COSENTYX®

secukinumab (*rch*)

NAME OF THE MEDICINE

Active ingredient:	Secukinumab
Chemical name:	Recombinant human monoclonal anti-human Interleukin-17A (IL-17A, IL-17) antibody of the IgG1/kappa isotype
CAS Numbers:	875356-43-7 (heavy chain), 875356-44-8 (light chain)
Molecular formula:	$C_{6584}H_{10134}N_{1754}O_{2042}S_{44}$
Molecular weight:	Approximately 148 kDa
Structure:	The amino acid sequences of the light chain (215 amino acids) and the heavy chain (457 amino acids) respectively.

DESCRIPTION

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.

Powder for injection

Each vial of powder for injection contains 150 mg of secukinumab as a lyophilised cake in glass vials. Excipients: water for injections, sucrose, histidine, histidine hydrochloride monohydrate, polysorbate 80.

Solution for injection

Solution for injection in a single-use, pre-filled syringe and/or pen (auto-injector).

Prefilled syringe

Each single-use pre-filled syringe contains 150 mg/mL of secukinumab. Excipients: trehalose dihydrate, histidine, histidine hydrochloride monohydrate, polysorbate 80, methionine, water for injections.

Pen

Each single-use prefilled pen contains 150 mg/mL of secukinumab. Excipients: trehalose dihydrate, histidine, histidine hydrochloride monohydrate, polysorbate 80, methionine, water for injections.

PHARMACOLOGY

Pharmacotherapeutic group**:** interleukin inhibitors; ATC Code**:** L04AC10

Mechanism of action

Secukinumab is a fully human IgG1 antibody that selectively binds to and neutralises the proinflammatory cytokine interleukin-17A (IL-17A). 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. 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 plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis and affected

skin of patients with plaque psoriasis. IL-17A is highly up-regulated in lesional skin in contrast to non-lesional skin of plaque psoriasis patients. Higher frequency of IL-17- producing cells was detected in the synovial fluid of patients with psoriatic arthritis and in the subchondral bone marrow of facet joints from patients with ankylosing spondylitis. IL-17A also promotes tissue inflammation, neutrophil infiltration, bone and tissue destruction, and tissue remodelling including angiogenesis and fibrosis.

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.

Pharmacodynamics

Serum levels of total IL-17A (free and secukinumab-bound IL-17A) are increased due to reduced clearance of secukinumab-bound IL-17A within 2 to 7 days in patients receiving secukinumab, 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 in psoriatic arthritis and ankylosing spondylitis.

Pharmacokinetic properties

The mean pharmacokinetic parameters of secukinumab following single and multiple subcutaneous administration in adult patients with psoriasis, resulting from population pharmacokinetic analysis, are shown in Table 1. C_{max} and AUC were dose-proportional at 150 mg and 300 mg subcutaneous doses.

Table 1 Summary of pharmacokinetic parameters of COSENTYX at steady – state following 150 or 300 mg s.c. administration in adult patients with psoriasis

	COSENTYX 4-weekly dose			
	150 mg		300 mg	
Parameter	Mean (SD)	Range	Mean (SD)	Range
Cmax,ss (µg/mL)	27.6 (10.7)	(13.7, 47.4)	55.2 (21.5)	(27.5, 94.8)
Cav,ss (µg/mL)	22.2 (9.2)	(10.5, 39.0	44.5 (18.4)	(21.1, 77.9)
Tmax,ss (day)	6.0	(4.0, 8.0)	6.0	(4.0, 8.0)
AUCss (day.µg/mL)	622 (257)	(295, 1090)	1245 (515)	(590, 2180)

Absorption

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 ug/mL or 27.3 ± 9.5 ug/mL, respectively, between 5 to 6 days post dose.

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

Peak concentrations at steady-state (C_{max},ss) following subcutaneous administration of 150 mg or 300 mg were 27.6 ug/mL and 55.2 ug/mL, respectively. Steady-state is reached after 20 weeks with monthly dosing regimens.

Compared with exposure after a single dose, patients exhibited a 2-fold increase in peak serum concentrations and AUC following repeated monthly dosing during maintenance.

Secukinumab is absorbed with an average absolute bioavailability of 73%.

Distribution

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

Secukinumab concentrations in interstitial fluid in the skin of plaque psoriasis patients ranged from 28 % to 39 % of those in serum at 1 and 2 weeks after a single subcutaneous dose of 300 mg secukinumab.

Metabolism

The metabolic pathway of secukinumab has not been characterised. 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.

Elimination

Mean systemic clearance (CL) was 0.19 L/d in plaque psoriasis patients. Clearance was dose- and time-independent, as expected for a therapeutic IgG1 monoclonal antibody interacting with a soluble cytokine target, such as IL-17A.

The mean elimination half-life was estimated to be 27 days in plaque psoriasis patients. Estimated half-lives in individual plaque psoriasis patients range from 17 to 41 days.

Dose linearity

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

The pharmacokinetics properties of secukinumab observed in psoriatic arthritis and ankylosing spondylitis 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.

Pharmacokinetics in special patient groups

Paediatrics (< 18 years of age)

Specific studies of COSENTYX in paediatric patients have not been conducted.

Elderly patients

Of the 3,430 plaque psoriasis patients exposed to COSENTYX in clinical studies, a total of 230 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 PK analysis, clearance in elderly patients and patients less than 65 years of age was similar.

Patients with renal and hepatic impairment

No pharmacokinetic data are available in patients with hepatic or renal impairment.

Effect of weight on pharmacokinetics

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

CLINICAL TRIALS

Plaque psoriasis

The safety and efficacy of COSENTYX were evaluated versus placebo or etanercept in four randomised, double-blind, placebo-controlled phase 3 studies in adult patients with moderate to severe chronic plaque-type psoriasis poorly controlled by topical treatments and / or phototherapy and / or previous systemic therapy (ERASURE, FIXTURE, FEATURE, and JUNCTURE). The safety and efficacy of COSENTYX were evaluated versus placebo or etanercept in four randomised, double-blind, placebo-controlled phase 3 studies in patients with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy (ERASURE, FIXTURE, FEATURE, and JUNCTURE). In addition, one study assessed a chronic treatment regimen versus a 'retreatment as needed' regimen (SCULPTURE). 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.

Key exclusion criteria across pivotal trials were: forms of psoriasis other than chronic plaque-type; drug-induced psoriasis; ongoing use of certain psoriasis treatments, e.g. topical or systemic corticosteroids or UV therapy; patients with active, ongoing inflammatory disease; patients with active, ongoing, chronic or recurrent infectious disease; evidence of tuberculosis infection (enrolment was allowed for patients with latent tuberculosis if appropriate treatment was initiated and maintained according to the local treatment guideline); history of HIV, hepatitis B or hepatitis C; underlying immunocompromising conditions; presence of lymphoproliferative disease, malignancy or history of malignancy within the past 5 years; significant medical problems including uncontrolled hypertension and congestive heart failure (NYHA Class III and IV); patients with serum creatinine >176.8 micromol/L or with white blood cell count <2,500 /microL, platelets <100,000/microL, neutrophils <1,500/microL or haemoglobin <8.5 g/dL; pregnant or nursing women; and women of child-bearing potential not using effective contraception during the study.

Of the 2,403 patients who were included in the placebo-controlled studies, 79 % were biologic-naïve, 45 % were non-biologic failures, 8 % were biologic failures, 6 % were anti-TNF failures, and 2 % were anti-p40 failures. Baseline disease characteristics were generally consistent across all treatment groups with a median baseline Psoriasis Area Severity Index (PASI) score from 19 to 20, IGA mod 2011 baseline score ranged from "moderate" (62 %) to "severe" (38 %), median baseline Body Surface Area (BSA) ≥ 27 and median Dermatology Life Quality Index (DLQI) score from 10 to 12. Approximately 15 to 25 % of patients in phase III studies had psoriatic arthritis (PsA) at baseline.

ERASURE Study (A2302)

This trial evaluated 738 patients. Patients were randomised to COSENTYX received 150 mg or 300 mg doses at weeks 0, 1, 2, and 3, followed by the same dose every month starting at week 4. Patients were randomised to receive placebo who were non-responders at week 12 were 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.

FIXTURE Study (A2303)

This trial evaluated 1,306 patients. Patients were randomised to COSENTYX received 150 mg or 300 mg doses at weeks 0, 1, 2, and 3, followed by the same dose every month starting at week 4. Patients were randomised to etanercept received 50 mg doses twice per week for 12 weeks followed by 50 mg

every week. Patients were 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.

FEATURE Study (A2308)

This trial 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. Patients randomised to COSENTYX received 150 mg or 300 mg doses at weeks 0, 1, 2, and 3, followed by the same dose every month starting at week 4. Patients were also randomised to receive placebo at weeks 0, 1, 2, and 3, followed by the same dose every month starting at week 4.

JUNCTURE Study (A2309)

This trial 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. Patients were randomised to COSENTYX received 150 mg or 300 mg doses at weeks 0, 1, 2, and 3, followed by the same dose every month starting at week 4. Patients were also randomised to receive placebo at weeks 0, 1, 2, and 3, followed by the same dose every month starting at week 4.

SCULPTURE Study (A2304)

This trial 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.

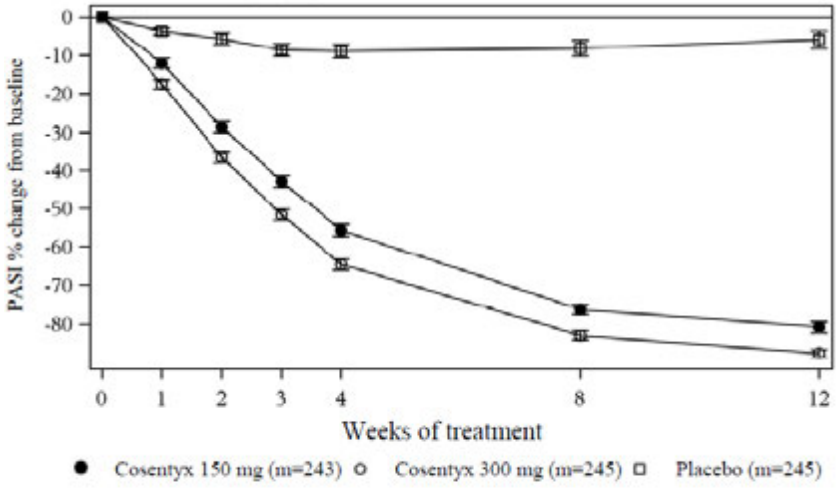
Results

The 300 mg dose provided improved skin clearance across efficacy endpoints of PASI 75/90/100, and IGA mod 2011 'clear' or 'almost clear' responses across all studies with peak effects seen at week 16 (see to Table 2 and Table 3). Therefore the 300 mg dose is recommended.

COSENTYX was efficacious in biologic-naive, biologic/anti-TNF-exposed and biologic/anti-TNF-failure patients.

COSENTYX was associated with a fast onset of efficacy as shown in Figure 1 with a 50 % reduction in mean PASI by week 3 for 300 mg.

Figure 1 Time course of percentage change from baseline of mean PASI



m = number of patients evaluable

Table 2 Summary of clinical response in ERASURE, FEATURE and JUNCTURE trials

	Week 12			Week 16		Week 52	
	Placebo	150 mg	300 mg	150 mg	300 mg	150 mg	300 mg
	ERASURE						
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%)
FEATURE							
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%)**	-	-	-	-
JUNCTURE							
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 coloration 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 in FIXTURE trial

	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

All plaque psoriasis phase III studies included approximately 15 to 25% of patients with concurrent

psoriatic arthritis at baseline. Improvements in PASI 75 in this patient population were similar to those in the overall plaque psoriasis population.

In the subset of psoriatic arthritis patients in the ERASURE and FIXTURE studies, physical function was assessed using the HAQ Disability Index (HAQ-DI). In these studies, patients treated with 150 mg or 300 mg COSENTYX showed greater improvement from baseline in the HAQ-DI score (mean decreases of -27.5% and -50.2% at week 12) compared to placebo (-8.9%). This improvement was maintained up to week 52.

Patients in the SCULPTURE study that were randomised after week 12 to a "retreatment as needed" maintenance regimen did not achieve adequate maintenance of response to either dose used. After 52 weeks of treatment patients with 300 mg "retreatment as needed" regimen achieved a PASI 75 of 41.0% and a PASI 90 of 13.8%, whereas patients with a monthly maintenance regimen of 300 mg achieved a PASI 75 of 78.2% and a PASI 90 of 59.7%. Similarly, patients with 150 mg "retreatment as needed" regimen achieved a PASI 75 of 35.0% and a PASI 90 of 11.2%, whereas patients with a monthly maintenance regimen of 150 mg achieved a PASI 75 of 62.1% and a PASI 90 of 45.8% after 52 weeks of treatment. Therefore a fixed monthly maintenance regimen is recommended.

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), these improvements were maintained for 52 weeks (Studies 1 and 2).

Statistically significant improvements at week 12 from baseline compared to placebo (ERASURE and FIXTURE Studies) in patient reported signs and symptoms of itching, pain and scaling were demonstrated in the validated Psoriasis Symptom Diary.

Psoriatic Arthritis

The safety and efficacy of Cosentyx were assessed in 1,003 patients in two randomized, 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), corticosteroids 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 . Approximately half of all enrolled patients had at least 3% BSA involvement with skin psoriasis at baseline. Over 62% and 47% of the PsA patients had enthesitis and dactylitis at baseline, respectively.

In FUTURE 1 Study (PsA1 Study) and FUTURE 2 Study (PsA2 Study) 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). For both studies, the primary endpoint was American College of Rheumatology (ACR) 20 response at Week 24.

Key exclusion criteria across pivotal trials were: use of high potency opioid analgesics; ongoing use of certain psoriasis treatments, e.g. topical or systemic corticosteroids or UV therapy; previous exposure to secukinumab or any other biologic drugs for psoriasis and PsA except for those targeting TNFα, patients with active, ongoing inflammatory disease other than PsA; patients with active, ongoing, chronic or recurrent infectious disease; evidence of tuberculosis infection (enrolment was allowed for patients with latent tuberculosis if appropriate treatment was initiated and maintained according to the local treatment guideline); history of HIV, hepatitis B or hepatitis C; underlying immunocompromising conditions; presence of lymphoproliferative disease, malignancy or history of malignancy within the past 5 years; significant medical problems including uncontrolled hypertension and congestive heart failure (NYHA Class III and IV); patients with serum creatinine >132.6 micromol/L or with white blood cell count <3,000 /microL,, platelets <100,000/microL, neutrophils <1,500/microL or haemoglobin <8.5 g/dL; pregnant or nursing women; and women of child-bearing

potential not using effective contraception during the study.

FUTURE 1 Study (F2306)

PsA1 Study evaluated 606 patients, of whom 60.7% had concomitant MTX. Patients randomized to Cosentyx received 10 mg/kg, i.v. at Weeks 0, 2, and 4, followed by either 75 mg or 150 mg s.c. every month starting at Week 8. Patients randomized to receive 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) at Week 16 followed by the same dose every month.

FUTURE 2 Study (F2312)

PsA2 Study evaluated 397 patients, of whom 46.6% had concomitant MTX. Patients randomized to Cosentyx received 75 mg, 150 mg or 300 mg s.c. at Weeks 0, 1, 2, and 3, followed by the same dose every month starting at Week 4. Patients randomized 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, s.c.) at Week 16 followed by the same dose every month. Patients randomized to receive placebo who were responders at Week 16 were crossed over to receive Cosentyx (either 150 mg or 300 mg) at Week 24 followed by the same dose every month.

Signs and symptoms

In PsA2 Study, treatment with Cosentyx resulted in significant improvement in the measure of disease activity compared to placebo at Weeks 16 and 24 (see Table 4).

Table 4 Clinical response in PsA 2 Study at Week 24

	Week 24			
	Placebo	75 mg	150 mg	300 mg
Number of patients randomized	98	99	100	100
ACR 20 response n (%)	15 (15.3%)	29 (29.3%*)	51 (51.0%***)	54 (54.0%***)
ACR 50 response n (%)	7 (7.1%)	18 (18.2%*)	35 (35.0%)	35 (35.0%***)
ACR 70 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<0.00l; 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

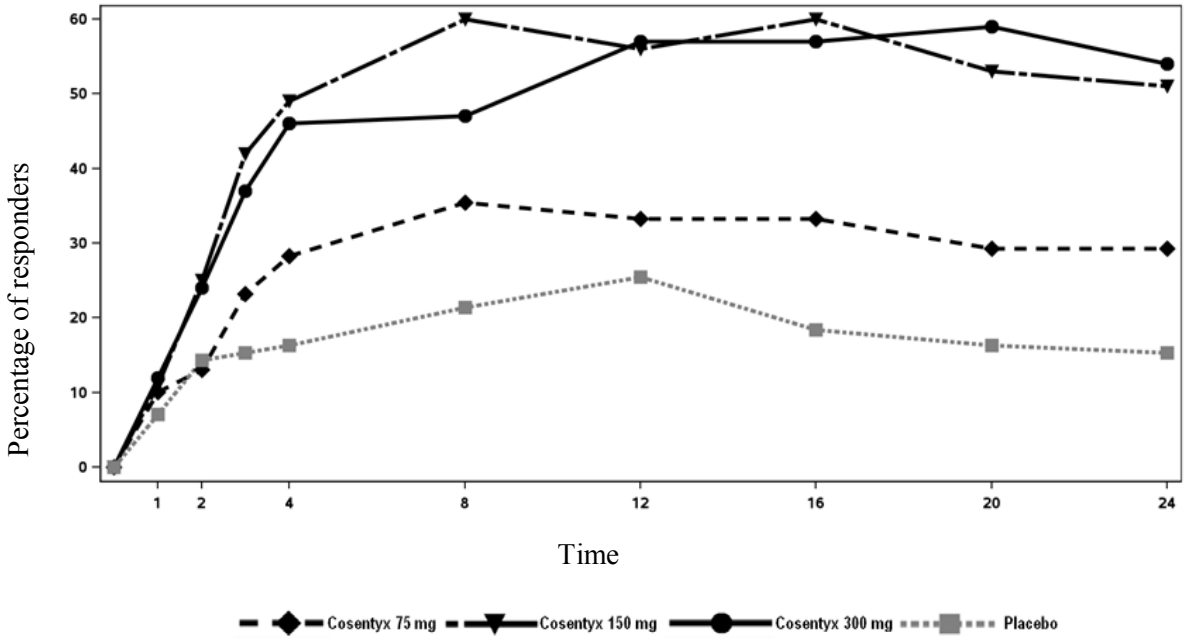
† In patients with dactylitis at baseline (n=27, 33, 32, 46, respectively)
‡ In patients with enthesitis at baseline (n=65, 68, 64, 56, respectively)

The onset of action of Cosentyx occurred as early as Week 2. Statistically significant difference in

ACR 20 vs 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 ACR20 response by visit is shown in Figure 2.

Figure 2 ACR 20 response in PsA 2 Study 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.

Both, anti-TNFα-naïve 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- naïve group (anti-TNFα-naïve: 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%). Anti-TNFα–IR patients on 300mg showed higher response rates on ACR20 compared to placebo patients ($p<0.05$) and demonstrated clinical meaningful benefit over 150 mg on multiple secondary endpoints. Improvements in the PASI75 response were seen in both subgroups and the 300 mg dose showed statistically significant benefit in the anti-TNFα-IR patients.

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 (38.4%, 62.0% and 63.0% for 75 mg, 150 mg and 300 mg, respectively) compared to placebo (29.6%) 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.

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 5.

Table 5 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 not adjusted, p-value

[1] **10 mg/kg at Weeks 0, 2 and 4 followed s.c. 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 modified total Sharp score of ≤0.5) from randomization to Week 24 was 92.3% in secukinumab 10 mg/kg i.v. load – 75 mg s.c. maintenance, 82.3% in secukinumab 10 mg/kg i.v. load – 150 mg s.c. maintenance and 75.7% in placebo. The percentage of patients with no-disease progression, from Week 24 to Week 52, for the same above described regimen, was 85.8%, 85.7% and 86.8%, respectively.

Inhibition of progression of structural damage in PsA has not been demonstrated using the subcutaneous loading regimen approved for clinical use.

Physical function and health related quality of life

In PsA Study 2, patients treated with Cosentyx 150 mg and 300 mg showed improvement in physical function compared to patients treated with placebo as assessed by Heath Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24 (and up to Week 52 in PsA Study 1). Improvements in HAQ-DI scores were seen regardless of previous anti-TNFα exposure.

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).

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 MEASURE 1 Study (AS1 Study) and MEASURE 2 Study (AS2 Study) 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).

Key exclusion criteria across pivotal trials were: patients with total ankylosis of the spine; use of high potency opioid analgesics; previous exposure to secukinumab or any other biologic drugs except for those targeting TNFα, patients with active, ongoing inflammatory disease, other than AS; patients with active, ongoing, chronic or recurrent infectious disease; evidence of tuberculosis infection (enrolment was allowed for patients with latent tuberculosis if appropriate treatment was initiated and maintained according to the local treatment guideline); history of HIV, hepatitis B or hepatitis C; underlying immunocompromising conditions; presence of lymphoproliferative disease, malignancy or history of malignancy within the past 5 years; significant medical problems including uncontrolled hypertension and congestive heart failure (NYHA Class III and IV); patients with serum creatinine >132.6

micromol/L or with white blood cell count <3,000 /microL, platelets <100,000/microL, neutrophils <1,500/microL or haemoglobin <8.5 g/dL; pregnant or nursing women; and women of child-bearing potential not using effective contraception during the study.

AS1 Study evaluated 371 patients, of whom 14.8% and 33.4% used concomitant MTX or sulfasalazine, respectively. Patients randomised to COSENTYX received 10 mg/kg, i.v. at Weeks 0, 2, and 4, followed by either 75 mg or 150 mg s.c. 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 s.c.), followed by the same dose every month.

AS2 Study 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 s.c. at Weeks 0, 1, 2, and 3, followed by the same dose every month starting at Week 4. At Week 16, patients who were randomised to placebo at baseline were re-randomised to receive COSENTYX (either 75 mg or 150 mg) s.c. every month.

Signs and symptoms

In AS2 Study, treatment with COSENTYX 150 mg resulted in greater improvement in measures of disease activity compared with placebo at Week 16 (see Table6).

Table 6 Clinical response in AS2 Study at Week 16

Outcome (p-value vs placebo)	Placebo (n = 74)	75 mg (n = 73)	150 mg (n = 72)
Efficacy at Week 16			
ASAS20 response, %	28.4	41.1	61.1***
ASAS40 response, %	10.8	26.0	36.1***
hsCRP, (post-BSL/BSL ratio)	1.13	0.61	0.55***
ASAS5/6, %	8.1	34.2	43.1***
ASAS partial remission, %	4.1	15.1	13.9
BASDAI50, %	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 vs. placebo

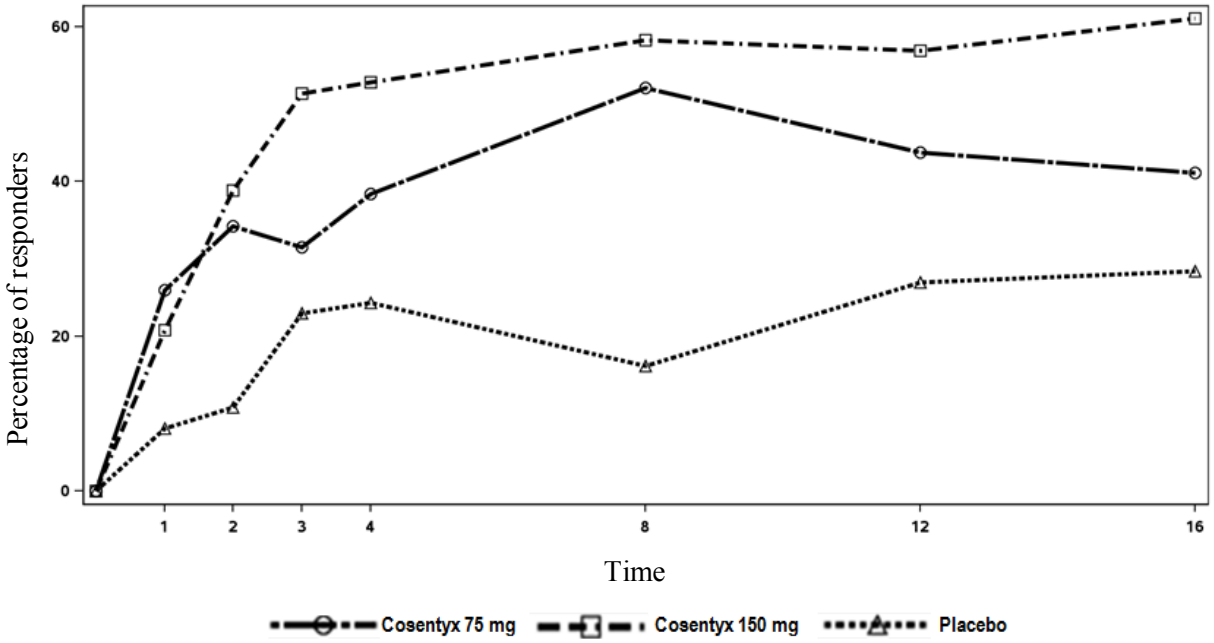
All p-values adjusted for multiplicity of testing based on pre-defined hierarchy, except BASDAI50 and ASDAS-CRP

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; LS: least square

The onset of action of COSENTYX 150 mg occurred as early as Week 1 for ASAS20 and Week 2 for ASAS40 (superior to placebo) in AS2 Study.

Figure 3 ASAS20 responses in AS 2 Study over time up to Week 16



ASAS20 responses were improved at Week 16 in both antiTNFα-naïve patients (68.2% vs. 31.1%; p<0.05) and anti-TNFα-IR patients (50.0% vs. 24.1%; p<0.05) for COSENTYX 150 mg compared with placebo, respectively.

In both AS studies, COSENTYX -treated patients (150 mg in AS2 Study and both regimens in AS1 Study) demonstrated significantly improved signs and symptoms at Week 16, with comparable magnitude of response and efficacy was 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 2, patients treated with COSENTYX 150 mg showed improvements in health-related quality of life as measured by ASQoL p = 0.001) and SF-36 PCS (p< 0.001). These improvements were sustained up to Week 52.

Patients treated with Cosentyx 150 mg also showed 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)..

INDICATION

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.

Psoriatic arthritis

Cosentyx is indicated for the treatment of adult patients with active psoriatic arthritis when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

Ankylosing spondylitis

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

CONTRAINDICATIONS

Severe hypersensitivity reactions to the active substance or to any of the excipients (see ingredients in DESCRIPTION, and ADVERSE EFFECTS).

Clinically important, active infections (see PRECAUTIONS).

PRECAUTIONS

Infections

COSENTYX has the potential to increase the risk of infections. In clinical studies, infections have been observed in patients receiving COSENTYX (see ADVERSE EFFECTS). Most of these were mild or moderate.

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 Adverse Effects).

A similar increase in risk of infection was seen in placebo-controlled trials in patients with psoriatic arthritis and ankylosing spondylitis. The incidence of some types of infections appeared to be dose-dependent in clinical studies (see Adverse Effects).

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.

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.

Crohn's disease

Caution should be exercised, 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.

Patients who are treated with COSENTYX should be monitored for signs and symptoms of inflammatory bowel disease.

Hypersensitivity reactions

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

Latex-sensitive individuals – prefilled-syringe/pen only

The removable cap of the COSENTYX pre-filled syringe/pen contains a derivative of natural rubber

latex. Although no natural rubber latex is detected in the cap, the safe use of COSENTYX pre-filled syringe/pen in latex-sensitive individuals has not been studied.

Vaccinations

Live vaccines should not be given concurrently with COSENTYX (see INTERACTIONS WITH OTHER MEDICINES).

Patients treated with COSENTYX may receive vaccinations, except for live vaccines. In a study, after *meningococcal* and inactivated *influenza* vaccinations, a similar proportion of COSENTYX-treated and placebo-treated patients were able to mount an adequate immune response of at least a 4-fold increase in antibody titres to *meningococcal* or *influenza* vaccines. The data suggest that COSENTYX does not suppress the humoral immune response to the meningococcal and influenza vaccines.

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

Use in Patients with Hepatic or Renal Impairment

No data are available in patients with hepatic or renal impairment.

Fertility

The effect of COSENTYX on human fertility has not been evaluated.

Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

Fertility was unaffected in mice treated with an anti-murine IL17-A antibody.

Women of child-bearing potential

There are no special recommendations for women of child-bearing potential.

Use in Pregnancy (Category C)

There are no adequate data from the use of COSENTYX in pregnant women. Secukinumab was shown to cross the placenta in monkeys. Use of secukinumab during pregnancy may compromise the immunity of the fetus and neonate.

In an embryofetal development study in cynomolgus monkeys, secukinumab showed no maternal toxicity, embryofetal toxicity or teratogenicity when administered throughout organogenesis and late gestation at up to 150mg/kg/week.

COSENTYX should be used in pregnancy only if the benefits clearly outweigh the potential risks.

If secukinumab has been used during pregnancy, administration of live vaccines to newborns/ infants for 16 weeks after the mother's last dose of secukinumab is generally not recommended.

Use in Lactation

It is not known whether secukinumab is excreted in human milk. Because immunoglobulins are excreted in human milk, caution should be exercised when COSENTYX is administered to a woman who is breast-feeding and a decision on whether to discontinue breast-feeding during treatment should be made.

Paediatric Use

Safety and effectiveness in patients below the age of 18 years have not yet been established.

Use in the Elderly

Based on population PK analysis, clearance in patients aged 65 and older (n=230) and patients less than 65 years of age was similar.

Carcinogenicity

Secukinumab has not been evaluated for carcinogenic potential.

Genotoxicity

COSENTYX has not been evaluated for genotoxic potential.

Effect on laboratory tests

There is no known interference between COSENTYX and routine laboratory tests.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use of machines have been performed.

INTERACTIONS WITH OTHER MEDICINES

Live vaccines should not be given concurrently with COSENTYX (see also PRECAUTIONS).

No interaction studies have been performed in humans. There is no direct evidence for the role of IL-l 7 A in the expression of CYP450 enzymes. The formation of some CYP450 enzymes is suppressed by increased levels of cytokines during chronic inflammation. Thus, anti-inflammatory treatments, such as with the IL-17 A inhibitor secukinumab, may result in normalisation of CYP450 levels with accompanying lower exposure of CYP450-metabolised co-medications. Therefore, a clinically relevant effect on CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g. warfarin) cannot be excluded. On initiation of secukinumab therapy in patients being treated with these types of medicinal products, therapeutic monitoring should be considered.

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).

ADVERSE EFFECTS

Summary of the safety profile

A total of 6,200 patients have been treated with COSENTYX in blinded and open-label clinical studies in various indications (plaque psoriasis and other autoimmune conditions), representing 4,649 patient years of exposure. Of these, 3,671 patients were exposed to COSENTYX for at least one year, representing 6,267 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 events were mild or moderate in severity.

In the placebo-controlled period of plaque psoriasis phase III studies the proportion of patients who discontinued treatment due to adverse events was approximately 1.2 % in the COSENTYX arm and 1.2 % in the placebo arm.

The adverse reactions from clinical studies (Table 7 and Table 8) are listed by MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency. 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, ≤ 1/10); uncommon (> 1/1,000, ≤ 1/100); rare (≥ 1/10,000, ≤ 1/1,000) very rare (< 1/10,000).

Table 7 Adverse Drug Reactions reported by ≥ 1 % of psoriasis patients through Week 12 in Phase III ERASURE, FIXTURE, FEATURE and JUNCTURE studies

Adverse Reactions	COSENTYX 300 mg (N=690) n (%)	COSENTYX 150 mg (N=692) n (%)	Placebo (N=694) n (%)	Frequency category[1]
Infections and infestations				
Nasopharyngitis	79 (11.4)	85 (12.3)	60 (8.6)	Very common
Upper respiratory tract infection	17 (2.5)	22 (3.2)	5 (0.7)	Common
Rhinitis	10 (1.4)	10 (1.4)	5 (0.7)	Common
Oral herpes	9 (1.3)	1 (0.1)	2 (0.3)	Common
Pharyngitis	8 (1.2)	7 (1.0)	0 (0)	Common
Gastrointestinal disorders				
Diarrhoea	28 (4.1)	18 (2.6)	10 (1.4)	Common
Skin and subcutaneous tissue disorders				
Urticaria	4 (0.6)	8 (1.2)	1 (0.1)	Common
Respiratory, thoracic and mediastinal disorders				
Rhinorrhoea	8 (1.2)	2 (0.3)	1 (0.1)	Common

[1] ADR frequencies are based upon the highest percentage rate seen in any of the secukinumab groups

Table 8 Adverse Drug Reactions reported by ≥ 1 % of psoriasis patients through Week 12 in Phase III FIXTURE Study (A2303)

Adverse Reactions	COSENTYX 300 mg N=326 n (%)	COSENTYX 150 mg N=327 n (%)	Placebo N=327 n (%)	Etanercept N=323 n (%)	Frequency category[1]
Infections and infestations					
Nasopharyngitis	35 (10.7)	45 (13.8)	26 (8.0)	36 (11.1)	Very common
Upper Respiratory Tract Infection	7 (2.1)	10 (3.1)	3 (0.9)	7 (2.2)	Common
Rhinitis	7 (2.1)	4 (1.2)	4 (1.2)	3 (0.9)	Common
Oral Herpes	5 (1.5)	1 (0.3)	0 (0.0)	0 (0.0)	Common
Pharyngitis	4 (1.2)	5 (1.5)	0 (0.0)	0 (0.0)	Common
Gastrointestinal disorders					
Diarrhoea	17 (5.2)	12 (3.7)	6 (1.8)	11 (3.4)	Common
Skin and subcutaneous tissue disorders					
Urticaria	1 (0.3)	5 (1.5)	0 (0.0)	2 (0.6)	Common
Respiratory, thoracic and mediastinal disorders					
Rhinorrhoea	7 (2.1)	1 (0.3)	1 (0.3)	2 (0.6)	Common

[1] ADR frequencies are based upon the highest percentage rate seen in any of the secukinumab groups

Adverse reactions that occurred at less than 1 % frequency in the placebo-controlled period of the ERASURE, FIXTURE, FEATURE and JUNCTURE studies through week 12 are given in Table 9.

Table 9 Adverse effects reported at < 1 % frequency through Week 12 in psoriasis clinical trial patients

Infections and infestations	
Uncommon:	Sinusitis, tinea pedis, tonsillitis, oral candidiasis, otitis externa
Eye disorders	

Uncommon:	Conjunctivitis
Blood and lymphatic system disorders	
Uncommon:	Neutropenia

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. Most of these were mild or moderate. Serious infections occurred in 0.14 % of patients treated with COSENTYX and in 0.3 % of patients treated with placebo (see PRECAUTIONS).

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).

There was an increase in mucosal or cutaneous candidiasis, related to the mechanism of action. The cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Frequency of candida infection was 1.2% (secukinumab 300 mg) vs 0.3% (placebo and etanercept arms) in the induction period.

Infection rates as observed in psoriatic arthritis and ankylosing spondylitis clinical studies were similar to what was 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 <l.0-0.5 x $l0^9$/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 <0.5x 10^9/L (CTCAE Grade 4) were reported.

Hypersensitivity reactions

In clinical studies, urticaria and rare case of anaphylactic reaction to COSENTYX were observed.

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 PK abnormalities.

Reproductive system related adverse events

In the induction period of clinical studies, mild and moderate reproductive system adverse events were reported in females, including: dysmenorrhoea (secukinumab 300 mg, 1.9%; placebo, 0.5%; etanercept, 1.1%), menorrhagia (secukinumab 300 mg, 0.9%; placebo, 0%; etanercept, 0%) and metrorrhagia (including menometrorrhagia) (secukinumab 300 mg, 1.4%; placebo, 0%; etanercept, 0%). Women of child-bearing potential were included in studies only if using adequate contraception.

Major adverse cardiovascular events (MACE)

In the secukinumab clinical trials, MACE events were observed in patients receiving secukinumab. In the Phase 3 studies in psoriasis, PsA and AS, the exposure adjusted incidence rates of adjudication-

confirmed MACE cases per 100 patient-years was 0.49 (19/3911.6 patient-years, 95% CI 0.29, 0.76) for secukinumab versus 0.00 (0/351.3 patient-years, 95% CI 0.00, 1.05) for placebo. In the overall secukinumab program, the exposure adjusted incidence rates of adjudication-confirmed cases per 100 patient-years for secukinumab was 0.40 (25/6259.8 patient-years, 95% CI 0.26, 0.59) versus 0.39 (2/515.1 patient-years, 95% CI 0.05, 1.40) for placebo.

Adverse reactions in psoriatic arthritis

COSENTYX was studied in two placebo-controlled psoriatic arthritis trials 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 PsA1 Study and 245 days in PsA2 Study). 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 PRECAUTIONS).

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 PRECAUTIONS).

Cholesterol and triglycerides

CTCAE Grade 1 and Grade 2 elevations of blood cholesterol and triglyceride levels were reported in patients receiving secukinumab compared to placebo in psoriatic arthritis clinical trials.

The elevations of cholesterol levels were limited primarily to CTCAE Grade 1 (29.6% vs. 22.7%, respectively) and Grade 2 (1.6% vs. 0.3%, respectively). No cases of CTCAE Grade 3 and Grade 4 cholesterol levels were observed in either secukinumab or placebo groups during the placebo controlled period.

An increase in blood triglycerides levels was also observed in psoriatic arthritic patients receiving secukinumab compared to placebo (CTCAE Grade 1: 28.3% vs. 20.8%, Grade 2: 4.7% vs. 3.9%, Grade 3: 0.7% vs. 0.7% and Grade 4: 0.4% vs. 0.0%, respectively) up to Week 16.

Elevations (mainly CTCAE Grade 1 and Grade 2) in cholesterol and triglycerides were also observed during long-term treatment with secukinumab.

Hepatic transaminases

During the placebo-controlled period, increased incidence of elevated hepatic transaminases was observed in psoriatic arthritis patients treated with secukinumab compared to placebo. The elevations in hepatic transaminases were seen primarily in CTCAE Grade 1 (ALT: 18.6% vs 15.8%; AST: 13.0% vs. 12.4%, respectively). No difference in the incidence of elevated ALT and AST was seen between secukinumab and placebo in CTCAE Grade 2 and Grade 3. No cases of CTCAE Grade 4 were observed.

Elevations (mainly CTCAE Grade 1 and Grade 2) in ALT and AST was also observed during the long-term treatment with secukinumab.

Adverse reactions in ankylosing spondylitis

COSENTYX was studied in two placebo-controlled ankylosing spondylitis trials 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 1 Study and

460 days in AS 2 Study). 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 PRECAUTIONS).

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 PRECAUTIONS).

Cholesterol and triglycerides

CTCAE Grade 1 and Grade 2 elevations of blood cholesterol and triglyceride levels were reported in patients receiving secukinumab compared to placebo in ankylosing spondylitis clinical trials.

The elevations of cholesterol levels were limited primarily to CTCAE Grade 1 (20.0% vs. 19.8%, respectively) . Increase in CTCAE Grade 2 cholesterol levels was uncommon (0.8% vs. 0.0%, respectively) and no cases of CTCAE Grade 3 and Grade 4 cholesterol levels were observed in both secukinumab and placebo groups during the placebo controlled period.

An increase in blood triglycerides levels was also observed in ankylosing pondylitis patients receiving secukinumab or placebo (CTCAE Grade 1: 17.8% vs. 17.1%, Grade 2: 2.7% vs. 2.7%, and Grade 3: 0.8% vs. 0.5%, respectively). No cases of CTCAE Grade 4 triglyceride levels were reported during the placebo-controlled period.

Elevations (mainly CTCAE Grade 1 and Grade 2) in cholesterol and triglycerides were also observed during long-term treatment with secukinumab.

Hepatic transaminases

During the placebo-controlled period, increased incidence of elevated hepatic transaminases was observed in ankylosing spondylitis patients treated with secukinumab compared to placebo. The elevations in hepatic transaminases were seen primarily in CTCAE Grade 1 (ALT: 16.6% vs 7.1%; AST: 11.3% vs. 7.0%, respectively) . Increase in CTCAE Grade 2 and Grade 3 hepatic transaminase levels was uncommon in both secukinumab and placebo groups (Grade 2 ALT: 1.0% vs. 0.5%, AST: 0.5% vs. 0.0%; Grade 3 ALT: 0.8% vs. 0.0%, AST: 0.8% vs.1.6%, respectively). One case of CTCAE Grade 4 ALT levels was reported in the placebo group and no cases of CTCAE Grade 4 ALT and AST levels were reported in the secukinumab group.

Elevations (mainly CTCAE Grade 1 and Grade 2) in ALT and AST was also observed during the long-term treatment with secukinumab.

DOSAGE AND ADMINISTRATION

Dosage

Plaque psoriasis

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

Psoriatic arthritis

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

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

COSENTYX may be administered with or without methotrexate.

Ankylosing spondylitis

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

Assessment Prior to Initiation of COSENTYX

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with COSENTYX (see PRECAUTIONS)

Special populations

Patients with renal or hepatic impairment

COSENTYX has not been specifically studied in these patient populations. No dose recommendations can be made.

Paediatric and adolescent patients

Safety and effectiveness in patients below the age of 18 years have not yet been established.

Elderly patients (≥ 65 years of age)

No dose adjustment is needed for elderly patients.

Administration

The product is for single use in one patient only. Discard any residue.

Powder for injection

COSENTYX is administered by subcutaneous injection. Each vial of COSENTYX must be reconstituted with 1 mL of sterile water for injections to obtain a 150 mg/mL solution. The powder for injection should be administered by healthcare professionals only.

Prefilled syringe and pre-filled pen

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

Before injection, secukinumab may be allowed to reach room temperature (20 minutes) without removing the needle cap during this time.

Prior to administration, the liquid must be checked whether it is clear and colourless. The solution should not be used if discoloured, or cloudy, or if foreign particles are present.

After proper training in subcutaneous injection technique, patients or appropriate care giver may self-inject COSENTYX if a physician determines that it 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.

OVERDOSAGE

No case of overdose has been reported in clinical studies.

Doses up to 30 mg/kg (i.e. approximately 2,000 mg to 3,000 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.

Contact the Poisons Information Centre on 13 11 26 for advice on management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentations

Powder for Solution:	secukinumab 150 mg as a sterile white solid lyophilisate for subcutaneous injection. Packs containing 1* or 2* single-use vials.
Prefilled syringe:	secukinumab 150 mg/1 mL solution for subcutaneous injection in a single use pre-filled syringe (PFS). The sterile solution is colourless to slightly yellow. Packs containing 1* or 2* pre-filled syringes.
Prefilled pen:	secukinumab 150 mg/1 mL solution for subcutaneous injection in a single use pre-filled pen. The sterile solution is colourless to slightly yellow. The pen consists of a PFS assembled into a pen with a removable rubber cap. Packs containing 1* or 2* pre-filled pens.

**Not all pack sizes or presentations may be marketed.*

Storage

Powder for Solution:	Store at 2-8°C. Store in the original package.
Prefilled syringe:	Store at 2-8°C. Do not freeze. Protect from light. Store in the original package.
Prefilled pen:	Store at 2-8°C. Do not freeze. Protect from light. Store in the original package.

NAME AND ADDRESS OF THE SPONSOR

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® = Registered Trademark

POISON SCHEDULE OF THE MEDICINE

Schedule 4 - Prescription medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

12 January 2015: COSENTYX powder for solution*, AUST R 218798

12 January 2015: COSENTYX prefilled syringe, AUST R 218799

12 January 2015: COSENTYX prefilled pen, AUST R 218800

DATE OF MOST RECENT AMENDMENT

12 May 2016

For Internal Use Only

cos120516i based on CDS dated 27 February 2015