178 (89%) patients were still on treatment at Week 52. Of the 100 patients randomised to Cosentyx 150 mg, 64, 39 and 20 had an ACR 20/50/70 response, respectively. Of the 100 patients randomised to Cosentyx 300 mg, 64, 44 and 24 had an ACR 20/50/70 response, respectively.

Radiographic response
In PsA Study 3, inhibition of progression of structural damage was assessed radiographically and expressed by the modified Total Sharp Score (mTSS) and its components, the Erosion Score (ES) and the Joint Space Narrowing Score (JSN). Radiographs of hands, wrists, and feet were obtained at baseline, Week 16 and/or Week 24 and scored independently by at least two readers who were blinded to treatment group and visit number. Cosentyx 150 mg and 300 mg treatment significantly inhibited the rate of progression of peripheral joint damage compared with placebo treatment as measured by change from baseline in mTSS at Week 24 (Table 6).

Inhibition of progression of structural damage was also assessed in PsA Study 1 at Weeks 24 and 52, compared to baseline. Week 24 data are presented in Table 6.

Table 6 Change in modified Total Sharp Score in psoriatic arthritis

	PsA Study 3			PsA Study 1	
	Placebo n=296	**Cosentyx 150 mg[1] n=213**	**Cosentyx 300 mg[1] n=217**	**Placebo n=179**	**Cosentyx 150 mg[2] n=185**
Total score					
Baseline (SD)	15.0 (38.2)	13.5 (25.6)	12.9 (23.8)	28.4 (63.5)	22.3 (48.0)
Mean change at Week 24	0.50	0.13*	0.02*	0.57	0.13*

*p<0.05 based on nominal, but non adjusted, p-value
[1]Cosentyx 150 mg or 300 mg s.c. at Weeks 0, 1, 2, 3, and 4 followed by the same dose every month
[2]10 mg/kg at Weeks 0, 2 and 4 followed by subcutaneous doses of 75 mg or 150 mg

In PsA Study 1, inhibition of structural damage was maintained with Cosentyx treatment up to Week 52.

In PsA Study 3, the percentage of patients with no disease progression (defined as a change from baseline in mTSS of ≤0.5) from randomisation to Week 24 was 80.3%, 88.5% and 73.6% for secukinumab 150 mg, 300 mg and placebo, respectively. An effect of inhibition of structural damage was observed in anti-TNFα-naïve and anti-TNFα-IR patients and in patients treated with and without concomitant MTX.

In PsA Study 1, the percentage of patients with no disease progression (defined as a change from baseline in mTSS of ≤0.5) from randomisation to Week 24 was 82.3% in secukinumab 10 mg/kg intravenous load – 150 mg subcutaneous maintenance and 75.7% in placebo. The percentage of patients with no disease progression from Week 24 to Week 52 for secukinumab 10 mg/kg intravenous load – followed by 150 mg subcutaneous maintenance and for placebo patients who switched to 75 mg or 150 mg subcutaneous every 4 weeks at Week 16 or Week 24 was 85.7% and 86.8%, respectively.

Physical function and health-related quality of life
In PsA Study 2 and PsA Study 3, patients treated with Cosentyx 150 mg (p=0.0555 and p<0.0001) and 300 mg (p=0.0040 and p<0.0001) showed improvement in physical function compared to patients treated with placebo as assessed by Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24 and Week 16, respectively. Improvements in HAQ-DI scores were seen regardless of previous anti-TNFα exposure. Similar responses were seen in PsA Study 1.

Cosentyx-treated patients reported significant improvements in health-related quality of life as measured by the Short Form-36 Health Survey Physical Component Summary (SF-36 PCS) score (p<0.001). There were also statistically significant improvements demonstrated in exploratory endpoints assessed by the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scores for 150 mg and 300 mg compared to placebo (7.97, 5.97 versus 1.63, respectively) and these improvements were maintained up to Week 104 in PsA Study 2.

Similar responses were seen in PsA Study 1 and efficacy was maintained up to Week 52.

Ankylosing spondylitis
The safety and efficacy of Cosentyx were assessed in 590 patients in two randomised, double-blind, placebo-controlled phase III studies in patients with active ankylosing spondylitis (AS) with a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or disease-modifying anti-rheumatic drug (DMARD) therapy. Patients in these studies had a diagnosis of AS for a median of 2.7 to 5.8 years. For both studies, the primary endpoint was at least a 20% improvement in Assessment of Spondyloarthritis International Society (ASAS 20) criteria at Week 16.

In Ankylosing Spondylitis Study 1 (AS Study 1) and Ankylosing Spondylitis Study 2 (AS Study 2) 27.0% and 38.8% of patients, respectively, were previously treated with an anti-TNFα agent and discontinued the anti-TNFα agent for either lack of efficacy or intolerance (anti-TNFα-IR patients).

AS Study 1 (MEASURE 1) evaluated 371 patients, of whom 14.8% and 33.4% used concomitant MTX or sulfasalazine, respectively. Patients randomised to Cosentyx received 10 mg/kg intravenously at Weeks 0, 2, and 4, followed by either 75 mg or 150 mg subcutaneously every month starting at Week 8. Patients randomised to placebo who were non-responders at Week 16 (early rescue) and all other placebo patients at Week 24 were crossed over to receive Cosentyx (either 75 mg or 150 mg subcutaneously), followed by the same dose every month.

AS Study 2 (MEASURE 2) evaluated 219 patients, of whom 11.9% and 14.2% used concomitant MTX or sulfasalazine, respectively. Patients randomised to Cosentyx received 75 mg or 150 mg subcutaneously at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month. At Week 16, patients who were randomised to placebo at baseline were re-randomised to receive Cosentyx (either 75 mg or 150 mg subcutaneously) every month.

Signs and symptoms
In AS Study 2, treatment with Cosentyx 150 mg resulted in greater improvement in measures of disease activity compared with placebo at Week 16 (see Table 7).

Table 7 Clinical response in AS Study 2 at Week 16

Outcome (p-value versus placebo)	**Placebo (n = 74)**	**75 mg (n = 73)**	**150 mg (n = 72)**
ASAS 20 response, %	28.4	41.1	61.1***
ASAS 40 response, %	10.8	26.0	36.1***
hsCRP, (post-BSL/BSL ratio)	1.13	0.61	0.55***
ASAS 5/6, %	8.1	34.2	43.1***
ASAS partial remission, %	4.1	15.1	13.9
BASDAI 50, %	10.8	24.7*	30.6**
ASDAS-CRP major improvement	4.1	15.1*	25.0***

* $p<0.05$, ** $p<0.01$, *** $p<0.001$; versus placebo
All p-values adjusted for multiplicity of testing based on pre-defined hierarchy, except BASDAI 50 and ASDAS-CRP
Non-responder imputation used for missing binary endpoint

ASAS: Assessment of SpondyloArthritis International Society Criteria; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; hsCRP: high-sensitivity C-reactive protein; ASDAS: Ankylosing Spondylitis Disease Activity Score; BSL: baseline

The onset of action of Cosentyx 150 mg occurred as early as Week 1 for ASAS 20 and Week 2 for ASAS 40 (superior to placebo) in AS Study 2.

ASAS 20 responses were improved at Week 16 in both anti-TNFα-naïve patients (68.2% versus 31.1%; $p<0.05$) and anti-TNFα-IR patients (50.0% versus 24.1%; $p<0.05$) for Cosentyx 150 mg compared with placebo, respectively.

In both AS studies, Cosentyx-treated patients (150 mg in AS Study 2 and both regimens in AS Study 1) demonstrated significantly improved signs and symptoms at Week 16, with comparable magnitude of response and efficacy maintained up to Week 52 in both anti-TNFα-naive and anti-TNFα-IR patients. In AS Study 2, among 72 patients initially randomised to Cosentyx 150 mg, 61 (84.7%) patients were still on treatment at Week 52. Of the 72 patients randomised to Cosentyx 150 mg, 45 and 35 had an ASAS 20/40 response, respectively.

Spinal mobility
Patients treated with Cosentyx 150 mg showed improvements in spinal mobility as measured by change from baseline in BASMI at Week 16 for both AS Study 1 (-0.40 versus -0.12 for placebo; p=0.0114) and AS Study 2 (-0.51 versus -0.22 for placebo; p=0.0533). These improvements were sustained up to Week 52.

Physical function and health-related quality of life
In AS Study 1 and Study 2, patients treated with Cosentyx 150 mg showed improvements in health-related quality of life as measured by AS Quality of Life Questionnaire (ASQoL) (p=0.001) and SF-36 Physical Component Summary (SF-36PCS) (p<0.001). Patients treated with Cosentyx 150 mg also showed statistically significant improvements on exploratory endpoints in physical function as assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI) compared to placebo (-2.15 versus -0.68), and in fatigue as assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale compared to placebo (8.10 versus 3.30). These improvements were sustained up to Week 52.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Cosentyx in plaque psoriasis in paediatric patients aged from birth to less than 6 years and in chronic idiopathic arthritis for paediatric patients aged from birth to less than 2 years (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with Cosentyx in plaque psoriasis in paediatric patients aged from 6 years to less than 18 years and in chronic idiopathic arthritis for paediatric patients aged from 2 years to less than 18 years (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Plaque psoriasis

Absorption
Following a single subcutaneous dose of 300 mg as a liquid formulation in healthy volunteers, secukinumab reached peak serum concentrations of 43.2±10.4 µg/ml between 2 and 14 days post dose.

Based on population pharmacokinetic analysis, following a single subcutaneous dose of either 150 mg or 300 mg in plaque psoriasis patients, secukinumab reached peak serum concentrations of 13.7±4.8 µg/ml or 27.3±9.5 µg/ml, respectively, between 5 and 6 days post dose.

After initial weekly dosing during the first month, time to reach the maximum concentration was between 31 and 34 days based on population pharmacokinetic analysis.

On the basis of simulated data, peak concentrations at steady-state ($C_{max,ss}$) following subcutaneous administration of 150 mg or 300 mg were 27.6 µg/ml and 55.2 µg/ml, respectively. Population pharmacokinetic analysis suggests that steady-state is reached after 20 weeks with monthly dosing regimens.

Compared with exposure after a single dose, the population pharmacokinetic analysis showed that patients exhibited a 2-fold increase in peak serum concentrations and area under the curve (AUC) following repeated monthly dosing during maintenance.

Population pharmacokinetic analysis showed that secukinumab was absorbed with an average absolute bioavailability of 73% in patients with plaque psoriasis. Across studies, absolute bioavailabilities in the range between 60 and 77% were calculated.

Distribution
The mean volume of distribution during the terminal phase (V_z) following single intravenous administration ranged from 7.10 to 8.60 litres in plaque psoriasis patients, suggesting that secukinumab undergoes limited distribution to peripheral compartments.

Biotransformation
The majority of IgG elimination occurs via intracellular catabolism, following fluid-phase or receptor mediated endocytosis.

Elimination
Mean systemic clearance (CL) following a single intravenous administration to patients with plaque psoriasis ranged from 0.13 to 0.36 l/day. In a population pharmacokinetic analysis, the mean systemic clearance (CL) was 0.19 l/day in plaque psoriasis patients. The CL was not impacted by gender. Clearance was dose- and time-independent.

The mean elimination half-life, as estimated from population pharmacokinetic analysis, was 27 days in plaque psoriasis patients, ranging from 18 to 46 days across psoriasis studies with intravenous administration.

Linearity/non-linearity
The single and multiple dose pharmacokinetics of secukinumab in plaque psoriasis patients were determined in several studies with intravenous doses ranging from 1x 0.3 mg/kg to 3x 10 mg/kg and with subcutaneous doses ranging from 1x 25 mg to multiple doses of 300 mg. Exposure was dose proportional across all dosing regimens.

Psoriatic arthritis

The pharmacokinetic properties of secukinumab observed in psoriatic arthritis patients were similar to those displayed in plaque psoriasis patients. The bioavailability of secukinumab in PsA patients was 85% on the basis of the population pharmacokinetic model.

Ankylosing spondylitis

The pharmacokinetic properties of secukinumab observed in ankylosing spondylitis patients were similar to those displayed in plaque psoriasis patients.

Special populations

Elderly patients
Of the 3,430 plaque psoriasis patients exposed to Cosentyx in clinical studies, a total of 230 patients were 65 years of age or older and 32 patients were 75 years of age or older.

Of the 2,536 psoriatic arthritis patients exposed to Cosentyx in clinical studies, a total of 236 patients were 65 years of age or older and 25 patients were 75 years of age or older.

Of the 571 ankylosing spondylitis patients exposed to Cosentyx in clinical studies, a total of 24 patients were 65 years of age or older and 3 patients were 75 years of age or older.

Based on population pharmacokinetic analysis with a limited number of elderly patients (n=71 for age ≥65 years and n=7 for age ≥75 years), clearance in elderly patients and patients less than 65 years of age was similar.

Patients with renal or hepatic impairment
No pharmacokinetic data are available in patients with renal or hepatic impairment. The renal elimination of intact Cosentyx, an IgG monoclonal antibody, is expected to be low and of minor importance. IgGs are mainly eliminated via catabolism and hepatic impairment is not expected to influence clearance of Cosentyx.

Effect of weight on pharmacokinetics
Secukinumab clearance and volume of distribution increase as body weight increases.

5.3 Preclinical safety data

Non-clinical data revealed no special risks for humans based on tissue cross-reactivity testing, safety pharmacology, repeated dose and reproductive toxicity studies performed with secukinumab or a murine anti-murine IL-17A antibody.

Since secukinumab binds to cynomolgus monkey and human IL-17A, its safety was studied in the cynomolgus monkey. No undesirable effects of secukinumab were seen following subcutaneous administration to cynomolgus monkeys for up to 13 weeks and intravenous administration up to 26 weeks (including pharmacokinetic, pharmacodynamic, immunogenicity and immunotoxicity (e.g. T-cell dependent antibody response and NK cell activity) evaluations). The average serum concentrations observed in monkeys after 13 weekly subcutaneous doses of 150 mg/kg were considerably higher than the predicted average serum concentration expected in psoriatic patients at the highest clinical dose. Antibodies to secukinumab were detected in only one of the exposed animals. No non-specific tissue cross-reactivity was observed when secukinumab was applied to normal human tissue.

Animal studies have not been conducted to evaluate the carcinogenic potential of secukinumab.

In an embryofoetal development study in cynomolgus monkeys, secukinumab showed no maternal toxicity, embryotoxicity or teratogenicity when administered throughout organogenesis and late gestation.

No undesirable effects of a murine anti-murine IL-17A antibody were seen in fertility and early embryonic development and pre-and postnatal development studies in mice. The high dose used in these studies was in excess of the maximum effective dose in terms of IL-17A suppression and activity (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
L-histidine
L-histidine hydrochloride monohydrate
Polysorbate 80

6.2 Incompatibilities

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

6.3 Shelf life

3 years

After reconstitution

Chemical and physical in-use stability has been demonstrated for 24 hours at 2ºC to 8ºC.
From a microbiological point of view, unless the method of reconstitution 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 the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
For storage conditions after reconstitution of the medicinal product, see section 6.3

6.5 Nature and contents of container

Cosentyx is supplied in a colourless glass vial with a grey coated rubber stopper and aluminium cap with a white flip-off component containing 150 mg of secukinumab.

Cosentyx is available in packs containing one vial.

6.6 Special precautions for disposal and other handling

The single-use vial contains 150 mg secukinumab for reconstitution with sterile water for injections. The resulting solution should be clear and colourless to slightly yellow. Do not use if the lyophilised powder has not fully dissolved or if the liquid contains easily visible particles, is cloudy or is distinctly brown. Detailed instructions for use are provided in the package leaflet.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/980/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15.01.2015

10. DATE OF REVISION OF THE TEXT

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

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Cosentyx 150 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 150 mg secukinumab* in 1 ml.

*Secukinumab is a recombinant fully human monoclonal antibody selective for interleukin-17A. Secukinumab is of the IgG1/κ-class produced in Chinese Hamster Ovary (CHO) cells.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe (injection)

The solution is clear and colourless to slightly yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Plaque psoriasis

Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Psoriatic arthritis

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

Ankylosing spondylitis

Cosentyx is indicated for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

4.2 Posology and method of administration

Cosentyx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Cosentyx is indicated.

Posology

Plaque psoriasis
The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Each 300 mg dose is given as two subcutaneous injections of 150 mg.

Psoriatic arthritis
For patients with concomitant moderate to severe plaque psoriasis or who are anti-TNFα inadequate responders (IR), the recommended dose is 300 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Each 300 mg dose is given as two subcutaneous injections of 150 mg.

For other patients, the recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Based on clinical response, the dose can be increased to 300 mg.

Ankylosing spondylitis
The recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing.

For all of the above indications, available data suggest that a clinical response is usually achieved within 16 weeks of treatment. Consideration should be given to discontinuing treatment in patients who have shown no response by 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks.

Special populations

Elderly patients (aged 65 years and over)
No dose adjustment is required (see section 5.2).

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

Paediatric population
The safety and efficacy of Cosentyx in children below the age of 18 years have not yet been established. No data are available.

Method of administration

Cosentyx is to be administered by subcutaneous injection. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

After proper training in subcutaneous injection technique, patients may self-inject Cosentyx if a physician determines that this is appropriate. However, the physician should ensure appropriate follow-up of patients. Patients should be instructed to inject the full amount of Cosentyx according to the instructions provided in the package leaflet. Comprehensive instructions for administration are given in the package leaflet.

4.3 Contraindications

Severe hypersensitivity reactions 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

Infections

Cosentyx has the potential to increase the risk of infections. Serious infections have been observed in patients receiving Cosentyx in the post-marketing setting. Caution should be exercised when considering the use of Cosentyx in patients with a chronic infection or a history of recurrent infection.

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 Cosentyx should not be administered until the infection resolves.

In clinical studies, infections have been observed in patients receiving Cosentyx (see section 4.8). Most of these were mild or moderate upper respiratory tract infections such as nasopharyngitis and did not require treatment discontinuation.

Related to the mechanism of action of Cosentyx, non-serious mucocutaneous candida infections were more frequently reported for secukinumab than placebo in the psoriasis clinical studies (3.55 per 100 patient years for secukinumab 300 mg versus 1.00 per 100 patient years for placebo) (see section 4.8).

No increased susceptibility to tuberculosis was reported from clinical studies. However, Cosentyx should not be given to patients with active tuberculosis. Anti-tuberculosis therapy should be considered prior to initiation of Cosentyx in patients with latent tuberculosis.

Inflammatory bowel disease

Cases of new or exacerbations of Crohn's disease and ulcerative colitis have been reported. Caution should be exercised when prescribing Cosentyx to patients with inflammatory bowel disease, including Crohn's disease and ulcerative colitis. Patients should be closely monitored.

Hypersensitivity reactions

In clinical studies, rare cases of anaphylactic reactions have been observed in patients receiving Cosentyx. If an anaphylactic or other serious allergic reactions occur, administration of Cosentyx should be discontinued immediately and appropriate therapy initiated.

Latex-sensitive individuals

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

Vaccinations

Live vaccines should not be given concurrently with Cosentyx.

Patients receiving Cosentyx may receive concurrent inactivated or non-live vaccinations. In a study, after *meningococcal* and inactivated *influenza* vaccinations, a similar proportion of healthy volunteers treated with 150 mg of secukinumab and those treated with placebo were able to mount an adequate immune response of at least a 4-fold increase in antibody titres to *meningococcal* and *influenza* vaccines. The data suggest that Cosentyx does not suppress the humoral immune response to the *meningococcal* or *influenza* vaccines.

Concomitant immunosuppressive therapy

In psoriasis studies, the safety and efficacy of Cosentyx in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated (see also section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

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

In a study in subjects with plaque psoriasis, no interaction was observed between secukinumab and midazolam (CYP3A4 substrate).

No interaction was seen when Cosentyx was administered concomitantly with methotrexate (MTX) and/or corticosteroids in arthritis studies (including in patients with psoriatic arthritis and ankylosing spondylitis).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use an effective method of contraception during treatment and for at least 20 weeks after treatment.

Pregnancy

There are no adequate data from the use of secukinumab 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 Cosentyx in pregnancy.

Breast-feeding

It is not known whether secukinumab is excreted in human milk. Immunoglobulins are excreted in human milk and it is not known if secukinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from secukinumab, a decision on whether to discontinue breast-feeding during treatment and up to 20 weeks after treatment or to discontinue therapy with Cosentyx must be made taking into account the benefit of breast-feeding to the child and the benefit of Cosentyx therapy to the woman.

Fertility

The effect of secukinumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Over 11,900 patients have been treated with Cosentyx in blinded and open-label clinical studies in various indications (plaque psoriasis, psoriatic arthritis, ankylosing spondylitis and other autoimmune conditions), representing 20,995 patient years of exposure. Of these, over 7,100 patients were exposed to Cosentyx for at least one year.

Adverse reactions in plaque psoriasis

Four placebo-controlled phase III studies in plaque psoriasis were pooled to evaluate the safety of Cosentyx in comparison to placebo up to 12 weeks after treatment initiation. In total, 2,076 patients were evaluated (692 patients on 150 mg, 690 patients on 300 mg and 694 patients on placebo).

The most frequently reported adverse drug reactions (ADRs) were upper respiratory tract infections (most frequently nasopharyngitis, rhinitis). Most of the reactions were mild or moderate in severity.

Adverse reactions in psoriatic arthritis

In Cosentyx placebo-controlled psoriatic arthritis studies, there were 2,754 patients (1,871 patients on Cosentyx and 883 patients on placebo) with a total exposure of 4,478 patient-years of study exposure on Cosentyx. The safety profile observed in patients with psoriatic arthritis treated with Cosentyx is consistent with the safety profile in psoriasis.

Adverse reactions in ankylosing spondylitis

Cosentyx was studied in two placebo-controlled ankylosing spondylitis studies with 590 patients (394 patients on Cosentyx and 196 patients on placebo) for a total of 755 patient-years of study exposure (median duration of exposure for secukinumab-treated patients: 469 days in AS Study 1 and 460 days in AS Study 2). The safety profile observed in patients with ankylosing spondylitis treated with Cosentyx is consistent with the safety profile in psoriasis.

Tabulated list of adverse reactions

ADRs from psoriasis, psoriatic arthritis and ankylosing spondylitis clinical studies as well as from post-marketing experience (Table 1) are listed by MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available data).

Table 1 List of adverse reactions in clinical studies[1)] and post-marketing experience

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Very common	Upper respiratory tract infections
	Common	Oral herpes
	Uncommon	Oral candidiasis
		Tinea pedis
		Otitis externa
	Not known	Mucosal and cutaneous candidiasis (including oesophageal candidiasis)
Blood and lymphatic system disorders	Uncommon	Neutropenia
Immune system disorders	Rare	Anaphylactic reactions
Eye disorders	Uncommon	Conjunctivitis
Respiratory, thoracic and mediastinal disorders	Common	Rhinorrhoea
Gastrointestinal disorders	Common	Diarrhoea
Skin and subcutaneous disorders	Uncommon	Urticaria
[1)] Placebo-controlled clinical studies (phase III) in plaque psoriasis, PsA and AS patients exposed to 300 mg, 150 mg, 75 mg or placebo up to 12 weeks (psoriasis) or 16 weeks (PsA and AS) treatment duration		

Description of selected adverse reactions

Infections

In the placebo-controlled period of clinical studies in plaque psoriasis (a total of 1,382 patients treated with Cosentyx and 694 patients treated with placebo for up to 12 weeks), infections were reported in 28.7% of patients treated with Cosentyx compared with 18.9% of patients treated with placebo. The majority of infections consisted of non-serious and mild to moderate upper respiratory tract infections, such as nasopharyngitis, which did not necessitate treatment discontinuation. There was an increase in mucosal or cutaneous candidiasis, consistent with the mechanism of action, but the cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in 0.14% of patients treated with Cosentyx and in 0.3% of patients treated with placebo (see section 4.4).

Over the entire treatment period (a total of 3,430 patients treated with Cosentyx for up to 52 weeks for the majority of patients), infections were reported in 47.5% of patients treated with Cosentyx (0.9 per patient-year of follow-up). Serious infections were reported in 1.2% of patients treated with Cosentyx (0.015 per patient-year of follow-up).

Infection rates observed in psoriatic arthritis and ankylosing spondylitis clinical studies were similar to those observed in the psoriasis studies.

Neutropenia

In psoriasis phase 3 clinical studies, neutropenia was more frequently observed with secukinumab than with placebo, but most cases were mild, transient and reversible. Neutropenia <1.0-0.5x10^9/l (CTCAE Grade 3) was reported in 18 out of 3,430 (0.5%) patients on secukinumab, with no dose dependence and no temporal relationship to infections in 15 out of 18 cases. There were no reported cases of more severe neutropenia. Non-serious infections with usual response to standard care and not requiring discontinuation of Cosentyx were reported in the remaining 3 cases.

The frequency of neutropenia in psoriatic arthritis and ankylosing spondylitis is similar to psoriasis.

Rare cases of neutropenia <$0.5x10^9$/l (CTCAE Grade 4) were reported.

Hypersensitivity reactions
In clinical studies, urticaria and rare cases of anaphylactic reaction to Cosentyx were observed (see also section 4.4).

Immunogenicity
In psoriasis, psoriatic arthritis and ankylosing spondylitis clinical studies, less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. About half of the treatment-emergent anti-drug antibodies were neutralising, but this was not associated with loss of efficacy or pharmacokinetic abnormalities.

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

No cases of overdose have been reported in clinical studies.

Doses up to 30 mg/kg (approximately 2000 to 3000 mg) have been administered intravenously in clinical studies without dose-limiting toxicity. In the event 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: L04AC10

Mechanism of action

Secukinumab is a fully human IgG1/κ monoclonal antibody that selectively binds to and neutralises the proinflammatory cytokine interleukin-17A (IL-17A). Secukinumab works by targeting IL-17A and inhibiting its interaction with the IL-17 receptor, which is expressed on various cell types including keratinocytes. As a result, secukinumab inhibits the release of proinflammatory cytokines, chemokines and mediators of tissue damage and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases. Clinically relevant levels of secukinumab reach the skin and reduce local inflammatory markers. As a direct consequence treatment with secukinumab reduces erythema, induration and desquamation present in plaque psoriasis lesions.

IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. IL-17A plays a key role in the pathogenesis of plaque psoriasis, psoriatic arthritis and ankylosing spondylitis and is up-regulated in lesional skin in contrast to non-lesional skin of plaque psoriasis patients and in synovial tissue of psoriatic arthritis patients. The frequency of IL-17-producing cells was also significantly higher in the subchondral bone marrow of facet joints from patients with ankylosing spondylitis.

Pharmacodynamic effects

Serum levels of total IL-17A (free and secukinumab-bound IL-17A) are initially increased in patients receiving secukinumab. This is followed by a slow decrease due to reduced clearance of secukinumab-bound IL-17A, indicating that secukinumab selectively captures free IL-17A, which plays a key role in the pathogenesis of plaque psoriasis.

In a study with secukinumab, infiltrating epidermal neutrophils and various neutrophil-associated markers that are increased in lesional skin of plaque psoriasis patients were significantly reduced after one to two weeks of treatment.

Secukinumab has been shown to lower (within 1 to 2 weeks of treatment) levels of C-reactive protein, which is a marker of inflammation.

Clinical efficacy and safety

Plaque psoriasis
The safety and efficacy of Cosentyx were assessed in four randomised, double-blind, placebo-controlled phase III studies in patients with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy [ERASURE, FIXTURE, FEATURE, JUNCTURE]. The efficacy and safety of Cosentyx 150 mg and 300 mg were evaluated versus either placebo or etanercept. In addition, one study assessed a chronic treatment regimen versus a "retreatment as needed" regimen [SCULPTURE].

Of the 2,403 patients who were included in the placebo-controlled studies, 79% were biologic-naive, 45% were non-biologic failures and 8% were biologic failures (6% were anti-TNF failures, and 2% were anti-p40 failures). Approximately 15 to 25% of patients in phase III studies had psoriatic arthritis (PsA) at baseline.

Psoriasis Study 1 (ERASURE) evaluated 738 patients. Patients randomised to Cosentyx received 150 mg or 300 mg doses at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month. Psoriasis Study 2 (FIXTURE) evaluated 1,306 patients. Patients randomised to Cosentyx received 150 mg or 300 mg doses at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month. Patients randomised to etanercept received 50 mg doses twice per week for 12 weeks followed by 50 mg every week. In both Study 1 and Study 2, patients randomised to receive placebo who were non-responders at Week 12 then crossed over to receive Cosentyx (either 150 mg or 300 mg) at Weeks 12, 13, 14, and 15, followed by the same dose every month starting at Week 16. All patients were followed for up to 52 weeks following first administration of study treatment.

Psoriasis Study 3 (FEATURE) evaluated 177 patients using a pre-filled syringe compared with placebo after 12 weeks of treatment to assess the safety, tolerability, and usability of Cosentyx self-administration via the pre-filled syringe. Psoriasis Study 4 (JUNCTURE) evaluated 182 patients using a pre-filled pen compared with placebo after 12 weeks of treatment to assess the safety, tolerability, and usability of Cosentyx self-administration via the pre-filled pen. In both Study 3 and Study 4, patients randomised to Cosentyx received 150 mg or 300 mg doses at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month. Patients were also randomised to receive placebo at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month.

Psoriasis Study 5 (SCULPTURE) evaluated 966 patients. All patients received Cosentyx 150 mg or 300 mg doses at Weeks 0, 1, 2, 3, 4, 8 and 12 and then were randomised to receive either a maintenance regimen of the same dose every month starting at Week 12 or a "retreatment as needed" regimen of the same dose. Patients randomised to "retreatment as needed" did not achieve adequate maintenance of response and therefore a fixed monthly maintenance regimen is recommended.

The co-primary endpoints in the placebo and active-controlled studies were the proportion of patients who achieved a PASI 75 response and IGA mod 2011 "clear" or "almost clear" response versus placebo at Week 12 (see Tables 2 and 3). The 300 mg dose provided improved skin clearance particularly for "clear" or "almost clear" skin across the efficacy endpoints of PASI 90, PASI 100, and IGA mod 2011 0 or 1 response across all studies with peak effects seen at Week 16, therefore this dose is recommended.

Table 2 Summary of PASI 50/75/90/100 & IGA* mod 2011 "clear" or "almost clear" clinical response in Psoriasis Studies 1, 3 and 4 (ERASURE, FEATURE and JUNCTURE)

		Week 12		Week 16		Week 52	
	Placebo	**150 mg**	**300 mg**	**150 mg**	**300 mg**	**150 mg**	**300 mg**
Study 1							
Number of patients	246	244	245	244	245	244	245
PASI 50 response n (%)	22 (8.9%)	203 (83.5%)	222 (90.6%)	212 (87.2%)	224 (91.4%)	187 (77%)	207 (84.5%)
PASI 75 response n (%)	11 (4.5%)	174 (71.6%)**	200 (81.6%)**	188 (77.4%)	211 (86.1%)	146 (60.1%)	182 (74.3%)
PASI 90 response n (%)	3 (1.2%)	95 (39.1%)**	145 (59.2%)**	130 (53.5%)	171 (69.8%)	88 (36.2%)	147 (60.0%)
PASI 100 response n (%)	2 (0.8%)	31 (12.8%)	70 (28.6%)	51 (21.0%)	102 (41.6%)	49 (20.2%)	96 (39.2%)
IGA mod 2011 "clear" or "almost clear" response n (%)	6 (2.40%)	125 (51.2%)**	160 (65.3%)**	142 (58.2%)	180 (73.5%)	101 (41.4%)	148 (60.4%)
Study 3							
Number of patients	59	59	58	-	-	-	-
PASI 50 response n (%)	3 (5.1%)	51 (86.4%)	51 (87.9%)	-	-	-	-
PASI 75 response n (%)	0 (0.0%)	41 (69.5%)**	44 (75.9%)**	-	-	-	-
PASI 90 response n (%)	0 (0.0%)	27 (45.8%)	35 (60.3%)	-	-	-	-
PASI 100 response n (%)	0 (0.0%)	5 (8.5%)	25 (43.1%)	-	-	-	-
IGA mod 2011 "clear" or "almost clear" response n (%)	0 (0.0%)	31 (52.5%)**	40 (69.0%)**	-	-	-	-
Study 4							
Number of patients	61	60	60	-	-	-	-
PASI 50 response n (%)	5 (8.2%)	48 (80.0%)	58 (96.7%)	-	-	-	-
PASI 75 response n (%)	2 (3.3%)	43 (71.7%)**	52 (86.7%)**	-	-	-	-
PASI 90 response n (%)	0 (0.0%)	24 (40.0%)	33 (55.0%)	-	-	-	-
PASI 100 response n(%)	0 (0.0%)	10 (16.7%)	16 (26.7%)	-	-	-	-
IGA mod 2011 "clear" or "almost clear" response n (%)	0 (0.0%)	32 (53.3%)**	44 (73.3%)**	-	-	-	-

* The IGA mod 2011 is a 5-category scale including "0 = clear", "1 = almost clear", "2 = mild", "3 = moderate" or "4 = severe", indicating the physician's overall assessment of the psoriasis severity focusing on induration, erythema and scaling. Treatment success of "clear" or "almost clear" consisted of no signs of psoriasis or normal to pink colouration of lesions, no thickening of the plaque and none to minimal focal scaling.

** p values versus placebo and adjusted for multiplicity: $p<0.0001$.

Table 3 Summary of clinical response on Psoriasis Study 2 (FIXTURE)

	Week 12				Week 16			Week 52		
	Placebo	**150 mg**	**300 mg**	**Etanercept**	**150 mg**	**300 mg**	**Etanercept**	**150 mg**	**300 mg**	**Etanercept**
Number of patients	324	327	323	323	327	323	323	327	323	323
PASI 50 response n (%)	49 (15.1%)	266 (81.3%)	296 (91.6%)	226 (70.0%)	290 (88.7%)	302 (93.5%)	257 (79.6%)	249 (76.1%)	274 (84.8%)	234 (72.4%)
PASI 75 response n (%)	16 (4.9%)	219 (67.0%) **	249 (77.1%) **	142 (44.0%)	247 (75.5%)	280 (86.7%)	189 (58.5%)	215 (65.7%)	254 (78.6%)	179 (55.4%)
PASI 90 response n (%)	5 (1.5%)	137 (41.9%)	175 (54.2%)	67 (20.7%)	176 (53.8%)	234 (72.4%)	101 (31.3%)	147 (45.0%)	210 (65.0%)	108 (33.4%)
PASI 100 response n (%)	0 (0%)	47 (14.4%)	78 (24.1%)	14 (4.3%)	84 (25.7%)	119 (36.8%)	24 (7.4%)	65 (19.9%)	117 (36.2%)	32 (9.9%)
IGA mod 2011 “clear” or “almost clear” response n (%)	9 (2.8%)	167 (51.1%) **	202 (62.5%) **	88 (27.2%)	200 (61.2%)	244 (75.5%)	127 (39.3%)	168 (51.4%)	219 (67.8%)	120 (37.2%)

** p values versus etanercept: p=0.0250

In an additional psoriasis study (CLEAR) 676 patients were evaluated. Secukinumab 300 mg met the primary and secondary endpoints by showing superiority to ustekinumab based on PASI 90 response at Week 16 (primary endpoint), speed of onset of PASI 75 response at Week 4, and long-term PASI 90 response at Week 52. Greater efficacy of secukinumab compared to ustekinumab for the endpoints PASI 75/90/100 and IGA mod 2011 0 or 1 response (“clear” or “almost clear”) was observed early and continued through to Week 52.

Table 4 Summary of clinical response on CLEAR Study

	Week 4		Week 16		Week 52	
	Secukinumab 300 mg	**Ustekinumab***	**Secukinumab 300 mg**	**Ustekinumab***	**Secukinumab 300 mg**	**Ustekinumab***
Number of patients	334	335	334	335	334	335
PASI 75 response n (%)	166 (49.7%)**	69 (20.6%)	311 (93.1%)	276 (82.4%)	306 (91.6%)	262 (78.2%)
PASI 90 response n (%)	70 (21.0%)	18 (5.4%)	264 (79.0%)**	192 (57.3%)	250 (74.9%)***	203 (60.6%)
PASI 100 response n (%)	14 (4.2%)	3 (0.9%)	148 (44.3%)	95 (28.4%)	150 (44.9%)	123 (36.7%)
IGA mod 2011 “clear” or “almost clear” response n (%)	128 (38.3%)	41 (12.2%)	278 (83.2%)	226 (67.5%)	261 (78.1%)	213 (63.6%)

* Patients treated with secukinumab received 300 mg doses at Weeks 0, 1, 2 3 and 4, followed by the same dose every 4 weeks until Week 52. Patients treated with ustekinumab received 45 mg or 90 mg at Weeks 0 and 4, then every 12 weeks until Week 52 (dosed by weight as per approved posology)

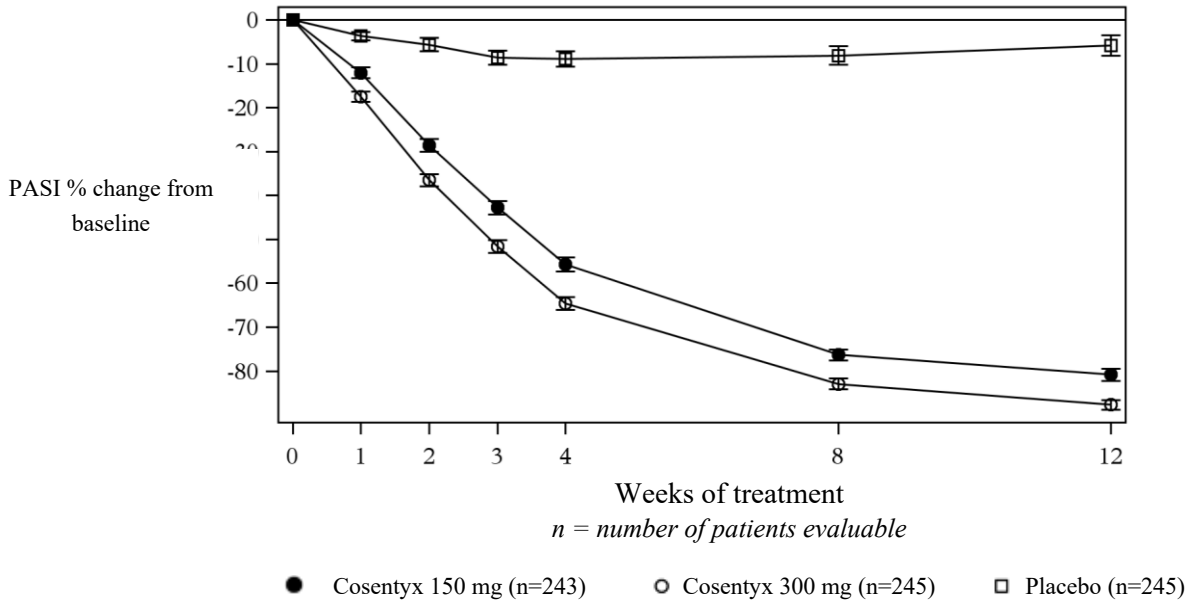
** p values versus ustekinumab: p<0.0001 for primary endpoint of PASI 90 at Week 16 and secondary endpoint of PASI 75 at Week 4

*** p values versus ustekinumab: p=0.0001 for secondary endpoint of PASI 90 at Week 52

Cosentyx was efficacious in systemic treatment-naive, biologic-naive, biologic/anti-TNF-exposed and biologic/anti-TNF-failure patients. Improvements in PASI 75 in patients with concurrent psoriatic arthritis at baseline were similar to those in the overall plaque psoriasis population.

Cosentyx was associated with a fast onset of efficacy with a 50% reduction in mean PASI by Week 3 for the 300 mg dose.

Figure 1 Time course of percentage change from baseline of mean PASI score in Study 1 (ERASURE)



Specific locations/forms of plaque psoriasis
In two additional placebo-controlled studies, improvement was seen in both nail psoriasis (TRANSFIGURE, 198 patients) and palmoplantar plaque psoriasis (GESTURE, 205 patients). In the TRANSFIGURE Study, secukinumab was superior to placebo at Week 16 (46.1% for 300 mg, 38.4% for 150 mg and 11.7% for placebo) as assessed by significant improvement from baseline in the Nail Psoriasis Severity Index (NAPSI %) for patients with moderate to severe plaque psoriasis with nail involvement. In the GESTURE Study, secukinumab was superior to placebo at Week 16 (33.3% for 300 mg, 22.1% for 150 mg, and 1.5% for placebo) as assessed by significant improvement of ppIGA 0 or 1 response ("clear" or "almost clear") for patients with moderate to severe palmoplantar plaque psoriasis.

A placebo-controlled study evaluated 102 patients with moderate to severe scalp psoriasis, defined as having a Psoriasis Scalp Severity Index (PSSI) score of ≥12, an IGA mod 2011 scalp only score of 3 or greater and at least 30% of the scalp surface area affected. Secukinumab 300 mg was superior to placebo at Week 12 as assessed by significant improvement from baseline in both the PSSI 90 response (52.9% versus 2.0%) and IGA mod 2011 0 or 1 scalp only response (56.9% versus 5.9%). Improvement in both endpoints was sustained for secukinumab patients who continued treatment through to Week 24.

Quality of life/patient-reported outcomes
Statistically significant improvements at Week 12 (Studies 1-4) from baseline compared to placebo were demonstrated in the DLQI (Dermatology Life Quality Index). Mean decreases (improvements) in DLQI from baseline ranged from -10.4 to -11.6 with secukinumab 300 mg, from -7.7 to -10.1 with secukinumab 150 mg, versus -1.1 to -1.9 for placebo at Week 12. These improvements were maintained for 52 weeks (Studies 1 and 2).

Forty percent of the participants in Studies 1 and 2 completed the Psoriasis Symptom Diary©. For the participants completing the diary in each of these studies, statistically significant improvements at Week 12 from baseline compared to placebo in patient-reported signs and symptoms of itching, pain and scaling were demonstrated.

Statistically significant improvements at Week 4 from baseline in patients treated with secukinumab compared to patients treated with ustekinumab (CLEAR) were demonstrated in the DLQI and these improvements were maintained for up to 52 weeks.

Statistically significant improvements in patient-reported signs and symptoms of itching, pain and scaling at Week 16 and Week 52 (CLEAR) were demonstrated in the Psoriasis Symptom Diary© in patients treated with secukinumab compared to patients treated with ustekinumab.

Statistically significant improvements (decreases) at Week 12 from baseline in the scalp psoriasis study were demonstrated in patient reported signs and symptoms of scalp itching, pain and scaling compared to placebo.

Psoriatic arthritis
The safety and efficacy of Cosentyx were assessed in 1,999 patients in three randomised, double-blind, placebo-controlled phase III studies in patients with active psoriatic arthritis (≥3 swollen and ≥3 tender joints) despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or disease-modifying anti-rheumatic drug (DMARD) therapy. Patients with each subtype of PsA were enrolled in these studies, including polyarticular arthritis with no evidence of rheumatoid nodules, spondylitis with peripheral arthritis, asymmetric peripheral arthritis, distal interphalangeal involvement and arthritis mutilans. Patients in these studies had a diagnosis of PsA of at least five years. The majority of patients also had active psoriasis skin lesions or a documented history of psoriasis. Over 61% and 42% of the PsA patients had enthesitis and dactylitis at baseline, respectively. For all studies, the primary endpoint was American College of Rheumatology (ACR) 20 response. For Psoriatic Arthritis Study 1 (PsA Study 1) and Psoriatic Arthritis Study 2 (PsA Study 2), the primary endpoint was at Week 24. For Psoriatic Arthritis Study 3 (PsA Study 3), the primary endpoint was at Week 16 with the key secondary endpoint, the change from baseline in modified Total Sharp Score (mTSS), at Week 24.

In PsA Study 1, PsA Study 2 and PsA Study 3, 29%, 35% and 30% of patients, respectively, were previously treated with an anti-TNFα agent and discontinued the anti-TNFα agent for either lack of efficacy or intolerance (anti-TNFα-IR patients).

PsA Study 1 (FUTURE 1) evaluated 606 patients, of whom 60.7% had concomitant MTX. Patients randomised to Cosentyx received 10 mg/kg intravenously at Weeks 0, 2, and 4, followed by either 75 mg or 150 mg subcutaneously every month starting at Week 8. Patients randomised to placebo who were non-responders at Week 16 (early rescue) and other placebo patients at Week 24 were crossed over to receive Cosentyx (either 75 mg or 150 mg subcutaneously) followed by the same dose every month.

PsA Study 2 (FUTURE 2) evaluated 397 patients, of whom 46.6% had concomitant MTX. Patients randomised to Cosentyx received 75 mg, 150 mg or 300 mg subcutaneously at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month. Patients randomised to receive placebo who were non-responders at Week 16 (early rescue) were crossed over to receive Cosentyx (either 150 mg or 300 mg subcutaneously) at Week 16 followed by the same dose every month. Patients randomised to receive placebo who were responders at Week 16 were crossed over to receive Cosentyx (either 150 mg or 300 mg subcutaneously) at Week 24 followed by the same dose every month.

PsA Study 3 (FUTURE 5) evaluated 996 patients, of whom 50.1% had concomitant MTX. Patients were randomised to receive Cosentyx 150 mg, 300 mg or placebo subcutaneously at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month, or a once monthly injection of Cosentyx 150 mg (without loading). Patients randomised to receive placebo who were non-responders at Week 16 (early rescue) were then crossed over to receive Cosentyx (either 150 mg or 300 mg subcutaneously) at Week 16 followed by the same dose every month. Patients randomised to receive placebo who were responders at Week 16 were crossed over to receive Cosentyx (either 150 mg or 300 mg subcutaneously) at Week 24 followed by the same dose every month.

Signs and symptoms
Treatment with Cosentyx resulted in significant improvement in measures of disease activity compared to placebo at Weeks 16 and 24 (see Table 5).

Table 5 Clinical response in PsA Study 2 and PsA Study 3 at Week 16 and Week 24

	PsA Study 2			PsA Study 3		
	Placebo	150 mg[1]	300 mg[1]	Placebo	150 mg[1]	300 mg[1]
Number of patients randomised	98	100	100	332	220	222
ACR20 response n (%)						
Week 16	18 (18.4%)	60 (60.0%***)	57 (57.0%***)	91◊ (27.4%)	122◊ (55.5%***)	139◊ (62.6%***)
Week 24	15◊ (15.3%)	51◊ (51.0%***)	54◊ (54.0%***)	78 (23.5%)	117 (53.2%***)	141 (63.5%***)
ACR50 response n (%)						
Week 16	6 (6.1%)	37 (37.0%***)	35 (35.0%***)	27 (8.1%)	79 (35.9%*)	88 (39.6%*)
Week 24	7 (7.1%)	35 (35.0%)	35 (35.0%**)	29 (8.7%)	86 (39.1%***)	97 (43.7%***)
ACR70 response n (%)						
Week 16	2 (2.0%)	17 (17.0%**)	15 (15.0%**)	14 (4.2%)	40 (18.2%***)	45 (20.3%***)
Week 24	1 (1.0%)	21 (21.0%**)	20 (20.0%**)	13 (3.9%)	53 (24.1%***)	57 (25.7%***)
DAS28-CRP						
Week 16	-0.50	-1.45***	-1.51***	-0.63	-1.29*	-1.49*
Week 24	-0.96	-1.58**	-1.61**	-0.84	-1.57***	-1.68***
Number of patients with ≥3% BSA psoriasis skin involvement at baseline	43 (43.9%)	58 (58.0%)	41 (41.0%)	162 (48.8%)	125 (56.8%)	110 (49.5%)
PASI 75 response n (%)						
Week 16	3 (7.0%)	33 (56.9%***)	27 (65.9%***)	20 (12.3%)	75 (60.0%*)	77 (70.0%*)
Week 24	7 (16.3%)	28 (48.3%**)	26 (63.4%***)	29 (17.9%)	80 (64.0%***)	78 (70.9%***)
PASI 90 response n (%)						
Week 16	3 (7.0%)	22 (37.9%***)	18 (43.9%***)	15 (9.3%)	46 (36.8%*)	59 (53.6%*)
Week 24	4 (9.3%)	19 (32.8%**)	20 (48.8%***)	19 (11.7%)	51 (40.8%***)	60 (54.5%***)
Dactylitis resolution n (%) †						
Week 16	10 (37%)	21 (65.6%*)	26 (56.5%)	40 (32.3%)	46 (57.5%*)	54 (65.9%*)
Week 24	4 (14.8%)	16 (50.0%**)	26 (56.5%**)	42 (33.9%)	51 (63.8%***)	52 (63.4%***)

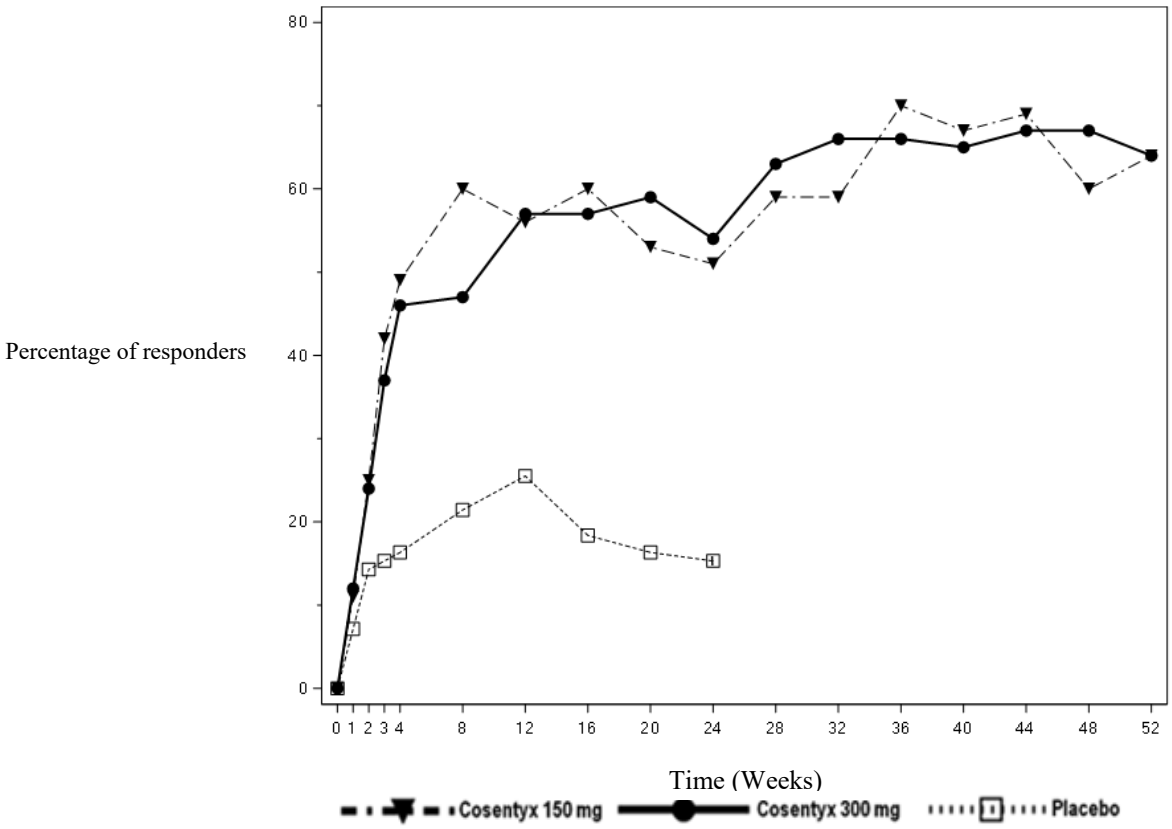
Enthesitis resolution n (%) ‡						
Week 16	17 (26.2%)	32 (50.0%**)	32 (57.1%***)	68 (35.4%)	77 (54.6%*)	78 (55.7%*)
Week 24	14 (21.5%)	27 (42.2%*)	27 (48.2%**)	66 (34.4%)	77 (54.6%***)	86 (61.4%***)

* p<0.05, ** p<0.01, *** p<0.001; versus placebo
All p-values are adjusted for multiplicity of testing based on pre-defined hierarchy at Week 24 for PsA Study 2, except for ACR70, Dactylitis and Enthesitis, which were exploratory endpoints and all endpoints at Week 16.
All p-values are adjusted for multiplicity of testing based on pre-defined hierarchy at Week 16 for PsA Study 3, except for ACR70 which was an exploratory endpoint and all endpoints at Week 24.
Non-responder imputation used for missing binary endpoint.
ACR: American College of Rheumatology; PASI: Psoriasis Area and Severity Index; DAS: Disease Activity Score; BSA: Body Surface Area
◊Primary Endpoint
[1]Cosentyx 150 mg or 300 mg s.c. at Weeks 0, 1, 2, 3, and 4 followed by the same dose every month
†In patients with dactylitis at baseline (n=27, 32, 46, respectively for PsA Study 2 and n=124, 80, 82, respectively for PsA Study 3)
‡In patients with enthesitis at baseline (n=65, 64, 56, respectively for PsA Study 2 and n=192, 141, 140, respectively for PsA Study 3)

The onset of action of Cosentyx occurred as early as Week 2. Statistically significant difference in ACR 20 versus placebo was reached at Week 3.

The percentage of patients achieving ACR 20 response by visit is shown in Figure 2.

Figure 2 ACR20 response in PsA Study 2 over time up to Week 52



Similar responses for primary and key secondary endpoints were seen in PsA patients regardless of whether they were on concomitant MTX treatment or not. In PsA Study 2, at Week 24, Cosentyx-treated patients with concomitant MTX use had a higher ACR 20 response (47.7% and 54.4% for 150 mg and 300 mg, respectively, compared to placebo 20.0%) and ACR 50 response (31.8% and 38.6% for 150 mg and 300 mg, respectively, compared to placebo 8.0%). Cosentyx-treated patients without concomitant MTX use had a higher ACR 20 response (53.6% and 53.6% for 150 mg and 300 mg, respectively, compared to placebo 10.4%) and ACR 50 response (37.5% and 32.1% for 150 mg and 300 mg, respectively, compared to placebo 6.3%).

In PsA Study 2, both anti-TNFα-naive and anti-TNFα-IR Cosentyx-treated patients had a significantly higher ACR 20 response compared to placebo at Week 24, with a slightly higher response in the anti-TNFα-naive group (anti-TNFα-naive: 64% and 58% for 150 mg and 300 mg, respectively, compared to placebo 15.9%; anti-TNFα-IR: 30% and 46% for 150 mg and 300 mg, respectively, compared to placebo 14.3%). In the anti-TNFα-IR patients subgroup, only the 300 mg dose showed significantly higher response rate for ACR 20 compared to placebo ($p<0.05$) and demonstrated clinical meaningful benefit over 150 mg on multiple secondary endpoints. Improvements in the PASI 75 response were seen in both subgroups and the 300 mg dose showed statistically significant benefit in the anti-TNFα-IR patients.

The number of PsA patients with axial involvement was too small to allow meaningful assessment.

Improvements were shown in all components of the ACR scores, including patient assessment of pain. In PsA Study 2, the proportion of patients achieving a modified PsA Response Criteria (PsARC) response was greater in the Cosentyx-treated patients (59.0% and 61.0% for 150 mg and 300 mg, respectively) compared to placebo (26.5%) at Week 24.

In PsA Study 1 and PsA Study 2, efficacy was maintained up to Week 104. In PsA Study 2, among 200 patients initially randomised to Cosentyx 150 mg and 300 mg, 178 (89%) patients were still on treatment at Week 52. Of the 100 patients randomised to Cosentyx 150 mg, 64, 39 and 20 had an ACR 20/50/70 response, respectively. Of the 100 patients randomised to Cosentyx 300 mg, 64, 44 and 24 had an ACR 20/50/70 response, respectively.

Radiographic response
In PsA Study 3, inhibition of progression of structural damage was assessed radiographically and expressed by the modified Total Sharp Score (mTSS) and its components, the Erosion Score (ES) and the Joint Space Narrowing Score (JSN). Radiographs of hands, wrists, and feet were obtained at baseline, Week 16 and/or Week 24 and scored independently by at least two readers who were blinded to treatment group and visit number. Cosentyx 150 mg and 300 mg treatment significantly inhibited the rate of progression of peripheral joint damage compared with placebo treatment as measured by change from baseline in mTSS at Week 24 (Table 6).

Inhibition of progression of structural damage was also assessed in PsA Study 1 at Weeks 24 and 52, compared to baseline. Week 24 data are presented in Table 6.

Table 6 Change in modified Total Sharp Score in psoriatic arthritis

	PsA Study 3			PsA Study 1	
	Placebo n=296	**Cosentyx 150 mg[1] n=213**	**Cosentyx 300 mg[1] n=217**	**Placebo n=179**	**Cosentyx 150 mg[2] n=185**
Total score					
Baseline (SD)	15.0 (38.2)	13.5 (25.6)	12.9 (23.8)	28.4 (63.5)	22.3 (48.0)
Mean change at Week 24	0.50	0.13*	0.02*	0.57	0.13*

*p<0.05 based on nominal, but non adjusted, p-value
[1]Cosentyx 150 mg or 300 mg s.c. at Weeks 0, 1, 2, 3, and 4 followed by the same dose every month
[2]10 mg/kg at Weeks 0, 2 and 4 followed by subcutaneous doses of 75 mg or 150 mg

In PsA Study 1, inhibition of structural damage was maintained with Cosentyx treatment up to Week 52.

In PsA Study 3, the percentage of patients with no disease progression (defined as a change from baseline in mTSS of ≤0.5) from randomisation to Week 24 was 80.3%, 88.5% and 73.6% for secukinumab 150 mg, 300 mg and placebo, respectively. An effect of inhibition of structural damage was observed in anti-TNFα-naïve and anti-TNFα-IR patients and in patients treated with and without concomitant MTX.

In PsA Study 1, the percentage of patients with no disease progression (defined as a change from baseline in mTSS of ≤0.5) from randomisation to Week 24 was 82.3% in secukinumab 10 mg/kg intravenous load – 150 mg subcutaneous maintenance and 75.7% in placebo. The percentage of patients with no disease progression from Week 24 to Week 52 for secukinumab 10 mg/kg intravenous load – followed by 150 mg subcutaneous maintenance and for placebo patients who switched to 75 mg or 150 mg subcutaneous every 4 weeks at Week 16 or Week 24 was 85.7% and 86.8%, respectively.

Physical function and health-related quality of life
In PsA Study 2 and PsA Study 3, patients treated with Cosentyx 150 mg (p=0.0555 and p<0.0001) and 300 mg (p=0.0040 and p<0.0001) showed improvement in physical function compared to patients treated with placebo as assessed by Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24 and Week 16, respectively. Improvements in HAQ-DI scores were seen regardless of previous anti-TNFα exposure. Similar responses were seen in PsA Study 1.

Cosentyx-treated patients reported significant improvements in health-related quality of life as measured by the Short Form-36 Health Survey Physical Component Summary (SF-36 PCS) score (p<0.001). There were also statistically significant improvements demonstrated in exploratory endpoints assessed by the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scores for 150 mg and 300 mg compared to placebo (7.97, 5.97 versus 1.63, respectively) and these improvements were maintained up to Week 104 in PsA Study 2.

Similar responses were seen in PsA Study 1 and efficacy was maintained up to Week 52.

Ankylosing spondylitis
The safety and efficacy of Cosentyx were assessed in 590 patients in two randomised, double-blind, placebo-controlled phase III studies in patients with active ankylosing spondylitis (AS) with a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or disease-modifying anti-rheumatic drug (DMARD) therapy. Patients in these studies had a diagnosis of AS for a median of 2.7 to 5.8 years. For both studies, the primary endpoint was at least a 20% improvement in Assessment of Spondyloarthritis International Society (ASAS 20) criteria at Week 16.

In Ankylosing Spondylitis Study 1 (AS Study 1) and Ankylosing Spondylitis Study 2 (AS Study 2) 27.0% and 38.8% of patients, respectively, were previously treated with an anti-TNFα agent and discontinued the anti-TNFα agent for either lack of efficacy or intolerance (anti-TNFα-IR patients).

AS Study 1 (MEASURE 1) evaluated 371 patients, of whom 14.8% and 33.4% used concomitant MTX or sulfasalazine, respectively. Patients randomised to Cosentyx received 10 mg/kg intravenously at Weeks 0, 2, and 4, followed by either 75 mg or 150 mg subcutaneously every month starting at Week 8. Patients randomised to placebo who were non-responders at Week 16 (early rescue) and all other placebo patients at Week 24 were crossed over to receive Cosentyx (either 75 mg or 150 mg subcutaneously), followed by the same dose every month.

AS Study 2 (MEASURE 2) evaluated 219 patients, of whom 11.9% and 14.2% used concomitant MTX or sulfasalazine, respectively. Patients randomised to Cosentyx received 75 mg or 150 mg subcutaneously at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month. At Week 16, patients who were randomised to placebo at baseline were re-randomised to receive Cosentyx (either 75 mg or 150 mg subcutaneously) every month.

Signs and symptoms
In AS Study 2, treatment with Cosentyx 150 mg resulted in greater improvement in measures of disease activity compared with placebo at Week 16 (see Table 7).

Table 7 Clinical response in AS Study 2 at Week 16

Outcome (p-value versus placebo)	**Placebo (n = 74)**	**75 mg (n = 73)**	**150 mg (n = 72)**
ASAS 20 response, %	28.4	41.1	61.1***
ASAS 40 response, %	10.8	26.0	36.1***
hsCRP, (post-BSL/BSL ratio)	1.13	0.61	0.55***
ASAS 5/6, %	8.1	34.2	43.1***
ASAS partial remission, %	4.1	15.1	13.9
BASDAI 50, %	10.8	24.7*	30.6**
ASDAS-CRP major improvement	4.1	15.1*	25.0***

* $p<0.05$, ** $p<0.01$, *** $p<0.001$; versus placebo
All p-values adjusted for multiplicity of testing based on pre-defined hierarchy, except BASDAI 50 and ASDAS-CRP
Non-responder imputation used for missing binary endpoint

ASAS: Assessment of SpondyloArthritis International Society Criteria; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; hsCRP: high-sensitivity C-reactive protein; ASDAS: Ankylosing Spondylitis Disease Activity Score; BSL: baseline

The onset of action of Cosentyx 150 mg occurred as early as Week 1 for ASAS 20 and Week 2 for ASAS 40 (superior to placebo) in AS Study 2.

ASAS 20 responses were improved at Week 16 in both anti-TNFα-naïve patients (68.2% versus 31.1%; $p<0.05$) and anti-TNFα-IR patients (50.0% versus 24.1%; $p<0.05$) for Cosentyx 150 mg compared with placebo, respectively.

In both AS studies, Cosentyx-treated patients (150 mg in AS Study 2 and both regimens in AS Study 1) demonstrated significantly improved signs and symptoms at Week 16, with comparable magnitude of response and efficacy maintained up to Week 52 in both anti-TNFα-naive and anti-TNFα-IR patients. In AS Study 2, among 72 patients initially randomised to Cosentyx 150 mg, 61 (84.7%) patients were still on treatment at Week 52. Of the 72 patients randomised to Cosentyx 150 mg, 45 and 35 had an ASAS 20/40 response, respectively.

Spinal mobility
Patients treated with Cosentyx 150 mg showed improvements in spinal mobility as measured by change from baseline in BASMI at Week 16 for both AS Study 1 (-0.40 versus -0.12 for placebo; p=0.0114) and AS Study 2 (-0.51 versus -0.22 for placebo; p=0.0533). These improvements were sustained up to Week 52.

Physical function and health-related quality of life
In AS Study 1 and Study 2, patients treated with Cosentyx 150 mg showed improvements in health-related quality of life as measured by AS Quality of Life Questionnaire (ASQoL) (p=0.001) and SF-36 Physical Component Summary (SF-36PCS) (p<0.001). Patients treated with Cosentyx 150 mg also showed statistically significant improvements on exploratory endpoints in physical function as assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI) compared to placebo (-2.15 versus -0.68), and in fatigue as assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale compared to placebo (8.10 versus 3.30). These improvements were sustained up to Week 52.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Cosentyx in plaque psoriasis in paediatric patients aged from birth to less than 6 years and in chronic idiopathic arthritis for paediatric patients aged from birth to less than 2 years (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with Cosentyx in plaque psoriasis in paediatric patients aged from 6 years to less than 18 years and in chronic idiopathic arthritis for paediatric patients aged from 2 years to less than 18 years (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Plaque psoriasis

Absorption
Following a single subcutaneous dose of 300 mg as a liquid formulation in healthy volunteers, secukinumab reached peak serum concentrations of 43.2±10.4 µg/ml between 2 and 14 days post dose.

Based on population pharmacokinetic analysis, following a single subcutaneous dose of either 150 mg or 300 mg in plaque psoriasis patients, secukinumab reached peak serum concentrations of 13.7±4.8 µg/ml or 27.3±9.5 µg/ml, respectively, between 5 and 6 days post dose.

After initial weekly dosing during the first month, time to reach the maximum concentration was between 31 and 34 days based on population pharmacokinetic analysis.

On the basis of simulated data, peak concentrations at steady-state ($C_{max,ss}$) following subcutaneous administration of 150 mg or 300 mg were 27.6 µg/ml and 55.2 µg/ml, respectively. Population pharmacokinetic analysis suggests that steady-state is reached after 20 weeks with monthly dosing regimens.

Compared with exposure after a single dose, the population pharmacokinetic analysis showed that patients exhibited a 2-fold increase in peak serum concentrations and area under the curve (AUC) following repeated monthly dosing during maintenance.

Population pharmacokinetic analysis showed that secukinumab was absorbed with an average absolute bioavailability of 73% in patients with plaque psoriasis. Across studies, absolute bioavailabilities in the range between 60 and 77% were calculated.

Distribution
The mean volume of distribution during the terminal phase (V_z) following single intravenous administration ranged from 7.10 to 8.60 litres in plaque psoriasis patients, suggesting that secukinumab undergoes limited distribution to peripheral compartments.

Biotransformation
The majority of IgG elimination occurs via intracellular catabolism, following fluid-phase or receptor mediated endocytosis.

Elimination
Mean systemic clearance (CL) following a single intravenous administration to patients with plaque psoriasis ranged from 0.13 to 0.36 l/day. In a population pharmacokinetic analysis, the mean systemic clearance (CL) was 0.19 l/day in plaque psoriasis patients. The CL was not impacted by gender. Clearance was dose- and time-independent.

The mean elimination half-life, as estimated from population pharmacokinetic analysis, was 27 days in plaque psoriasis patients, ranging from 18 to 46 days across psoriasis studies with intravenous administration.

Linearity/non-linearity
The single and multiple dose pharmacokinetics of secukinumab in plaque psoriasis patients were determined in several studies with intravenous doses ranging from 1x 0.3 mg/kg to 3x 10 mg/kg and with subcutaneous doses ranging from 1x 25 mg to multiple doses of 300 mg. Exposure was dose proportional across all dosing regimens.

Psoriatic arthritis

The pharmacokinetic properties of secukinumab observed in psoriatic arthritis patients were similar to those displayed in plaque psoriasis patients. The bioavailability of secukinumab in PsA patients was 85% on the basis of the population pharmacokinetic model.

Ankylosing spondylitis

The pharmacokinetic properties of secukinumab observed in ankylosing spondylitis patients were similar to those displayed in plaque psoriasis patients.

Special populations

Elderly patients
Of the 3,430 plaque psoriasis patients exposed to Cosentyx in clinical studies, a total of 230 patients were 65 years of age or older and 32 patients were 75 years of age or older.

Of the 2,536 psoriatic arthritis patients exposed to Cosentyx in clinical studies, a total of 236 patients were 65 years of age or older and 25 patients were 75 years of age or older.

Of the 571 ankylosing spondylitis patients exposed to Cosentyx in clinical studies, a total of 24 patients were 65 years of age or older and 3 patients were 75 years of age or older.

Based on population pharmacokinetic analysis with a limited number of elderly patients (n=71 for age ≥65 years and n=7 for age ≥75 years), clearance in elderly patients and patients less than 65 years of age was similar.

Patients with renal or hepatic impairment
No pharmacokinetic data are available in patients with renal or hepatic impairment. The renal elimination of intact Cosentyx, an IgG monoclonal antibody, is expected to be low and of minor importance. IgGs are mainly eliminated via catabolism and hepatic impairment is not expected to influence clearance of Cosentyx.

Effect of weight on pharmacokinetics
Secukinumab clearance and volume of distribution increase as body weight increases.

5.3 Preclinical safety data

Non-clinical data revealed no special risks for humans based on tissue cross-reactivity testing, safety pharmacology, repeated dose and reproductive toxicity studies performed with secukinumab or a murine anti-murine IL-17A antibody.

Since secukinumab binds to cynomolgus monkey and human IL-17A, its safety was studied in the cynomolgus monkey. No undesirable effects of secukinumab were seen following subcutaneous administration to cynomolgus monkeys for up to 13 weeks and intravenous administration up to 26 weeks (including pharmacokinetic, pharmacodynamic, immunogenicity and immunotoxicity (e.g. T-cell dependent antibody response and NK cell activity) evaluations). The average serum concentrations observed in monkeys after 13 weekly subcutaneous doses of 150 mg/kg were considerably higher than the predicted average serum concentration expected in psoriatic patients at the highest clinical dose. Antibodies to secukinumab were detected in only one of the exposed animals. No non-specific tissue cross-reactivity was observed when secukinumab was applied to normal human tissue.

Animal studies have not been conducted to evaluate the carcinogenic potential of secukinumab.

In an embryofoetal development study in cynomolgus monkeys, secukinumab showed no maternal toxicity, embryotoxicity or teratogenicity when administered throughout organogenesis and late gestation.

No undesirable effects of a murine anti-murine IL-17A antibody were seen in fertility and early embryonic development and pre-and postnatal development studies in mice. The high dose used in these studies was in excess of the maximum effective dose in terms of IL-17A suppression and activity (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trehalose dihydrate
L-histidine
L-histidine hydrochloride monohydrate
L-methionine
Polysorbate 80
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

18 months

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze. If necessary, Cosentyx may be stored unrefrigerated for a single period of up to 4 days at room temperature, not above 30°C.
Store the syringes in the original package in order to protect from light.

6.5 Nature and contents of container

Cosentyx is supplied in a pre-filled 1 ml glass syringe with a FluroTec-coated plunger stopper, staked 27G x ½″ needle and rigid needle shield of styrene butadiene rubber assembled in a passive safety device of polycarbonate.

Cosentyx is available in unit packs containing 1 or 2 pre-filled syringes and in multipacks containing 6 (3 packs of 2) pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Cosentyx 150 mg solution for injection is supplied in a single-use pre-filled syringe for individual use. Do not shake or freeze the syringe. The syringe should be taken out of the refrigerator 20 minutes before injecting to allow it to reach room temperature.

Prior to use, a visual inspection of the pre-filled syringe is recommended. The liquid should be clear. Its colour may vary from colourless to slightly yellow. You may see a small air bubble, which is normal. Do not use if the liquid contains easily visible particles, is cloudy or is distinctly brown. Detailed instructions for use are provided in the package leaflet.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/980/002
EU/1/14/980/003
EU/1/14/980/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15.01.2015

10. DATE OF REVISION OF THE TEXT

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

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Cosentyx 150 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 150 mg secukinumab* in 1 ml.

*Secukinumab is a recombinant fully human monoclonal antibody selective for interleukin-17A. Secukinumab is of the IgG1/κ-class produced in Chinese Hamster Ovary (CHO) cells.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen (SensoReady pen)

The solution is clear and colourless to slightly yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Plaque psoriasis

Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Psoriatic arthritis

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

Ankylosing spondylitis

Cosentyx is indicated for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

4.2 Posology and method of administration

Cosentyx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Cosentyx is indicated.

Posology

Plaque psoriasis
The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Each 300 mg dose is given as two subcutaneous injections of 150 mg.

Psoriatic arthritis
For patients with concomitant moderate to severe plaque psoriasis or who are anti-TNFα inadequate responders (IR), the recommended dose is 300 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Each 300 mg dose is given as two subcutaneous injections of 150 mg.

For other patients, the recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Based on clinical response, the dose can be increased to 300 mg.

Ankylosing spondylitis
The recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing.

For all of the above indications, available data suggest that a clinical response is usually achieved within 16 weeks of treatment. Consideration should be given to discontinuing treatment in patients who have shown no response by 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks.

Special populations

Elderly patients (aged 65 years and over)
No dose adjustment is required (see section 5.2).

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

Paediatric population
The safety and efficacy of Cosentyx in children below the age of 18 years have not yet been established. No data are available.

Method of administration

Cosentyx is to be administered by subcutaneous injection. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

After proper training in subcutaneous injection technique, patients may self-inject Cosentyx if a physician determines that this is appropriate. However, the physician should ensure appropriate follow-up of patients. Patients should be instructed to inject the full amount of Cosentyx according to the instructions provided in the package leaflet. Comprehensive instructions for administration are given in the package leaflet.

4.3 Contraindications

Severe hypersensitivity reactions 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

Infections

Cosentyx has the potential to increase the risk of infections. Serious infections have been observed in patients receiving Cosentyx in the post-marketing setting. Caution should be exercised when considering the use of Cosentyx in patients with a chronic infection or a history of recurrent infection.

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 Cosentyx should not be administered until the infection resolves.

In clinical studies, infections have been observed in patients receiving Cosentyx (see section 4.8). Most of these were mild or moderate upper respiratory tract infections such as nasopharyngitis and did not require treatment discontinuation.

Related to the mechanism of action of Cosentyx, non-serious mucocutaneous candida infections were more frequently reported for secukinumab than placebo in the psoriasis clinical studies (3.55 per 100 patient years for secukinumab 300 mg versus 1.00 per 100 patient years for placebo) (see section 4.8).

No increased susceptibility to tuberculosis was reported from clinical studies. However, Cosentyx should not be given to patients with active tuberculosis. Anti-tuberculosis therapy should be considered prior to initiation of Cosentyx in patients with latent tuberculosis.

Inflammatory bowel disease

Cases of new or exacerbations of Crohn's disease and ulcerative colitis have been reported. Caution should be exercised when prescribing Cosentyx to patients with inflammatory bowel disease, including Crohn's disease and ulcerative colitis. Patients should be closely monitored.

Hypersensitivity reactions

In clinical studies, rare cases of anaphylactic reactions have been observed in patients receiving Cosentyx. If an anaphylactic or other serious allergic reactions occur, administration of Cosentyx should be discontinued immediately and appropriate therapy initiated.

Latex-sensitive individuals

The removable cap of the Cosentyx pre-filled pen contains a derivative of natural rubber latex. No natural rubber latex has to date been detected in the removable cap. Nevertheless, the use of Cosentyx pre-filled pens in latex-sensitive individuals has not been studied and there is therefore a potential risk for hypersensitivity reactions which cannot be completely ruled out.

Vaccinations

Live vaccines should not be given concurrently with Cosentyx.

Patients receiving Cosentyx may receive concurrent inactivated or non-live vaccinations. In a study, after *meningococcal* and inactivated *influenza* vaccinations, a similar proportion of healthy volunteers treated with 150 mg of secukinumab and those treated with placebo were able to mount an adequate immune response of at least a 4-fold increase in antibody titres to *meningococcal* and *influenza* vaccines. The data suggest that Cosentyx does not suppress the humoral immune response to the *meningococcal* or *influenza* vaccines.

Concomitant immunosuppressive therapy

In psoriasis studies, the safety and efficacy of Cosentyx in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated (see also section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

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

In a study in subjects with plaque psoriasis, no interaction was observed between secukinumab and midazolam (CYP3A4 substrate).

No interaction was seen when Cosentyx was administered concomitantly with methotrexate (MTX) and/or corticosteroids in arthritis studies (including in patients with psoriatic arthritis and ankylosing spondylitis).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use an effective method of contraception during treatment and for at least 20 weeks after treatment.

Pregnancy

There are no adequate data from the use of secukinumab 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 Cosentyx in pregnancy.

Breast-feeding

It is not known whether secukinumab is excreted in human milk. Immunoglobulins are excreted in human milk and it is not known if secukinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from secukinumab, a decision on whether to discontinue breast-feeding during treatment and up to 20 weeks after treatment or to discontinue therapy with Cosentyx must be made taking into account the benefit of breast-feeding to the child and the benefit of Cosentyx therapy to the woman.

Fertility

The effect of secukinumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Over 11,900 patients have been treated with Cosentyx in blinded and open-label clinical studies in various indications (plaque psoriasis, psoriatic arthritis, ankylosing spondylitis and other autoimmune conditions), representing 20,995 patient years of exposure. Of these, over 7,100 patients were exposed to Cosentyx for at least one year.

Adverse reactions in plaque psoriasis

Four placebo-controlled phase III studies in plaque psoriasis were pooled to evaluate the safety of Cosentyx in comparison to placebo up to 12 weeks after treatment initiation. In total, 2,076 patients were evaluated (692 patients on 150 mg, 690 patients on 300 mg and 694 patients on placebo).

The most frequently reported adverse drug reactions (ADRs) were upper respiratory tract infections (most frequently nasopharyngitis, rhinitis). Most of the reactions were mild or moderate in severity.

Adverse reactions in psoriatic arthritis

In Cosentyx placebo-controlled psoriatic arthritis studies, there were 2,754 patients (1,871 patients on Cosentyx and 883 patients on placebo) with a total exposure of 4,478 patient-years of study exposure on Cosentyx. The safety profile observed in patients with psoriatic arthritis treated with Cosentyx is consistent with the safety profile in psoriasis.

Adverse reactions in ankylosing spondylitis

Cosentyx was studied in two placebo-controlled ankylosing spondylitis studies with 590 patients (394 patients on Cosentyx and 196 patients on placebo) for a total of 755 patient-years of study exposure (median duration of exposure for secukinumab-treated patients: 469 days in AS Study 1 and 460 days in AS Study 2). The safety profile observed in patients with ankylosing spondylitis treated with Cosentyx is consistent with the safety profile in psoriasis.

Tabulated list of adverse reactions

ADRs from psoriasis, psoriatic arthritis and ankylosing spondylitis clinical studies as well as from post-marketing experience (Table 1) are listed by MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available data).

Table 1 List of adverse reactions in clinical studies[1)] and post-marketing experience

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Very common	Upper respiratory tract infections
	Common	Oral herpes
	Uncommon	Oral candidiasis
		Tinea pedis
		Otitis externa
	Not known	Mucosal and cutaneous candidiasis (including oesophageal candidiasis)
Blood and lymphatic system disorders	Uncommon	Neutropenia
Immune system disorders	Rare	Anaphylactic reactions
Eye disorders	Uncommon	Conjunctivitis
Respiratory, thoracic and mediastinal disorders	Common	Rhinorrhoea
Gastrointestinal disorders	Common	Diarrhoea
Skin and subcutaneous disorders	Uncommon	Urticaria
[1)] Placebo-controlled clinical studies (phase III) in plaque psoriasis, PsA and AS patients exposed to 300 mg, 150 mg, 75 mg or placebo up to 12 weeks (psoriasis) or 16 weeks (PsA and AS) treatment duration		

Description of selected adverse reactions

Infections

In the placebo-controlled period of clinical studies in plaque psoriasis (a total of 1,382 patients treated with Cosentyx and 694 patients treated with placebo for up to 12 weeks), infections were reported in 28.7% of patients treated with Cosentyx compared with 18.9% of patients treated with placebo. The majority of infections consisted of non-serious and mild to moderate upper respiratory tract infections, such as nasopharyngitis, which did not necessitate treatment discontinuation. There was an increase in mucosal or cutaneous candidiasis, consistent with the mechanism of action, but the cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in 0.14% of patients treated with Cosentyx and in 0.3% of patients treated with placebo (see section 4.4).

Over the entire treatment period (a total of 3,430 patients treated with Cosentyx for up to 52 weeks for the majority of patients), infections were reported in 47.5% of patients treated with Cosentyx (0.9 per patient-year of follow-up). Serious infections were reported in 1.2% of patients treated with Cosentyx (0.015 per patient-year of follow-up).

Infection rates observed in psoriatic arthritis and ankylosing spondylitis clinical studies were similar to those observed in the psoriasis studies.

Neutropenia

In psoriasis phase 3 clinical studies, neutropenia was more frequently observed with secukinumab than with placebo, but most cases were mild, transient and reversible. Neutropenia <1.0-0.5x10^9/l (CTCAE Grade 3) was reported in 18 out of 3,430 (0.5%) patients on secukinumab, with no dose dependence and no temporal relationship to infections in 15 out of 18 cases. There were no reported cases of more severe neutropenia. Non-serious infections with usual response to standard care and not requiring discontinuation of Cosentyx were reported in the remaining 3 cases.

The frequency of neutropenia in psoriatic arthritis and ankylosing spondylitis is similar to psoriasis.

Rare cases of neutropenia <0.5x10^9/l (CTCAE Grade 4) were reported.

Hypersensitivity reactions
In clinical studies, urticaria and rare cases of anaphylactic reaction to Cosentyx were observed (see also section 4.4).

Immunogenicity
In psoriasis, psoriatic arthritis and ankylosing spondylitis clinical studies, less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. About half of the treatment-emergent anti-drug antibodies were neutralising, but this was not associated with loss of efficacy or pharmacokinetic abnormalities.

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

No cases of overdose have been reported in clinical studies.

Doses up to 30 mg/kg (approximately 2000 to 3000 mg) have been administered intravenously in clinical studies without dose-limiting toxicity. In the event 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: L04AC10

Mechanism of action

Secukinumab is a fully human IgG1/κ monoclonal antibody that selectively binds to and neutralises the proinflammatory cytokine interleukin-17A (IL-17A). Secukinumab works by targeting IL-17A and inhibiting its interaction with the IL-17 receptor, which is expressed on various cell types including keratinocytes. As a result, secukinumab inhibits the release of proinflammatory cytokines, chemokines and mediators of tissue damage and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases. Clinically relevant levels of secukinumab reach the skin and reduce local inflammatory markers. As a direct consequence treatment with secukinumab reduces erythema, induration and desquamation present in plaque psoriasis lesions.

IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. IL-17A plays a key role in the pathogenesis of plaque psoriasis, psoriatic arthritis and ankylosing spondylitis and is up-regulated in lesional skin in contrast to non-lesional skin of plaque psoriasis patients and in synovial tissue of psoriatic arthritis patients. The frequency of IL-17-producing cells was also significantly higher in the subchondral bone marrow of facet joints from patients with ankylosing spondylitis.

Pharmacodynamic effects

Serum levels of total IL-17A (free and secukinumab-bound IL-17A) are initially increased in patients receiving secukinumab. This is followed by a slow decrease due to reduced clearance of secukinumab-bound IL-17A, indicating that secukinumab selectively captures free IL-17A, which plays a key role in the pathogenesis of plaque psoriasis.

In a study with secukinumab, infiltrating epidermal neutrophils and various neutrophil-associated markers that are increased in lesional skin of plaque psoriasis patients were significantly reduced after one to two weeks of treatment.

Secukinumab has been shown to lower (within 1 to 2 weeks of treatment) levels of C-reactive protein, which is a marker of inflammation.

Clinical efficacy and safety

Plaque psoriasis
The safety and efficacy of Cosentyx were assessed in four randomised, double-blind, placebo-controlled phase III studies in patients with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy [ERASURE, FIXTURE, FEATURE, JUNCTURE]. The efficacy and safety of Cosentyx 150 mg and 300 mg were evaluated versus either placebo or etanercept. In addition, one study assessed a chronic treatment regimen versus a "retreatment as needed" regimen [SCULPTURE].

Of the 2,403 patients who were included in the placebo-controlled studies, 79% were biologic-naive, 45% were non-biologic failures and 8% were biologic failures (6% were anti-TNF failures, and 2% were anti-p40 failures). Approximately 15 to 25% of patients in phase III studies had psoriatic arthritis (PsA) at baseline.

Psoriasis Study 1 (ERASURE) evaluated 738 patients. Patients randomised to Cosentyx received 150 mg or 300 mg doses at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month. Psoriasis Study 2 (FIXTURE) evaluated 1,306 patients. Patients randomised to Cosentyx received 150 mg or 300 mg doses at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month. Patients randomised to etanercept received 50 mg doses twice per week for 12 weeks followed by 50 mg every week. In both Study 1 and Study 2, patients randomised to receive placebo who were non-responders at Week 12 then crossed over to receive Cosentyx (either 150 mg or 300 mg) at Weeks 12, 13, 14, and 15, followed by the same dose every month starting at Week 16. All patients were followed for up to 52 weeks following first administration of study treatment.

Psoriasis Study 3 (FEATURE) evaluated 177 patients using a pre-filled syringe compared with placebo after 12 weeks of treatment to assess the safety, tolerability, and usability of Cosentyx self-administration via the pre-filled syringe. Psoriasis Study 4 (JUNCTURE) evaluated 182 patients using a pre-filled pen compared with placebo after 12 weeks of treatment to assess the safety, tolerability, and usability of Cosentyx self-administration via the pre-filled pen. In both Study 3 and Study 4, patients randomised to Cosentyx received 150 mg or 300 mg doses at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month. Patients were also randomised to receive placebo at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month.

Psoriasis Study 5 (SCULPTURE) evaluated 966 patients. All patients received Cosentyx 150 mg or 300 mg doses at Weeks 0, 1, 2, 3, 4, 8 and 12 and then were randomised to receive either a maintenance regimen of the same dose every month starting at Week 12 or a "retreatment as needed" regimen of the same dose. Patients randomised to "retreatment as needed" did not achieve adequate maintenance of response and therefore a fixed monthly maintenance regimen is recommended.

The co-primary endpoints in the placebo and active-controlled studies were the proportion of patients who achieved a PASI 75 response and IGA mod 2011 "clear" or "almost clear" response versus placebo at Week 12 (see Tables 2 and 3). The 300 mg dose provided improved skin clearance particularly for "clear" or "almost clear" skin across the efficacy endpoints of PASI 90, PASI 100, and IGA mod 2011 0 or 1 response across all studies with peak effects seen at Week 16, therefore this dose is recommended.

Table 2 Summary of PASI 50/75/90/100 & IGA* mod 2011 "clear" or "almost clear" clinical response in Psoriasis Studies 1, 3 and 4 (ERASURE, FEATURE and JUNCTURE)

		Week 12		Week 16		Week 52	
	Placebo	**150 mg**	**300 mg**	**150 mg**	**300 mg**	**150 mg**	**300 mg**
Study 1							
Number of patients	246	244	245	244	245	244	245
PASI 50 response n (%)	22 (8.9%)	203 (83.5%)	222 (90.6%)	212 (87.2%)	224 (91.4%)	187 (77%)	207 (84.5%)
PASI 75 response n (%)	11 (4.5%)	174 (71.6%)**	200 (81.6%)**	188 (77.4%)	211 (86.1%)	146 (60.1%)	182 (74.3%)
PASI 90 response n (%)	3 (1.2%)	95 (39.1%)**	145 (59.2%)**	130 (53.5%)	171 (69.8%)	88 (36.2%)	147 (60.0%)
PASI 100 response n (%)	2 (0.8%)	31 (12.8%)	70 (28.6%)	51 (21.0%)	102 (41.6%)	49 (20.2%)	96 (39.2%)
IGA mod 2011 "clear" or "almost clear" response n (%)	6 (2.40%)	125 (51.2%)**	160 (65.3%)**	142 (58.2%)	180 (73.5%)	101 (41.4%)	148 (60.4%)
Study 3							
Number of patients	59	59	58	-	-	-	-
PASI 50 response n (%)	3 (5.1%)	51 (86.4%)	51 (87.9%)	-	-	-	-
PASI 75 response n (%)	0 (0.0%)	41 (69.5%)**	44 (75.9%)**	-	-	-	-
PASI 90 response n (%)	0 (0.0%)	27 (45.8%)	35 (60.3%)	-	-	-	-
PASI 100 response n (%)	0 (0.0%)	5 (8.5%)	25 (43.1%)	-	-	-	-
IGA mod 2011 "clear" or "almost clear" response n (%)	0 (0.0%)	31 (52.5%)**	40 (69.0%)**	-	-	-	-
Study 4							
Number of patients	61	60	60	-	-	-	-
PASI 50 response n (%)	5 (8.2%)	48 (80.0%)	58 (96.7%)	-	-	-	-
PASI 75 response n (%)	2 (3.3%)	43 (71.7%)**	52 (86.7%)**	-	-	-	-
PASI 90 response n (%)	0 (0.0%)	24 (40.0%)	33 (55.0%)	-	-	-	-
PASI 100 response n(%)	0 (0.0%)	10 (16.7%)	16 (26.7%)	-	-	-	-
IGA mod 2011 "clear" or "almost clear" response n (%)	0 (0.0%)	32 (53.3%)**	44 (73.3%)**	-	-	-	-

* The IGA mod 2011 is a 5-category scale including "0 = clear", "1 = almost clear", "2 = mild", "3 = moderate" or "4 = severe", indicating the physician's overall assessment of the psoriasis severity focusing on induration, erythema and scaling. Treatment success of "clear" or "almost clear" consisted of no signs of psoriasis or normal to pink colouration of lesions, no thickening of the plaque and none to minimal focal scaling.

** p values versus placebo and adjusted for multiplicity: $p<0.0001$.

Table 3 Summary of clinical response on Psoriasis Study 2 (FIXTURE)

	Week 12				Week 16			Week 52		
	Placebo	**150 mg**	**300 mg**	**Etanercept**	**150 mg**	**300 mg**	**Etanercept**	**150 mg**	**300 mg**	**Etanercept**
Number of patients	324	327	323	323	327	323	323	327	323	323
PASI 50 response n (%)	49 (15.1%)	266 (81.3%)	296 (91.6%)	226 (70.0%)	290 (88.7%)	302 (93.5%)	257 (79.6%)	249 (76.1%)	274 (84.8%)	234 (72.4%)
PASI 75 response n (%)	16 (4.9%)	219 (67.0%) **	249 (77.1%) **	142 (44.0%)	247 (75.5%)	280 (86.7%)	189 (58.5%)	215 (65.7%)	254 (78.6%)	179 (55.4%)
PASI 90 response n (%)	5 (1.5%)	137 (41.9%)	175 (54.2%)	67 (20.7%)	176 (53.8%)	234 (72.4%)	101 (31.3%)	147 (45.0%)	210 (65.0%)	108 (33.4%)
PASI 100 response n (%)	0 (0%)	47 (14.4%)	78 (24.1%)	14 (4.3%)	84 (25.7%)	119 (36.8%)	24 (7.4%)	65 (19.9%)	117 (36.2%)	32 (9.9%)
IGA mod 2011 “clear” or “almost clear” response n (%)	9 (2.8%)	167 (51.1%) **	202 (62.5%) **	88 (27.2%)	200 (61.2%)	244 (75.5%)	127 (39.3%)	168 (51.4%)	219 (67.8%)	120 (37.2%)

** p values versus etanercept: p=0.0250

In an additional psoriasis study (CLEAR) 676 patients were evaluated. Secukinumab 300 mg met the primary and secondary endpoints by showing superiority to ustekinumab based on PASI 90 response at Week 16 (primary endpoint), speed of onset of PASI 75 response at Week 4, and long-term PASI 90 response at Week 52. Greater efficacy of secukinumab compared to ustekinumab for the endpoints PASI 75/90/100 and IGA mod 2011 0 or 1 response (“clear” or “almost clear”) was observed early and continued through to Week 52.

Table 4 Summary of clinical response on CLEAR Study

	Week 4		Week 16		Week 52	
	Secukinumab 300 mg	**Ustekinumab***	**Secukinumab 300 mg**	**Ustekinumab***	**Secukinumab 300 mg**	**Ustekinumab***
Number of patients	334	335	334	335	334	335
PASI 75 response n (%)	166 (49.7%)**	69 (20.6%)	311 (93.1%)	276 (82.4%)	306 (91.6%)	262 (78.2%)
PASI 90 response n (%)	70 (21.0%)	18 (5.4%)	264 (79.0%)**	192 (57.3%)	250 (74.9%)***	203 (60.6%)
PASI 100 response n (%)	14 (4.2%)	3 (0.9%)	148 (44.3%)	95 (28.4%)	150 (44.9%)	123 (36.7%)
IGA mod 2011 “clear” or “almost clear” response n (%)	128 (38.3%)	41 (12.2%)	278 (83.2%)	226 (67.5%)	261 (78.1%)	213 (63.6%)

* Patients treated with secukinumab received 300 mg doses at Weeks 0, 1, 2, 3 and 4, followed by the same dose every 4 weeks until Week 52. Patients treated with ustekinumab received 45 mg or 90 mg at Weeks 0 and 4, then every 12 weeks until Week 52 (dosed by weight as per approved posology)

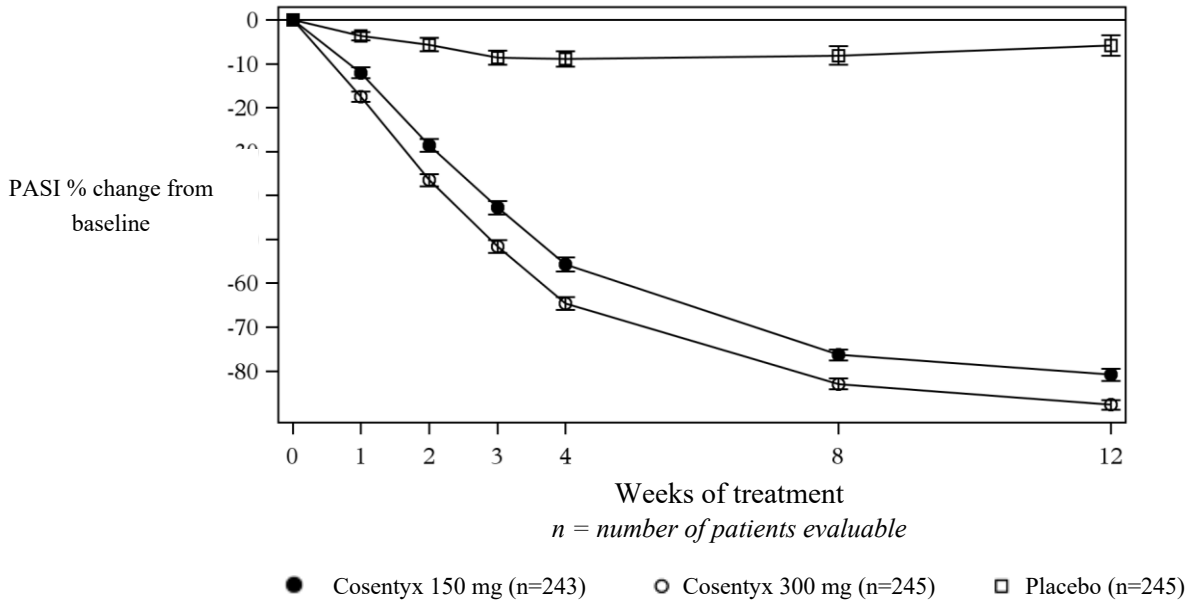
** p values versus ustekinumab: p<0.0001 for primary endpoint of PASI 90 at Week 16 and secondary endpoint of PASI 75 at Week 4

*** p values versus ustekinumab: p=0.0001 for secondary endpoint of PASI 90 at Week 52

Cosentyx was efficacious in systemic treatment-naive, biologic-naive, biologic/anti-TNF-exposed and biologic/anti-TNF-failure patients. Improvements in PASI 75 in patients with concurrent psoriatic arthritis at baseline were similar to those in the overall plaque psoriasis population.

Cosentyx was associated with a fast onset of efficacy with a 50% reduction in mean PASI by Week 3 for the 300 mg dose.

Figure 1 Time course of percentage change from baseline of mean PASI score in Study 1 (ERASURE)



Specific locations/forms of plaque psoriasis
In two additional placebo-controlled studies, improvement was seen in both nail psoriasis (TRANSFIGURE, 198 patients) and palmoplantar plaque psoriasis (GESTURE, 205 patients). In the TRANSFIGURE Study, secukinumab was superior to placebo at Week 16 (46.1% for 300 mg, 38.4% for 150 mg and 11.7% for placebo) as assessed by significant improvement from baseline in the Nail Psoriasis Severity Index (NAPSI %) for patients with moderate to severe plaque psoriasis with nail involvement. In the GESTURE Study, secukinumab was superior to placebo at Week 16 (33.3% for 300 mg, 22.1% for 150 mg, and 1.5% for placebo) as assessed by significant improvement of ppIGA 0 or 1 response ("clear" or "almost clear") for patients with moderate to severe palmoplantar plaque psoriasis.

A placebo-controlled study evaluated 102 patients with moderate to severe scalp psoriasis, defined as having a Psoriasis Scalp Severity Index (PSSI) score of ≥12, an IGA mod 2011 scalp only score of 3 or greater and at least 30% of the scalp surface area affected. Secukinumab 300 mg was superior to placebo at Week 12 as assessed by significant improvement from baseline in both the PSSI 90 response (52.9% versus 2.0%) and IGA mod 2011 0 or 1 scalp only response (56.9% versus 5.9%). Improvement in both endpoints was sustained for secukinumab patients who continued treatment through to Week 24.

Quality of life/patient-reported outcomes
Statistically significant improvements at Week 12 (Studies 1-4) from baseline compared to placebo were demonstrated in the DLQI (Dermatology Life Quality Index). Mean decreases (improvements) in DLQI from baseline ranged from -10.4 to -11.6 with secukinumab 300 mg, from -7.7 to -10.1 with secukinumab 150 mg, versus -1.1 to -1.9 for placebo at Week 12. These improvements were maintained for 52 weeks (Studies 1 and 2).

Forty percent of the participants in Studies 1 and 2 completed the Psoriasis Symptom Diary©. For the participants completing the diary in each of these studies, statistically significant improvements at Week 12 from baseline compared to placebo in patient-reported signs and symptoms of itching, pain and scaling were demonstrated.

Statistically significant improvements at Week 4 from baseline in patients treated with secukinumab compared to patients treated with ustekinumab (CLEAR) were demonstrated in the DLQI and these improvements were maintained for up to 52 weeks.

Statistically significant improvements in patient-reported signs and symptoms of itching, pain and scaling at Week 16 and Week 52 (CLEAR) were demonstrated in the Psoriasis Symptom Diary© in patients treated with secukinumab compared to patients treated with ustekinumab.

Statistically significant improvements (decreases) at Week 12 from baseline in the scalp psoriasis study were demonstrated in patient reported signs and symptoms of scalp itching, pain and scaling compared to placebo.

Psoriatic arthritis
The safety and efficacy of Cosentyx were assessed in 1,999 patients in three randomised, double-blind, placebo-controlled phase III studies in patients with active psoriatic arthritis (≥3 swollen and ≥3 tender joints) despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or disease-modifying anti-rheumatic drug (DMARD) therapy. Patients with each subtype of PsA were enrolled in these studies, including polyarticular arthritis with no evidence of rheumatoid nodules, spondylitis with peripheral arthritis, asymmetric peripheral arthritis, distal interphalangeal involvement and arthritis mutilans. Patients in these studies had a diagnosis of PsA of at least five years. The majority of patients also had active psoriasis skin lesions or a documented history of psoriasis. Over 61% and 42% of the PsA patients had enthesitis and dactylitis at baseline, respectively. For all studies, the primary endpoint was American College of Rheumatology (ACR) 20 response. For Psoriatic Arthritis Study 1 (PsA Study 1) and Psoriatic Arthritis Study 2 (PsA Study 2), the primary endpoint was at Week 24. For Psoriatic Arthritis Study 3 (PsA Study 3), the primary endpoint was at Week 16 with the key secondary endpoint, the change from baseline in modified Total Sharp Score (mTSS), at Week 24.

In PsA Study 1, PsA Study 2 and PsA Study 3, 29%, 35% and 30% of patients, respectively, were previously treated with an anti-TNFα agent and discontinued the anti-TNFα agent for either lack of efficacy or intolerance (anti-TNFα-IR patients).

PsA Study 1 (FUTURE 1) evaluated 606 patients, of whom 60.7% had concomitant MTX. Patients randomised to Cosentyx received 10 mg/kg intravenously at Weeks 0, 2, and 4, followed by either 75 mg or 150 mg subcutaneously every month starting at Week 8. Patients randomised to placebo who were non-responders at Week 16 (early rescue) and other placebo patients at Week 24 were crossed over to receive Cosentyx (either 75 mg or 150 mg subcutaneously) followed by the same dose every month.

PsA Study 2 (FUTURE 2) evaluated 397 patients, of whom 46.6% had concomitant MTX. Patients randomised to Cosentyx received 75 mg, 150 mg or 300 mg subcutaneously at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month. Patients randomised to receive placebo who were non-responders at Week 16 (early rescue) were crossed over to receive Cosentyx (either 150 mg or 300 mg subcutaneously) at Week 16 followed by the same dose every month. Patients randomised to receive placebo who were responders at Week 16 were crossed over to receive Cosentyx (either 150 mg or 300 mg subcutaneously) at Week 24 followed by the same dose every month.

PsA Study 3 (FUTURE 5) evaluated 996 patients, of whom 50.1% had concomitant MTX. Patients were randomised to receive Cosentyx 150 mg, 300 mg or placebo subcutaneously at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month, or a once monthly injection of Cosentyx 150 mg (without loading). Patients randomised to receive placebo who were non-responders at Week 16 (early rescue) were then crossed over to receive Cosentyx (either 150 mg or 300 mg subcutaneously) at Week 16 followed by the same dose every month. Patients randomised to receive placebo who were responders at Week 16 were crossed over to receive Cosentyx (either 150 mg or 300 mg subcutaneously) at Week 24 followed by the same dose every month.

Signs and symptoms
Treatment with Cosentyx resulted in significant improvement in measures of disease activity compared to placebo at Weeks 16 and 24 (see Table 5).

Table 5 Clinical response in PsA Study 2 and PsA Study 3 at Week 16 and Week 24

	PsA Study 2			PsA Study 3		
	Placebo	150 mg[1]	300 mg[1]	Placebo	150 mg[1]	300 mg[1]
Number of patients randomised	98	100	100	332	220	222
ACR20 response n (%)						
Week 16	18 (18.4%)	60 (60.0%***)	57 (57.0%***)	91◊ (27.4%)	122◊ (55.5%***)	139◊ (62.6%***)
Week 24	15◊ (15.3%)	51◊ (51.0%***)	54◊ (54.0%***)	78 (23.5%)	117 (53.2%***)	141 (63.5%***)
ACR50 response n (%)						
Week 16	6 (6.1%)	37 (37.0%***)	35 (35.0%***)	27 (8.1%)	79 (35.9%*)	88 (39.6%*)
Week 24	7 (7.1%)	35 (35.0%)	35 (35.0%**)	29 (8.7%)	86 (39.1%***)	97 (43.7%***)
ACR70 response n (%)						
Week 16	2 (2.0%)	17 (17.0%**)	15 (15.0%**)	14 (4.2%)	40 (18.2%***)	45 (20.3%***)
Week 24	1 (1.0%)	21 (21.0%**)	20 (20.0%**)	13 (3.9%)	53 (24.1%***)	57 (25.7%***)
DAS28-CRP						
Week 16	-0.50	-1.45***	-1.51***	-0.63	-1.29*	-1.49*
Week 24	-0.96	-1.58**	-1.61**	-0.84	-1.57***	-1.68***
Number of patients with ≥3% BSA psoriasis skin involvement at baseline	43 (43.9%)	58 (58.0%)	41 (41.0%)	162 (48.8%)	125 (56.8%)	110 (49.5%)
PASI 75 response n (%)						
Week 16	3 (7.0%)	33 (56.9%***)	27 (65.9%***)	20 (12.3%)	75 (60.0%*)	77 (70.0%*)
Week 24	7 (16.3%)	28 (48.3%**)	26 (63.4%***)	29 (17.9%)	80 (64.0%***)	78 (70.9%***)
PASI 90 response n (%)						
Week 16	3 (7.0%)	22 (37.9%***)	18 (43.9%***)	15 (9.3%)	46 (36.8%*)	59 (53.6%*)
Week 24	4 (9.3%)	19 (32.8%**)	20 (48.8%***)	19 (11.7%)	51 (40.8%***)	60 (54.5%***)
Dactylitis resolution n (%) †						
Week 16	10 (37%)	21 (65.6%*)	26 (56.5%)	40 (32.3%)	46 (57.5%*)	54 (65.9%*)
Week 24	4 (14.8%)	16 (50.0%**)	26 (56.5%**)	42 (33.9%)	51 (63.8%***)	52 (63.4%***)

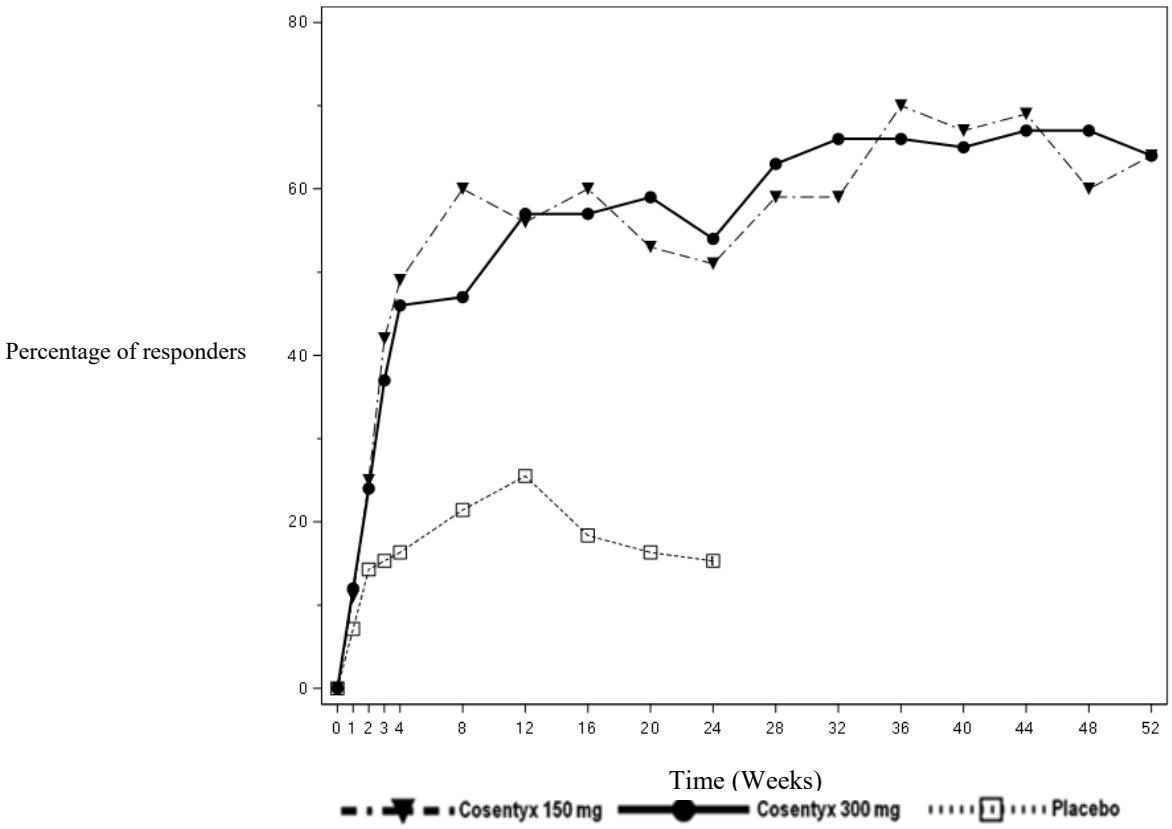
Enthesitis resolution n (%) ‡						
Week 16	17 (26.2%)	32 (50.0%**)	32 (57.1%***)	68 (35.4%)	77 (54.6%*)	78 (55.7%*)
Week 24	14 (21.5%)	27 (42.2%*)	27 (48.2%**)	66 (34.4%)	77 (54.6%***)	86 (61.4%***)

* p<0.05, ** p<0.01, *** p<0.001; versus placebo
All p-values are adjusted for multiplicity of testing based on pre-defined hierarchy at Week 24 for PsA Study 2, except for ACR70, Dactylitis and Enthesitis, which were exploratory endpoints and all endpoints at Week 16.
All p-values are adjusted for multiplicity of testing based on pre-defined hierarchy at Week 16 for PsA Study 3, except for ACR70 which was an exploratory endpoint and all endpoints at Week 24.
Non-responder imputation used for missing binary endpoint.
ACR: American College of Rheumatology; PASI: Psoriasis Area and Severity Index; DAS: Disease Activity Score; BSA: Body Surface Area
◊Primary Endpoint
[1]Cosentyx 150 mg or 300 mg s.c. at Weeks 0, 1, 2, 3, and 4 followed by the same dose every month
†In patients with dactylitis at baseline (n=27, 32, 46, respectively for PsA Study 2 and n=124, 80, 82, respectively for PsA Study 3)
‡In patients with enthesitis at baseline (n=65, 64, 56, respectively for PsA Study 2 and n=192, 141, 140, respectively for PsA Study 3)

The onset of action of Cosentyx occurred as early as Week 2. Statistically significant difference in ACR 20 versus placebo was reached at Week 3.

The percentage of patients achieving ACR 20 response by visit is shown in Figure 2.

Figure 2 ACR20 response in PsA Study 2 over time up to Week 52



Similar responses for primary and key secondary endpoints were seen in PsA patients regardless of whether they were on concomitant MTX treatment or not. In PsA Study 2, at Week 24, Cosentyx-treated patients with concomitant MTX use had a higher ACR 20 response (47.7% and 54.4% for 150 mg and 300 mg, respectively, compared to placebo 20.0%) and ACR 50 response (31.8% and 38.6% for 150 mg and 300 mg, respectively, compared to placebo 8.0%). Cosentyx-treated patients without concomitant MTX use had a higher ACR 20 response (53.6% and 53.6% for 150 mg and 300 mg, respectively, compared to placebo 10.4%) and ACR 50 response (37.5% and 32.1% for 150 mg and 300 mg, respectively, compared to placebo 6.3%).

In PsA Study 2, both anti-TNFα-naive and anti-TNFα-IR Cosentyx-treated patients had a significantly higher ACR 20 response compared to placebo at Week 24, with a slightly higher response in the anti-TNFα-naive group (anti-TNFα-naive: 64% and 58% for 150 mg and 300 mg, respectively, compared to placebo 15.9%; anti-TNFα-IR: 30% and 46% for 150 mg and 300 mg, respectively, compared to placebo 14.3%). In the anti-TNFα-IR patients subgroup, only the 300 mg dose showed significantly higher response rate for ACR 20 compared to placebo ($p<0.05$) and demonstrated clinical meaningful benefit over 150 mg on multiple secondary endpoints. Improvements in the PASI 75 response were seen in both subgroups and the 300 mg dose showed statistically significant benefit in the anti-TNFα-IR patients.

The number of PsA patients with axial involvement was too small to allow meaningful assessment.

Improvements were shown in all components of the ACR scores, including patient assessment of pain. In PsA Study 2, the proportion of patients achieving a modified PsA Response Criteria (PsARC) response was greater in the Cosentyx-treated patients (59.0% and 61.0% for 150 mg and 300 mg, respectively) compared to placebo (26.5%) at Week 24.

In PsA Study 1 and PsA Study 2, efficacy was maintained up to Week 104. In PsA Study 2, among 200 patients initially randomised to Cosentyx 150 mg and 300 mg, 178 (89%) patients were still on treatment at Week 52. Of the 100 patients randomised to Cosentyx 150 mg, 64, 39 and 20 had an ACR 20/50/70 response, respectively. Of the 100 patients randomised to Cosentyx 300 mg, 64, 44 and 24 had an ACR 20/50/70 response, respectively.

Radiographic response
In PsA Study 3, inhibition of progression of structural damage was assessed radiographically and expressed by the modified Total Sharp Score (mTSS) and its components, the Erosion Score (ES) and the Joint Space Narrowing Score (JSN). Radiographs of hands, wrists, and feet were obtained at baseline, Week 16 and/or Week 24 and scored independently by at least two readers who were blinded to treatment group and visit number. Cosentyx 150 mg and 300 mg treatment significantly inhibited the rate of progression of peripheral joint damage compared with placebo treatment as measured by change from baseline in mTSS at Week 24 (Table 6).

Inhibition of progression of structural damage was also assessed in PsA Study 1 at Weeks 24 and 52, compared to baseline. Week 24 data are presented in Table 6.

Table 6 Change in modified Total Sharp Score in psoriatic arthritis

	PsA Study 3			PsA Study 1	
	Placebo n=296	**Cosentyx 150 mg[1] n=213**	**Cosentyx 300 mg[1] n=217**	**Placebo n=179**	**Cosentyx 150 mg[2] n=185**
Total score					
Baseline (SD)	15.0 (38.2)	13.5 (25.6)	12.9 (23.8)	28.4 (63.5)	22.3 (48.0)
Mean change at Week 24	0.50	0.13*	0.02*	0.57	0.13*

*p<0.05 based on nominal, but non adjusted, p-value
[1]Cosentyx 150 mg or 300 mg s.c. at Weeks 0, 1, 2, 3, and 4 followed by the same dose every month
[2]10 mg/kg at Weeks 0, 2 and 4 followed by subcutaneous doses of 75 mg or 150 mg

In PsA Study 1, inhibition of structural damage was maintained with Cosentyx treatment up to Week 52.

In PsA Study 3, the percentage of patients with no disease progression (defined as a change from baseline in mTSS of ≤0.5) from randomisation to Week 24 was 80.3%, 88.5% and 73.6% for secukinumab 150 mg, 300 mg and placebo, respectively. An effect of inhibition of structural damage was observed in anti-TNFα-naïve and anti-TNFα-IR patients and in patients treated with and without concomitant MTX.

In PsA Study 1, the percentage of patients with no disease progression (defined as a change from baseline in mTSS of ≤0.5) from randomisation to Week 24 was 82.3% in secukinumab 10 mg/kg intravenous load – 150 mg subcutaneous maintenance and 75.7% in placebo. The percentage of patients with no disease progression from Week 24 to Week 52 for secukinumab 10 mg/kg intravenous load – followed by 150 mg subcutaneous maintenance and for placebo patients who switched to 75 mg or 150 mg subcutaneous every 4 weeks at Week 16 or Week 24 was 85.7% and 86.8%, respectively.

Physical function and health-related quality of life
In PsA Study 2 and PsA Study 3, patients treated with Cosentyx 150 mg (p=0.0555 and p<0.0001) and 300 mg (p=0.0040 and p<0.0001) showed improvement in physical function compared to patients treated with placebo as assessed by Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24 and Week 16, respectively. Improvements in HAQ-DI scores were seen regardless of previous anti-TNFα exposure. Similar responses were seen in PsA Study 1.

Cosentyx-treated patients reported significant improvements in health-related quality of life as measured by the Short Form-36 Health Survey Physical Component Summary (SF-36 PCS) score (p<0.001). There were also statistically significant improvements demonstrated in exploratory endpoints assessed by the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scores for 150 mg and 300 mg compared to placebo (7.97, 5.97 versus 1.63, respectively) and these improvements were maintained up to Week 104 in PsA Study 2.

Similar responses were seen in PsA Study 1 and efficacy was maintained up to Week 52.

Ankylosing spondylitis
The safety and efficacy of Cosentyx were assessed in 590 patients in two randomised, double-blind, placebo-controlled phase III studies in patients with active ankylosing spondylitis (AS) with a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or disease-modifying anti-rheumatic drug (DMARD) therapy. Patients in these studies had a diagnosis of AS for a median of 2.7 to 5.8 years. For both studies, the primary endpoint was at least a 20% improvement in Assessment of Spondyloarthritis International Society (ASAS 20) criteria at Week 16.

In Ankylosing Spondylitis Study 1 (AS Study 1) and Ankylosing Spondylitis Study 2 (AS Study 2) 27.0% and 38.8% of patients, respectively, were previously treated with an anti-TNFα agent and discontinued the anti-TNFα agent for either lack of efficacy or intolerance (anti-TNFα-IR patients).

AS Study 1 (MEASURE 1) evaluated 371 patients, of whom 14.8% and 33.4% used concomitant MTX or sulfasalazine, respectively. Patients randomised to Cosentyx received 10 mg/kg intravenously at Weeks 0, 2, and 4, followed by either 75 mg or 150 mg subcutaneously every month starting at Week 8. Patients randomised to placebo who were non-responders at Week 16 (early rescue) and all other placebo patients at Week 24 were crossed over to receive Cosentyx (either 75 mg or 150 mg subcutaneously), followed by the same dose every month.

AS Study 2 (MEASURE 2) evaluated 219 patients, of whom 11.9% and 14.2% used concomitant MTX or sulfasalazine, respectively. Patients randomised to Cosentyx received 75 mg or 150 mg subcutaneously at Weeks 0, 1, 2, 3 and 4, followed by the same dose every month. At Week 16, patients who were randomised to placebo at baseline were re-randomised to receive Cosentyx (either 75 mg or 150 mg subcutaneously) every month.

Signs and symptoms
In AS Study 2, treatment with Cosentyx 150 mg resulted in greater improvement in measures of disease activity compared with placebo at Week 16 (see Table 7).

Table 7 Clinical response in AS Study 2 at Week 16

Outcome (p-value versus placebo)	**Placebo (n = 74)**	**75 mg (n = 73)**	**150 mg (n = 72)**
ASAS 20 response, %	28.4	41.1	61.1***
ASAS 40 response, %	10.8	26.0	36.1***
hsCRP, (post-BSL/BSL ratio)	1.13	0.61	0.55***
ASAS 5/6, %	8.1	34.2	43.1***
ASAS partial remission, %	4.1	15.1	13.9
BASDAI 50, %	10.8	24.7*	30.6**
ASDAS-CRP major improvement	4.1	15.1*	25.0***

* $p<0.05$, ** $p<0.01$, *** $p<0.001$; versus placebo
All p-values adjusted for multiplicity of testing based on pre-defined hierarchy, except BASDAI 50 and ASDAS-CRP
Non-responder imputation used for missing binary endpoint

ASAS: Assessment of SpondyloArthritis International Society Criteria; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; hsCRP: high-sensitivity C-reactive protein; ASDAS: Ankylosing Spondylitis Disease Activity Score; BSL: baseline

The onset of action of Cosentyx 150 mg occurred as early as Week 1 for ASAS 20 and Week 2 for ASAS 40 (superior to placebo) in AS Study 2.

ASAS 20 responses were improved at Week 16 in both anti-TNFα-naïve patients (68.2% versus 31.1%; $p<0.05$) and anti-TNFα-IR patients (50.0% versus 24.1%; $p<0.05$) for Cosentyx 150 mg compared with placebo, respectively.

In both AS studies, Cosentyx-treated patients (150 mg in AS Study 2 and both regimens in AS Study 1) demonstrated significantly improved signs and symptoms at Week 16, with comparable magnitude of response and efficacy maintained up to Week 52 in both anti-TNFα-naive and anti-TNFα-IR patients. In AS Study 2, among 72 patients initially randomised to Cosentyx 150 mg, 61 (84.7%) patients were still on treatment at Week 52. Of the 72 patients randomised to Cosentyx 150 mg, 45 and 35 had an ASAS 20/40 response, respectively.

Spinal mobility
Patients treated with Cosentyx 150 mg showed improvements in spinal mobility as measured by change from baseline in BASMI at Week 16 for both AS Study 1 (-0.40 versus -0.12 for placebo; p=0.0114) and AS Study 2 (-0.51 versus -0.22 for placebo; p=0.0533). These improvements were sustained up to Week 52.

Physical function and health-related quality of life
In AS Study 1 and Study 2, patients treated with Cosentyx 150 mg showed improvements in health-related quality of life as measured by AS Quality of Life Questionnaire (ASQoL) (p=0.001) and SF-36 Physical Component Summary (SF-36PCS) (p<0.001). Patients treated with Cosentyx 150 mg also showed statistically significant improvements on exploratory endpoints in physical function as assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI) compared to placebo (-2.15 versus -0.68), and in fatigue as assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale compared to placebo (8.10 versus 3.30). These improvements were sustained up to Week 52.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Cosentyx in plaque psoriasis in paediatric patients aged from birth to less than 6 years and in chronic idiopathic arthritis for paediatric patients aged from birth to less than 2 years (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with Cosentyx in plaque psoriasis in paediatric patients aged from 6 years to less than 18 years and in chronic idiopathic arthritis for paediatric patients aged from 2 years to less than 18 years (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Plaque psoriasis

Absorption
Following a single subcutaneous dose of 300 mg as a liquid formulation in healthy volunteers, secukinumab reached peak serum concentrations of 43.2±10.4 µg/ml between 2 and 14 days post dose.

Based on population pharmacokinetic analysis, following a single subcutaneous dose of either 150 mg or 300 mg in plaque psoriasis patients, secukinumab reached peak serum concentrations of 13.7±4.8 µg/ml or 27.3±9.5 µg/ml, respectively, between 5 and 6 days post dose.

After initial weekly dosing during the first month, time to reach the maximum concentration was between 31 and 34 days based on population pharmacokinetic analysis.

On the basis of simulated data, peak concentrations at steady-state ($C_{max,ss}$) following subcutaneous administration of 150 mg or 300 mg were 27.6 µg/ml and 55.2 µg/ml, respectively. Population pharmacokinetic analysis suggests that steady-state is reached after 20 weeks with monthly dosing regimens.

Compared with exposure after a single dose, the population pharmacokinetic analysis showed that patients exhibited a 2-fold increase in peak serum concentrations and area under the curve (AUC) following repeated monthly dosing during maintenance.

Population pharmacokinetic analysis showed that secukinumab was absorbed with an average absolute bioavailability of 73% in patients with plaque psoriasis. Across studies, absolute bioavailabilities in the range between 60 and 77% were calculated.

Distribution
The mean volume of distribution during the terminal phase (V_z) following single intravenous administration ranged from 7.10 to 8.60 litres in plaque psoriasis patients, suggesting that secukinumab undergoes limited distribution to peripheral compartments.

Biotransformation
The majority of IgG elimination occurs via intracellular catabolism, following fluid-phase or receptor mediated endocytosis.

Elimination
Mean systemic clearance (CL) following a single intravenous administration to patients with plaque psoriasis ranged from 0.13 to 0.36 l/day. In a population pharmacokinetic analysis, the mean systemic clearance (CL) was 0.19 l/day in plaque psoriasis patients. The CL was not impacted by gender. Clearance was dose- and time-independent.

The mean elimination half-life, as estimated from population pharmacokinetic analysis, was 27 days in plaque psoriasis patients, ranging from 18 to 46 days across psoriasis studies with intravenous administration.

Linearity/non-linearity
The single and multiple dose pharmacokinetics of secukinumab in plaque psoriasis patients were determined in several studies with intravenous doses ranging from 1x 0.3 mg/kg to 3x 10 mg/kg and with subcutaneous doses ranging from 1x 25 mg to multiple doses of 300 mg. Exposure was dose proportional across all dosing regimens.

Psoriatic arthritis

The pharmacokinetic properties of secukinumab observed in psoriatic arthritis patients were similar to those displayed in plaque psoriasis patients. The bioavailability of secukinumab in PsA patients was 85% on the basis of the population pharmacokinetic model.

Ankylosing spondylitis

The pharmacokinetic properties of secukinumab observed in ankylosing spondylitis patients were similar to those displayed in plaque psoriasis patients.

Special populations

Elderly patients
Of the 3,430 plaque psoriasis patients exposed to Cosentyx in clinical studies, a total of 230 patients were 65 years of age or older and 32 patients were 75 years of age or older.

Of the 2,536 psoriatic arthritis patients exposed to Cosentyx in clinical studies, a total of 236 patients were 65 years of age or older and 25 patients were 75 years of age or older.

Of the 571 ankylosing spondylitis patients exposed to Cosentyx in clinical studies, a total of 24 patients were 65 years of age or older and 3 patients were 75 years of age or older.

Based on population pharmacokinetic analysis with a limited number of elderly patients (n=71 for age ≥65 years and n=7 for age ≥75 years), clearance in elderly patients and patients less than 65 years of age was similar.

Patients with renal or hepatic impairment
No pharmacokinetic data are available in patients with renal or hepatic impairment. The renal elimination of intact Cosentyx, an IgG monoclonal antibody, is expected to be low and of minor importance. IgGs are mainly eliminated via catabolism and hepatic impairment is not expected to influence clearance of Cosentyx.

Effect of weight on pharmacokinetics
Secukinumab clearance and volume of distribution increase as body weight increases.

5.3 Preclinical safety data

Non-clinical data revealed no special risks for humans based on tissue cross-reactivity testing, safety pharmacology, repeated dose and reproductive toxicity studies performed with secukinumab or a murine anti-murine IL-17A antibody.

Since secukinumab binds to cynomolgus monkey and human IL-17A, its safety was studied in the cynomolgus monkey. No undesirable effects of secukinumab were seen following subcutaneous administration to cynomolgus monkeys for up to 13 weeks and intravenous administration up to 26 weeks (including pharmacokinetic, pharmacodynamic, immunogenicity and immunotoxicity (e.g. T-cell dependent antibody response and NK cell activity) evaluations). The average serum concentrations observed in monkeys after 13 weekly subcutaneous doses of 150 mg/kg were considerably higher than the predicted average serum concentration expected in psoriatic patients at the highest clinical dose. Antibodies to secukinumab were detected in only one of the exposed animals. No non-specific tissue cross-reactivity was observed when secukinumab was applied to normal human tissue.

Animal studies have not been conducted to evaluate the carcinogenic potential of secukinumab.

In an embryofoetal development study in cynomolgus monkeys, secukinumab showed no maternal toxicity, embryotoxicity or teratogenicity when administered throughout organogenesis and late gestation.

No undesirable effects of a murine anti-murine IL-17A antibody were seen in fertility and early embryonic development and pre-and postnatal development studies in mice. The high dose used in these studies was in excess of the maximum effective dose in terms of IL-17A suppression and activity (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trehalose dihydrate
L-histidine
L-histidine hydrochloride monohydrate
L-methionine
Polysorbate 80
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

18 months

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze. If necessary, Cosentyx may be stored unrefrigerated for a single period of up to 4 days at room temperature, not above 30°C.
Store the pens in the original package in order to protect from light.

6.5 Nature and contents of container

Cosentyx is supplied in a single-use pre-filled syringe assembled into a triangular-shaped pen with transparent window and label (SensoReady pen). The pre-filled syringe inside the pen is a 1 ml glass syringe with a FluroTec-coated plunger stopper, staked 27G x ½″ needle and rigid needle shield of styrene butadiene rubber.

Cosentyx is available in unit packs containing 1 or 2 pre-filled pens and in multipacks containing 6 (3 packs of 2) pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Cosentyx 150 mg solution for injection is supplied in a single-use pre-filled pen for individual use. Do not shake or freeze the pen. The pen should be taken out of the refrigerator 20 minutes before injecting to allow it to reach room temperature.

Prior to use, a visual inspection of the pre-filled pen is recommended. The liquid should be clear. Its colour may vary from colourless to slightly yellow. You may see a small air bubble, which is normal. Do not use if the liquid contains easily visible particles, is cloudy or is distinctly brown. Detailed instructions for use are provided in the package leaflet.

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
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Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/980/004
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EU/1/14/980/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15.01.2015

10. DATE OF REVISION OF THE TEXT

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