The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in March 2016 and updated in accordance with the Ministry of Health guidelines on October 2018.

1. NAME OF THE MEDICINAL PRODUCT

Cosentyx® 150 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

*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
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.

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 150 mg solution for injection in pre-filled syringe and pre-filled pen (SensoReady pen)
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/pre-filled pen 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/pre-filled pen 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

A total of 6,804 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). Of these, 3,671 patients were exposed to Cosentyx for at least one year, representing ~6,450 patient years of exposure.

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

Cosentyx was studied in two placebo-controlled psoriatic arthritis studies with 1,003 patients (703 patients on Cosentyx and 300 patients on placebo) for a total exposure of 1,061 patient-years of study exposure (median duration of exposure for secukinumab-treated patients: 456 days in PsA Study 1 and 245 days in PsA Study 2). 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 $<1.0\text{-}0.5 \times 10^9$/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 to the Ministry of Health according to the National Regulation by using an online form (https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il).

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 responses 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.

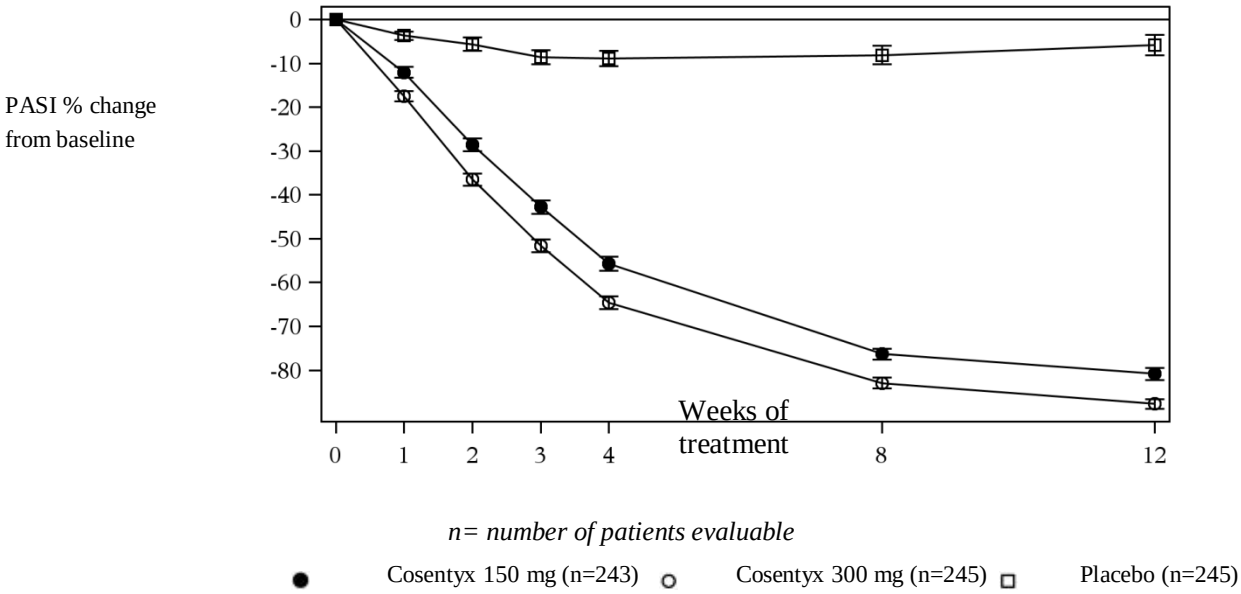
Table 4 Summary of clinical response on CLEAR Study

	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-naïve, 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 1,003 patients in two 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 for a median of 3.9 to 5.3 years. The majority of patients also had active psoriasis skin lesions or a documented history of psoriasis. Over 62% and 47% of the PsA patients had enthesitis and dactylitis at baseline, respectively. For both studies, the primary endpoint was American College of Rheumatology (ACR) 20 response at Week 24.

In Psoriatic Arthritis Study 1 (PsA Study 1) and Psoriatic Arthritis Study 2 (PsA Study 2) 29% and 35% 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.

Signs and symptoms

Treatment with Cosentyx resulted in significant improvement in measures of disease activity compared to placebo at Week 24 (see Table 5).

Table 5 Clinical response in PsA Study 2 at Week 24

	Week 24			
	Placebo	75 mg	150 mg	300 mg
Number of patients randomised	98	99	100	100
ACR20 response n (%)	15 (15.3%)	29 (29.3%*)	51 (51.0%***)	54 (54.0%***)
ACR50 response n (%)	7 (7.1%)	18 (18.2%)	35 (35.0%)	35 (35.0%**)
ACR70 response n (%)	1 (1.0%)	6 (6.1%)	21 (21.0%**)	20 (20.0%**)
DAS28-CRP	-0.96	-1.12	-1.58**	-1.61**
Number of patients with ≥3% BSA psoriasis skin involvement at baseline	43 (43.9%)	50 (50.5%)	58 (58.0%)	41 (41.0%)
PASI 75 response n (%)	7 (16.3%)	14 (28.0%)	28 (48.3%**)	26 (63.4%***)
PASI 90 response n (%)	4 (9.3%)	6 (12.0%)	19 (32.8%**)	20 (48.8%***)
Dactylitis Resolution n (%) †	4 (14.8%)	10 (30.3%)	16 (50.0%**)	26 (56.5%**)
Enthesitis Resolution n (%) ‡	14 (21.5%)	22 (32.4%)	27 (42.2%*)	27 (48.2%**)

* 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, except for ACR70, Dactylitis and Enthesitis, which were exploratory endpoints.

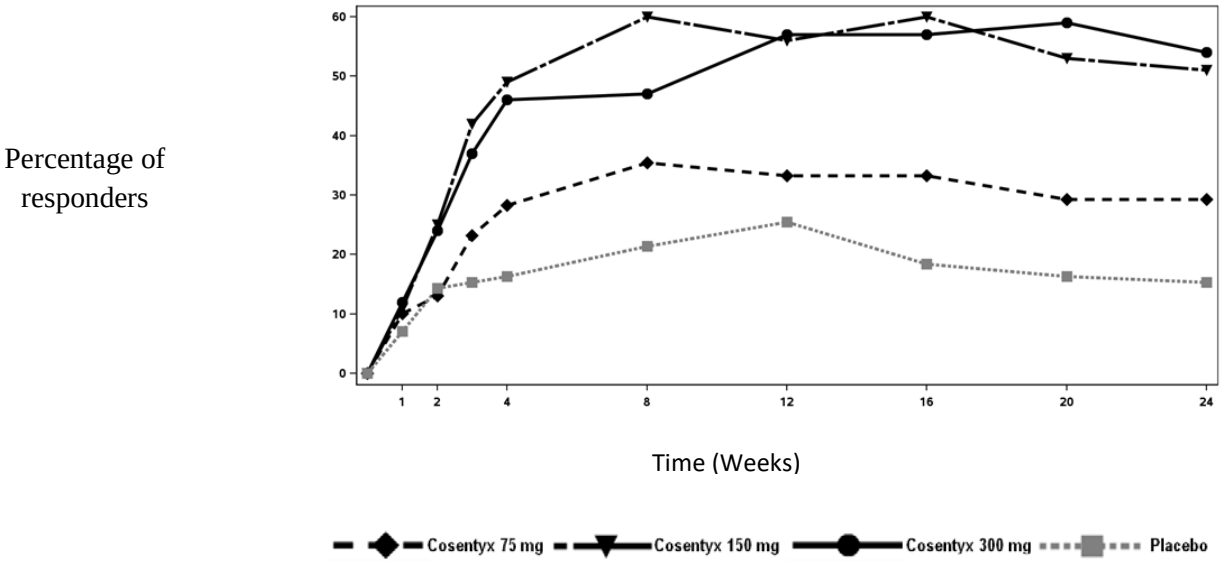
Non-responder imputation used for missing binary endpoint.

ACR: American College of Rheumatology; PASI: Psoriasis Area and Severity Index; DAS: Disease Activity Score; BSA: Body Surface Area
†In patients with dactylitis at baseline (n=27, 33, 32, 46, respectively)
‡In patients with enthesitis at baseline (n=65, 68, 64, 56, respectively)

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. At Week 16, Cosentyx-treated patients demonstrated significant improvements in signs and symptoms among which significantly higher responses in ACR 20 (33.3%, 60.0% and 57.0% for 75 mg, 150 mg and 300 mg, respectively) compared to placebo (18.4%).

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 24



Similar responses for primary and key secondary endpoints were seen in PsA patients regardless of whether they were on concomitant MTX treatment or not. At Week 24, Cosentyx-treated patients with concomitant MTX use had a higher ACR 20 response (44.7%, 47.7% and 54.4% for 75 mg, 150 mg and 300 mg, respectively, compared to placebo 20.0%) and ACR 50 response (27.7%, 31.8% and 38.6% for 75 mg, 150 mg and 300 mg, respectively, compared to placebo 8.0%). Cosentyx-treated patients without concomitant MTX use had a higher ACR 20 response (15.4%, 53.6% and 53.6% for 75 mg, 150 mg and 300 mg, respectively, compared to placebo 10.4%) and ACR 50 response (9.6%, 37.5% and 32.1% for 75 mg, 150 mg and 300 mg, respectively, compared to placebo 6.3%).

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: 37%, 64% and 58% for 75 mg, 150 mg and 300 mg, respectively, compared to placebo 15.9%; anti-TNFα-IR: 15%, 30% and 46% for 75 mg, 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. The proportion of patients achieving a modified PsA Response Criteria (PsARC) response was greater in the Cosentyx-treated patients (37.4%, 59.0% and 61.0% for 75 mg, 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 52. 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
Inhibition of progression of structural damage in PsA has not yet been demonstrated using the subcutaneous loading regimen approved for clinical use.

In PsA Study 1, inhibition of progression of structural damage was assessed radiographically and expressed as the change in modified total Sharp Score (mTSS) and its components, the Erosion Score (ES) and the Joint Space Narrowing score (JSN) 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

	Placebo N=179	**Cosentyx 75 mg[1] N=181**	**Cosentyx 150 mg[1] N=185**
Total score			
Baseline (SD)	28.4 (63.5)	20.4 (39.4)	22.3 (48.0)
Mean change at Week 24	0.57	0.02*	0.13*
*p<0.05 based on nominal, but non adjusted, p-value [1]10 mg/kg at Weeks 0, 2 and 4 followed by subcutaneous doses of 75 mg or 150 mg			

Inhibition of structural damage was maintained with Cosentyx treatment up to Week 52.

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 92.3% in secukinumab 10 mg/kg intravenous load – 75 mg subcutaneous maintenance, 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 either 75 mg or 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 85.8%, 85.7% and 86.8%, respectively.

Physical function and health-related quality of life
In PsA Study 2, patients treated with Cosentyx 150 mg (p=0.0555) and 300 mg (p=0.0040) showed

improvement in physical function compared to patients treated with placebo as assessed by Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24. 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). 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 company was granted waiver of 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 company got deferring of 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 974 psoriatic arthritis patients exposed to Cosentyx in clinical studies, a total of 85 patients were 65 years of age or older and 4 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

Cosentyx 150 mg solution for injection in pre-filled syringe and pre-filled pen (SensoReady pen)

Trehalose dihydrate
L-histidine/ L-histidine hydrochloride monohydrate
L-methionine
Polysorbate 80
Water for injections

6.2 Incompatibilities

Cosentyx 150 mg solution for injection in pre-filled syringe and pre-filled pen (SensoReady pen)
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Cosentyx 150 mg solution for injection in pre-filled syringe and pre-filled pen (SensoReady pen)
The expiry date of the product is printed on the package materials.

6.4 Special precautions for storage

Cosentyx 150 mg solution for injection in pre-filled syringe and pre-filled pen (SensoReady pen)
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 and pens in the original package in order to protect from light.

6.5 Nature and contents of container

Cosentyx 150 mg solution for injection in pre-filled syringe

Cosentyx150 mg solution for injection 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.
Not all pack sizes may be marketed.

Cosentyx 150 mg solution for injection in pre-filled pen (SensoReady pen)

Cosentyx 150 mg solution for injection 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 pack containing 1 or 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 in pre-filled syringe and pre-filled pen

Cosentyx 150 mg solution for injection is supplied in a single-use pre-filled syringe/pen for individual use. Do not shake or freeze the syringe or the pen. The syringe or 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 syringe/ 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. MANUFACTURER:

Novartis Pharma Stein, AG, Stein Switzerland
For Novartis Pharma AG, Basel, Switzerland

8. REGISTRATION HOLDER:

Novartis Israel Ltd.
36 Shacham St.,
Petach-Tikva

9. REGISTRATION NUMBER: 154-20-34342

Cosentyx 150 mg solution for injection in a pre-filled syringe and pre-filled pen (Sensoready pen)