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 lyophilized 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 neutralizes 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 and immunity against infections. Increased numbers of IL-17A producing lymphocytes and innate immune cells and increased levels of IL-17A have been found in the blood 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. 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.

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.

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 (Cmax,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 characterized. As a human IgG1κ monoclonal antibody secukinumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

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.

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.

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.

CLINICAL TRIALS

The safety and efficacy of Cosentyx were evaluated versus placebo or etanercept in four randomized, 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 randomized, 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 randomized 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 randomized 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 randomized 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 randomized to etanercept received 50 mg doses twice per week for 12 weeks followed by 50 mg every week. Patients were randomized 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 randomized 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 randomized 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 randomized 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 randomized 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 randomized 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.

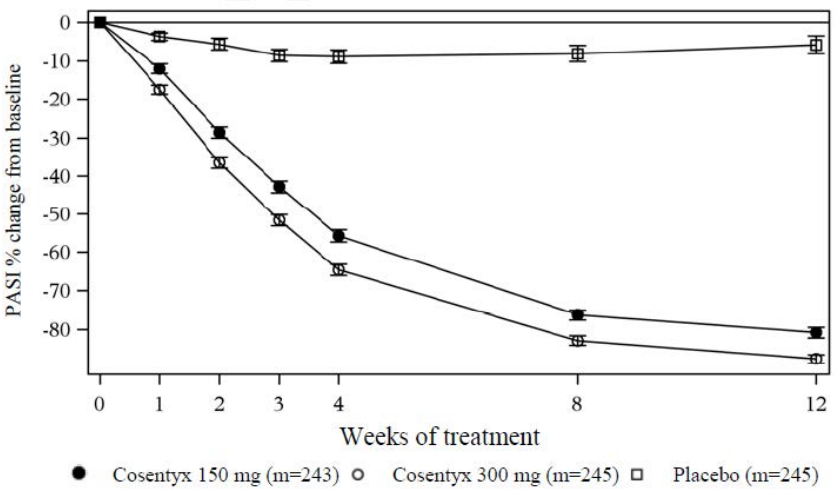
Results

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 score in ERASURE trial (m = number of patients evaluable)



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 randomized 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.

INDICATION

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

CONTRAINDICATIONS

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

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.

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 active Crohn's disease as exacerbations of Crohn's disease, in some cases serious, were observed in clinical studies in both Cosentyx and placebo groups. Patients who are treated with Cosentyx and have active Crohn's disease should be followed closely.

Hypersensitivity reactions

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. Cosentyx has been concomitantly administered with methotrexate in arthritis studies where no interaction was seen.

ADVERSE EFFECTS

Summary of the safety profile

A total of 4,498 patients have been treated with Cosentyx in blinded and open-label clinical studies in various indications (plaque psoriasis and other autoimmune conditions). Of these, 1,900 patients were exposed to Cosentyx for at least one year, representing 3,588 patient years of exposure.

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 6 and Table 7) 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 6 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 7 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 8.

Table 8 Adverse effects reported at < 1 % frequency through Week 12 in psoriasis clinical trial patients

Infections and infestations	
Uncommon:	Sinusitis, tinea pedis, tonsillitis, oral candidiasis
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.

Hypersensitivity reactions

In clinical studies, urticaria and one case of anaphylactic reaction to Cosentyx were observed .

Immunogenicity

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 neutralizing, 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.

DOSAGE AND ADMINISTRATION

Dosage

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.

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

Novartis Pharmaceuticals Australia Pty Limited

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54 Waterloo Road

North Ryde NSW 2113

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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