PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**COSENTYX®**

Secukinumab

75 mg/0.5 mL Solution for injection

150 mg/1 mL Solution for injection

150 mg Powder for solution for injection*

Biological Response Modifier

COSENTYX (secukinumab) should be prescribed only by health care professionals who have sufficient knowledge of plaque psoriasis, psoriatic arthritis and ankylosing spondylitis and who have fully familiarized themselves with the efficacy/safety profile of the drug.

COSENTYX has been issued market authorization without conditions.

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*single-use vial not available in Canada

RECENT MAJOR LABEL CHANGES

1 INDICATION, Plaque psoriasis	03/2021
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

COSENTYX® (secukinumab) is indicated for:

Plaque psoriasis

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

Pediatric patients
COSENTYX (secukinumab) is indicated for the treatment of moderate to severe plaque psoriasis in patients 6 year and older 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. COSENTYX can be used alone or in combination with methotrexate (see **14 CLINICAL TRIALS, Psoriatic arthritis**).

Axial spondyloarthritis (axSpA)

Ankylosing spondylitis (AS, radiographic axial spondyloarthritis)
COSENTYX is indicated for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy (see **14 CLINICAL TRIALS, Ankylosing spondylitis**).

Non-radiographic axial spondyloarthritis (nr-axSpA)
COSENTYX is indicated for the treatment of active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

2 CONTRAINDICATIONS

- Severe hypersensitivity reactions to COSENTYX active substance (secukinumab) or to any of the components (see **7 WARNINGS AND PRECAUTIONS**, Hypersensitivity reactions). For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** section.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- COSENTYX is intended for use under the guidance of a health care professional. Patients may self-inject after proper training and when deemed appropriate. Prior to subcutaneous administration, visually inspect the solution for particulate matter and discoloration. The solution is colorless to slightly yellow. Prior to initiating treatment with COSENTYX, patients should be evaluated for tuberculosis (TB) infection. COSENTYX should not be given to patients with active tuberculosis (see **7 WARNINGS AND PRECAUTIONS**).

4.2 Recommended Dose and Dosage Adjustment

- **Plaque psoriasis**

Adult patients

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

Pediatric patients aged 6 years and older

The recommended dose is based on body weight (Table 1) and administered by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3, and 4 followed by monthly maintenance dosing. Each 75 mg dose is given as 1 subcutaneous injection of 75 mg. Each 150 mg dose is given as 1 subcutaneous injection of 150 mg. Each 300 mg dose is given as 2 subcutaneous injections of 150 mg.

Table 1 Recommended dose of COSENTYX for pediatric plaque psoriasis

Body weight at time of dosing	Recommended Dose
<50 kg	75 mg
≥50 kg	150 mg (*may be increased to 300 mg)

**Some patients may derive additional benefit from the higher dose.*

- **Psoriatic arthritis**

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

For psoriatic arthritis patients with coexistent moderate to severe plaque psoriasis, use the dosing and administration recommendations for plaque psoriasis (see **4 DOSAGE AND ADMINISTRATION, Plaque psoriasis**).

If a patient is an anti-TNF-alpha inadequate responder (IR) or continues to have active psoriatic arthritis, consider using the 300 mg dose.

- **Axial spondyloarthritis (axSpA)**

Ankylosing spondylitis (AS, radiographic axial spondyloarthritis)

The recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3, and 4 followed by monthly maintenance dosing. If a patient continues to have active ankylosing spondylitis, consider a monthly maintenance dosage of 300 mg. Each 300 mg dose is given as two subcutaneous injections of 150 mg.

Non-radiographic axial spondyloarthritis (nr-axSpA)

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

For all of the above indications, available data suggest that a clinical response is usually achieved within 16 weeks of treatment. Consideration should be given to discontinuing treatment in patients who have

shown no response by 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks.

Special populations:

Renal impairment / hepatic impairment
COSENTYX has not been studied specifically in these patient populations.

4.3 Reconstitution

Parenteral Products:

- Powder for solution for injection* COSENTYX is administered subcutaneous injection. COSENTYX powder for solution must be reconstituted before use (see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING)**.

  *single-use vial not available in Canada

4.4 Administration

Pre-filled syringe & SensoReady pen
COSENTYX is intended for use under the guidance and supervision of a physician. COSENTYX is administered by subcutaneous injection. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

After proper training in subcutaneous injection technique, patients may self-inject COSENTYX or may be injected by a caregiver if a physician determines that it is appropriate and provides instructions. However, the physician should ensure appropriate follow-up of patients. Patients or caregivers should be instructed to inject the full amount of COSENTYX according to the instructions provided in the Patient Medication Information. Comprehensive instructions for administration are given in the Patient Medication Information.

For patients receiving the 75 mg dose, the 75 mg/0.5 mL pre-filled syringe should be used.

Powder for solution for injection*
COSENTYX is administered by subcutaneous injection. COSENTYX powder for solution must be reconstituted before use (see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING)**.

*single-use vial not available in Canada
Instructions for use are provided in **12 SPECIAL HANDLING INSTRUCTIONS**.

4.5 Missed Dose

In the case of a missed or late dose of COSENTYX, the next dose should be given as soon as possible. The following dose should be given according to the regular dosing schedule.

5 OVERDOSAGE

Doses up to 30 mg/kg (i.e. approximately 2,000 to 3,000 mg) have been administered intravenously in clinical studies in adults 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

•75 mg/0.5 mL solution for injection in pre-filled syringe consisting of a sterile solution in a single use pre-filled syringe (PFS) with a staked 27 gauge fixed ½ inch needle with plunger stopper and rigid needle shield. The syringe is fitted with a passive safety guard.

•150 mg/1 mL solution for injection in pre-filled syringe consisting of a sterile solution in a single use pre-filled syringe (PFS) with a staked 27 gauge fixed ½ inch needle with plunger stopper and rigid needle shield. The syringe is fitted with a passive safety guard.

•150 mg/1 mL solution for injection in pre-filled SensoReady pen consisting of a sterile solution in a single use pre-filled syringe with a 27 gauge fixed ½ inch needle with plunger stopper and rigid needle shield assembled into a pen of a triangular shape with a removable rubber cap.

•COSENTYX (secukinumab) is also supplied as a powder for solution in a single-use (type 1) glass vial with a coated stopper*. Each vial of powder for solution for subcutaneous injection contains 150 mg of COSENTYX when reconstituted with 1 mL water for injection.

Table 2 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous Injection (s.c.)	75 mg/0.5 mL in a carton containing one (1) pre-filled glass syringe. 150 mg/mL in a carton containing one (1) pre-filled glass syringe.	L-histidine/histidine hydrochloride monohydrate, L-methionine, polysorbate 80, Trehalose dehydrate, water for injection.
	150 mg/mL in a carton containing two (2) pre-filled glass syringes.	
	150 mg/mL in a carton containing one (1) pre-filled SensoReady pen	
	150 mg/mL in a carton containing two (2) pre-filled SensoReady pen	

	150mg/mL single use vial* (lyophilized powder)	Sucrose, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, water for injection

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

Each 0.5 mL pre-filled syringe contains 75 mg secukinumab.
Each 1 mL pre-filled syringe or SensoReady pen contains 150 mg secukinumab.

COSENTYX does not contain preservatives.

*single-use vial not available in Canada

7 WARNINGS AND PRECAUTIONS

General

Infections
COSENTYX has the potential to increase the risk of infections. In clinical studies, higher rates of infections have been observed in patients receiving COSENTYX compared with placebo (see **8 ADVERSE REACTIONS**). 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.

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

Carcinogenesis and Mutagenesis

Carcinogenicity studies have not been conducted for secukinumab.

Gastrointestinal

Inflammatory Bowel Disease
Cases of new onset and exacerbations of inflammatory bowel disease, in some cases serious occurred in clinical studies in both COSENTYX and placebo groups. In addition, cases of new onset inflammatory bowel disease have been reported with post-marketing use (see **8 ADVERSE REACTIONS**). Patients who are treated with COSENTYX should be monitored for signs and symptoms of inflammatory bowel disease.

Immune

Vaccinations
Prior to initiating therapy with COSENTYX, consider completion of all age appropriate immunizations according to current immunization guidelines. Live vaccines should not be given concurrently with COSENTYX (see **9 DRUG INTERACTIONS**). Patients receiving COSENTYX may receive concurrent inactivated or non-live vaccinations. In a study, after meningococcal and inactivated influenza vaccinations, a similar proportion of healthy adult volunteers treated with 150 mg of secukinumab and those treated with placebo were able to mount an adequate immune response of at least a 4-fold increase in antibody titres to meningococcal and influenza vaccines. The data suggest that COSENTYX does not suppress the humoral immune response to the meningococcal or influenza vaccines in adults.

Reproductive Health: Female and Male Potential

- **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.

Sensitivity/Resistance

Hypersensitivity reactions
Rare cases of anaphylaxis and cases of urticaria occurred in COSENTYX-treated patients in clinical trials. If an anaphylactic or other serious allergic reaction occurs, administration of COSENTYX should be discontinued immediately and appropriate therapy initiated.

Latex-sensitive individuals – pre-filled syringe/SensoReady pen
The removable cap of the COSENTYX pre-filled syringe/SensoReady 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/SensoReady pen in latex-sensitive individuals has not been studied.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well controlled clinical trials of COSENTYX in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see **16 NON-CLINICAL TOXICOLOGY**). COSENTYX should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus

7.1.2 Breast-feeding

It is not known whether secukinumab is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when COSENTYX is administered to a nursing woman.

7.1.3 Pediatrics

Pediatrics (< 18 years of age)

Safety and effectiveness in pediatric patients with moderate to severe plaque psoriasis below the age of 6 years have not been established.

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

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age)

Of the 3430 plaque psoriasis patients exposed to COSENTYX in clinical trials, a total of 230 were 65 years or older, and 32 subjects were 75 years and older.

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

Of the 794 ankylosing spondylitis patients exposed to COSENTYX in clinical studies, a total of 29 patients were 65 years of age or older and 3 patients were 75 years of age or older.

Of the 524 non-radiographic axial spondyloarthritis patients exposed to COSENTYX in clinical studies, a total of 9 patients were 65 years of age or older and 2 patients were 75 years of age or older.

Although limited in patient number, no differences in safety and efficacy were observed between older and younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

In the placebo-controlled period of the phase III studies the proportion of patients who discontinued treatment due to adverse events was approximately 1.2% in the COSENTYX arms and 1.2% in the placebo arm in the plaque psoriasis studies, 1.6% in the COSENTYX arms and 2.7% in the placebo arm in the psoriatic arthritis studies, and 2.0% in the COSENTYX arms and 3.7% in the placebo arm in the ankylosing spondylitis studies and 0.8 in the COSENTYX arms and 1.6% in the placebo arm in the 20 week placebo-controlled period of the non-radiographic axial spondyloarthritis study.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Over 18,000 patients have been treated with COSENTYX in blinded and open-label clinical studies in various indications (plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis and other autoimmune conditions), representing 30,565 patient years of exposure. Of these, over 11,700 patients were exposed to COSENTYX for at least one year.

Adverse drug reactions in plaque psoriasis

Adult patients

Four randomized, double-blind, placebo-controlled phase III studies in moderate to severe 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); one trial contained an active comparator arm, etanercept, of 323 patients.

Table 3 presents the adverse reactions that occurred at a rate ≥ 1% in patients treated with COSENTYX through Week 12 in the placebo controlled period of studies 1, 2, 3 and 4 [ERASURE, FIXTURE, FEATURE and JUNCTURE].

Table 3 - Adverse Drug Reactions Reported by ≥ 1% of Patients Through Week 12 in Phase III Studies 1, 2, 3 and 4 [ERASURE, FIXTURE, FEATURE and JUNCTURE]

Adverse Reactions	COSENTYX		Placebo (N=694) n (%)	Etanercept* (N=323) n (%)
	300 mg (N=690) n (%)	150 mg (N=692) n (%)		
Infections and Infestations				
Nasopharyngitis	79 (11.4)	85 (12.3)	60 (8.6)	36 (11.1)
Upper respiratory tract infection	17 (2.5)	22 (3.2)	5 (0.7)	7 (2.2)
Rhinitis	10 (1.4)	10 (1.4)	5 (0.7)	3 (0.9)
Oral herpes	9 (1.3)	1 (0.1)	2 (0.3)	0
Pharyngitis	8 (1.2)	7 (1.0)	0	0
Gastrointestinal Disorders				
Diarrhea	28 (4.1)	18 (2.6)	10 (1.4)	11 (3.4)
Skin and Subcutaneous Tissue Disorders				
Urticaria	4 (0.6)	8 (1.2)	1 (0.1)	2 (0.6)
Respiratory, Thoracic, and Mediastinal Disorders				
Rhinorrhea	8 (1.2)	2 (0.3)	1 (0.1)	2 (0.6)

* Etanercept data from FIXTURE study only

Pediatric patients

The safety of COSENTYX was assessed in two phase III studies in pediatric patients with plaque psoriasis. Study A2310, was double-blind, placebo and active controlled study of 162 patients from 6 to less than 18 years of age with severe plaque psoriasis.

Study A2311, was an open-label study of 84 patients from 6 to less than 18 years of age with moderate to severe plaque psoriasis. The safety profile reported in these studies for patients who received

COSENTYX up to week 52 in study A2310, and up to week 24 in study A2311 was consistent with the safety profile reported in adult plaque psoriasis patients.

Adverse drug reactions in psoriatic arthritis

COSENTYX was studied in three placebo-controlled psoriatic arthritis trials with 1,999 patients (1,367 patients on COSENTYX and 632 patients on placebo) for a total exposure of 1,285 patient- years of study exposure on COSENTYX (median duration of exposure for secukinumab-treated patients: 456 days in PsA1 Study, 245 days in PsA2 Study and 169 days in PsA3 Study). The safety profile observed in patients with psoriatic arthritis treated with COSENTYX is consistent with the safety profile in psoriasis.

Of the 703 patients, who received COSENTYX, 299 patients received a subcutaneous loading dose of COSENTYX (PsA2 Study) and 404 patients received an intravenous loading dose of secukinumab (PsA1 Study) followed by COSENTYX administered by subcutaneous injection every four weeks. During the 16-week placebo-controlled portion of the trials in patients with psoriatic arthritis, the overall proportion of patients with adverse events was similar in the secukinumab and placebo-treatment groups (59% and 58%, respectively).

Table 4 presents the adverse drug reactions that occurred at a rate ≥ 1% in patients treated with COSENTYX through Week 16 in the placebo controlled Phase III Psoriatic Arthritis studies PsA1 (FUTURE 1) and PsA2 (FUTURE 2).

Table 4 - Adverse Drug Reactions Reported by ≥ 1% of patients through Week 16 in Phase III Study PsA1 (FUTURE 1) and Study PsA2 (FUTURE 2)

	COSENTYX (PsA2)			COSENTYX (PsA1)		Placebo
Adverse Reactions	**75 mg N=99 n (%)**	**150 mg N=100 n (%)**	**300 mg N=100 n (%)**	**10 mg/kg 75 mg N=202 n (%)**	**10 mg/kg 150 mg N=202 n (%)**	**N=300 n (%)**
Infections and Infestations						
Upper respiratory tract infections	10 (10.1)	8 (8.0)	4 (4.0)	9 (4.5)	13 (6.4)	17 (5.7)
Nasopharyngitis	6 (6.1)	4 (4.0)	6 (6.0)	14 (6.9)	19 (9.4)	17 (5.7)
Pharyngitis	1 (1.0)	0	1 (1.0)	2 (1.0)	4 (2.0)	0
Rhinitis	3 (3.0)	2 (2.0)	0	3 (1.5)	0	0
Conjunctivitis	0	2 (2.0)	0	1 (0.5)	3 (1.5)	0
Oral herpes	1 (1.0)	0	4 (4.0)	0	5 (2.5)	3 (1.0)
Tinea pedis	0	0	0	3 (1.5)	1 (0.5)	0
Skin and Subcutaneous Tissue Disorders						
Urticaria	1 (1.0)	0	2 (2.0)	1 (0.5)	1 (0.5)	0

The safety profile observed in Study PsA3 (FUTURE 5) was generally similar to that observed in studies PsA1 (FUTURE 1) and PsA2 (FUTURE 2).

COSENTYX was studied in one placebo-controlled trial (MAXIMISE) with 498 PsA patients with axial manifestations included in the safety analysis set (332 patients received COSENTYX 150 mg or 300 mg, see 14.1.2 for details; and 166 patients on placebo) for a total exposure of 249.4 patient-years on COSENTYX 300 mg and 245.9 patient-years on COSENTYX 150 mg (median duration of total exposure for secukinumab-treated patients: 418 days). The safety profile observed in Study MAXIMISE was consistent with the safety profile of COSENTYX in the previous PsA studies.

Adverse drug reactions in axial spondyloarthritis (axSpA)

Ankylosing spondylitis (AS, radiographic axial spondyloarthritis)

COSENTYX was studied in three placebo-controlled ankylosing spondylitis trials with 816 patients (544 patients on COSENTYX and 272 patients on placebo). The median duration of exposure for secukinumab-treated patients was 469 days in AS 1 Study, 460 days in AS 2 Study and 1,142 days in AS3 Study. The safety profile observed in patients with ankylosing spondylitis treated with COSENTYX is consistent with the safety profile in psoriasis.

Of the 544 patients who received COSENTYX, 145 patients received a subcutaneous load of COSENTYX (AS2-Study) and 399 received an intravenous loading dose of secukinumab (AS1 Study and AS3-Study) followed by COSENTYX administered by subcutaneous injection every four weeks. During the 16-week placebo-controlled period, the proportion of patients with adverse events (AEs) was numerically higher in the secukinumab groups than the placebo-treatment groups (60% and 55%, respectively), driven primarily by AEs in the infections and infestations SOC (mainly nasopharyngitis).

Table 5 presents the adverse drug reactions that occurred at a rate ≥ 1% in patients treated with COSENTYX through Week 16 in the placebo controlled phase III ankylosing spondylitis studies AS1 (MEASURE 1), AS2 (MEASURE 2) and AS3 (MEASURE 3).

Table 5 - Adverse Drug Reactions Reported by ≥ 1% of Patients through Week 16 in Phase III Study AS1 (MEASURE 1), Study AS2 (MEASURE 2) and Study AS3 (MEASURE 3)

	COSENTYX (AS2)		COSENTYX (AS1)		COSENTYX (AS3)		Placebo
	75 mg N=73 n (%)	150 mg N=72 n (%)	10 mg/kg 75 mg N=124 n (%)	10 mg/kg 150 mg N=125 n (%)	10 mg/kg 150 mg N=74 n (%)	10 mg/kg 300 mg N=76 N(%)	N=271 n (%)
Adverse Reactions							
Infections and Infestations							
Nasopharyngitis	6 (8.2)	8 (11.1)	13 (10.5)	17 (13.6)	6 (8.1)	3 (3.9)	14 (5.2)
Upper respiratory tract infection	4 (5.5)	1 (1.4)	4 (3.2)	1 (0.8)	0	0	6 (2.2)
Pharyngitis	0	0	2 (1.6)	3 (2.4)	1 (1.4)	3 (3.9)	2 (0.7)

	COSENTYX (AS2)		COSENTYX (AS1)		COSENTYX (AS3)		Placebo
	75 mg N=73 n (%)	150 mg N=72 n (%)	10 mg/kg 75 mg N=124 n (%)	10 mg/kg 150 mg N=125 n (%)	10 mg/kg 150 mg N=74 n (%)	10 mg/kg 300 mg N=76 N(%)	N=271 n (%)
Adverse Reactions							
Oral herpes	0	2 (2.8)	2 (1.6)	1 (0.8)	0	0	1 (0.4)

Non-radiographic axial spondyloarthritis (nr-axSpA)

COSENTYX was studied in one randomized, double-blind, placebo-controlled non-radiographic axial spondyloarthritis trial with 555 patients (369 patients on COSENTYX and 186 patients on placebo) for a total of 758 patient-years of study exposure (median duration of exposure for secukinumab-treated patients: 540 days). The most commonly reported adverse drug reactions up to Week 20 in secukinumab patients were nasopharyngitis (12.5%), diarrhea (6.2%), headache (6.0%), and upper respiratory tract infections (6.0%). The safety profile observed in patients with axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis) treated with COSENTYX is consistent with the safety profile in psoriasis.

Description of Select Adverse Reactions

Infections

Adult patients

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 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 **7 WARNINGS AND PRECAUTIONS**).

Over the entire treatment period (a total of 3,430 plaque psoriasis 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).

Similar to clinical trials in patients with plaque psoriasis, in the psoriatic arthritis clinical trials there was an increased proportion of patients with infections in the COSENTYX groups (29%) compared to placebo group (26%) in the 16-week placebo-controlled period with 1.3% serious infections in the COSENTYX groups compared to 0.3% in the placebo group. Over the entire treatment period, infections were reported in 51% of patients treated with COSENTYX, of which 2.6% were serious infections (see **7 WARNINGS AND PRECAUTIONS**, Infections).

Similar to clinical trials in patients with plaque psoriasis, in the ankylosing spondylitis clinical trials there was an increased proportion of patients with infections in the COSENTYX groups (29%) compared to the placebo group (19%) in the 16-week placebo-controlled period with 0.2% serious infections in the

COSENTYX groups. Over the entire treatment period, infections were reported in 56% of patients treated with COSENTYX, with 1.3% cases of serious infections (see **7 WARNINGS AND PRECAUTIONS**, Infections).

In the nr-axSpA clinical trial, the proportion of patients with infections in the COSENTYX groups (35.5%) was similar to the proportion in the placebo group (32.8%) in the 20-week placebo-controlled period with 0.5% cases of serious infections in the COSENTYX groups. Over the entire treatment period, infections were reported in 59.5% of patients treated with COSENTYX, with 2.2% cases of serious infections (see **7 WARNINGS AND PRECAUTIONS,** Infections).

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

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

Pediatric patients

In pediatric patients, in the 12 week placebo-controlled period of Study A2310, infections were reported in 37.5% of patients in the high-dose COSENTYX group, 32.5% of patients in the low dose group and 39.0% of patients in the placebo group. The most frequently reported infections in COSENTYX-treated patients were upper respiratory tract infections (22.5%). Over the 24 week treatment period, a total of 114 patients were treated with COSENTYX, including placebo cross-over patients. The rate of reported infections during this period was 49.1%; the most commonly reported infections were upper respiratory tract infections (32.5 %). During this study, serious infections events were reported in 3.5% of COSENTYX-treated patients and included toxic shock syndrome, bronchitis, bacterial enterocolitis, and lung abscess/pneumonia/infectious pleural effusion in one patient each. Over the 24 week treatment period, newly occurring or worsening neutropenia was reported in 18 (15.8%) COSENTYX-treated patients (17 out of 18 CTCAE Grade 1 and/or 2).

Hypersensitivity Reactions

Rare cases of anaphylaxis and cases of urticaria occurred in COSENTYX-treated patients in clinical trials (see **7 WARNINGS AND PRECAUTIONS**).

Immunogenicity

In psoriasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis 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 neutralizing, but this was not associated with loss of efficacy or PK abnormalities.

Inflammatory bowel disease

In psoriatic arthritis clinical trials, 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 **7 WARNINGS AND PRECAUTIONS**, Inflammatory Bowel Disease).

Among the 794 patients exposed to COSENTYX in the ankylosing spondylitis clinical trials, there were 8 cases of inflammatory bowel disease during the treatment period (5 Crohn's (0.4 per 100 patient-years)

and 3 ulcerative colitis (0.2 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 **7 WARNINGS AND PRECAUTIONS**, Inflammatory Bowel Disease).

In the non-radiographic axial spondyloarthritis program, with 524 patients exposed to COSENTYX there were 7 cases of inflammatory bowel disease during the entire treatment period (5 Crohn's (0.5 per 100 patient-years) and 2 ulcerative colitis (0.2 per 100 patient-years)). Of the 7 cases, one case of Crohn's and one case of ulcerative colitis were reported as exacerbations. There were 2 serious events of ulcerative colitis and 1 serious event of Crohn's disease reported. During the placebo-controlled period, there was 1 case of Crohn's disease. (see **7 WARNINGS AND PRECAUTIONS, Gastrointestinal**)

8.3 Less Common Clinical Trial Adverse Reactions

Adult patients
Adverse reactions that occurred at rates less than 1% in the placebo-controlled period of the plaque psoriasis studies 1, 2, 3, and 4 through Week 12 included: sinusitis, tinea pedis, conjunctivitis, tonsillitis, oral candidiasis, and neutropenia. No new less common adverse reactions were identified in the clinical trials in psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.

Pediatric patients
Adverse reactions that occurred at rates less than 2% (i.e., in one patient) in patients treated with COSENTYX during the placebo-controlled period (12 weeks) of the pediatric plaque psoriasis study A2310 included abscess limb, folliculitis, fungal skin infection, gastrointestinal viral infection, herpes virus infection, hordeolum, impetigo, nail candida, pyoderma, toxic shock syndrome, viral upper respiratory tract infection, urticaria and injection-site hypersensitivity.

8.5 Post-Market Adverse Reactions

The following adverse drug reactions in Table 6 have been derived from post-marketing experience with COSENTYX via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

Table 6 Adverse drug reactions from spontaneous reports and literature

Infections and Infestations
Mucosal and cutaneous candidiasis
Inflammatory bowel disease (including Crohn's disease and ulcerative colitis)

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

The formation of CYP450 enzymes may be altered by increased levels of cytokines (e.g., TNFα, IL-1β, IL-6, IFN) during chronic inflammation. In a study in subjects with plaque psoriasis, no interaction was

observed between secukinumab and midazolam (CYP 3A4 substrate).

Live vaccines should not be given concurrently with COSENTYX (see also **7 WARNINGS AND PRECAUTIONS**).

In a study, after meningococcal and inactivated influenza vaccinations, a similar proportion of adult patients treated with COSENTYX and patients treated with placebo were able to mount an adequate immune response of at least a 4-fold increase in antibody titers to meningococcal and influenza vaccines.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Secukinumab is a human IgG1κ antibody, a first-in-class agent that selectively binds to and neutralizes interleukin-17A (IL-17A), a naturally occurring cytokine involved in normal inflammatory and immune responses. IL-17A is highly upregulated in lesional skin in contrast to non-lesional skin of plaque psoriasis patients. 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 psoriasis, psoriatic arthritis, ankylosing spondylitis and ankylosing spondylitis and non-radiographic axial spondyloarthritis. The frequency of IL-17-producing cells was higher in the subchondral bone marrow of facet joints from patients with ankylosing spondylitis. Increased numbers of IL-17A producing lymphocytes have also been found in patients with non-radiographic axial spondyloarthritis. Secukinumab works by targeting IL-17A and inhibiting its interaction with the IL-17 receptor, which is expressed on various cell types including keratinocytes and synoviocytes and enthesial cells. Secukinumab inhibits the release of proinflammatory cytokines and chemokines. Inhibition of IL-17A was shown to be effective in the treatment of AS, thus establishing the key role of this cytokine in axial spondyloarthritis (see **14 CLINICAL TRIALS, Ankylosing spondylitis**).

10.2 Pharmacodynamics

Serum levels of total IL-17A (free and secukinumab-bound IL-17A) measured at Week 4 and 12 were increased following secukinumab treatment in adult subjects with psoriasis. In a clinical exploratory study with secukinumab, infiltrating epidermal neutrophils and various neutrophil associated markers that were increased in lesional skin of adult plaque psoriasis patients were significantly reduced after one to two weeks of treatment. The relationship between the pharmacodynamic activity and its clinical

effects is unknown.

Secukinumab has also been shown to lower levels of C-reactive protein by approximately 50% by Week 1, in both psoriatic arthritis and ankylosing spondylitis. Compared to placebo, the difference was approximately 29% by Week 16 in non-radiographic axial spondyloarthritis.

10.3 Pharmacokinetics

Secukinumab exhibited dose-proportional pharmacokinetics in adult subjects with plaque psoriasis over a dose range from 25 mg to 300 mg following subcutaneous administrations. The PK properties of secukinumab observed in adult ankylosing spondylitis and non-radiographic axial spondyloarthritis patients were similar to those displayed in adult plaque psoriasis patients.

Absorption

Following a single subcutaneous dose of 150 mg or 300 mg in adult plaque psoriasis patients, secukinumab reached mean (± SD) peak serum concentrations of 13.7 ± 4.8 mcg/mL and 27.3 ± 9.5 mcg/mL, respectively, between 5 and 6 days post dose.

Following subcutaneous administration of 150 or 300 mg every 4 weeks in adult plaque psoriasis patients, the mean (±SD) serum trough concentrations of secukinumab ranged from 22.8 ± 10.2 mcg/mL (150 mg) to 45.4 ± 21.2 mcg/mL (300 mg) at Week 12. Steady-state concentrations of secukinumab were achieved by Week 24 following the every 4 week dosing regimens. The mean (+SD) steady-state trough concentrations ranged from 16.7 ± 8.2 mcg/mL (150 mg) to 34.4 ± 16.6 mcg/mL (300 mg).

Based on cross-study comparisons of adult patients, the mean trough concentrations were similar at Week 4 and Week 12 following 150 mg or 300 mg the lyophilized powder or the prefilled syringe but approximately 25% lower than from the SensoReady pen.

Secukinumab absolute bioavailability following subcutaneous dose of 150 mg was estimated 55% (90% CI; 43% to 70%) in adult subjects with plaque psoriasis in a small crossover pharmacokinetic study.

Distribution:

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

Secukinumab concentrations in interstitial fluid in the skin of adult 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

The mean systemic clearance (CL) was 0.19 L/d (ranged 0.14 – 0.22 L/day) and the mean half-life was estimated 27 days (ranged 22 to 31 days) in adult plaque psoriasis patients following intravenous administration. Secukinumab clearance increase as body weight increases.

Special Populations and Conditions

- **Pediatrics (<18 years of age):** In a pool of the two pediatric studies, patients with moderate to severe plaque psoriasis (6 to less than 18 years of age) were administered secukinumab at the recommended pediatric dosing regimen. At Week 24, secukinumab steady state mean ± SD serum trough concentrations were 32.6 ± 10.8 mcg/mL (n = 8), 19.8 ± 6.96 mcg/mL (n = 24), and 27.3 ± 10.1 mcg/mL (n = 36), in subjects weighing < 25 kg and receiving 75 mg of secukinumab, subjects weighing ≥ 25 and < 50 kg and receiving 75 mg of secukinumab, and subjects weighing ≥ 50 kg and receiving 150 mg of secukinumab, respectively.
- **Geriatrics:** Based on population PK analysis, clearance in elderly patients and patients less than 65 years of age was similar.
- **Sex:** The impact of sex differences on exposure is considered to be not clinically relevant.
- **Ethnic Origin:** The impact of race differences on exposure is considered to be not clinically relevant.
- **Hepatic Insufficiency:** No pharmacokinetic data are available in patients with hepatic impairment.
- **Renal Insufficiency:** No pharmacokinetic data are available in patients with renal impairment.

11 STORAGE, STABILITY AND DISPOSAL

Store COSENTYX in a refrigerator at 2°C to 8°C and protect from light. Keep the product in the original carton until the time of use. Do not shake.

For the pre-filled syringe and SensoReady pen only: Do not freeze.
If necessary, the pre-filled syringe and the SensoReady pen may be stored unrefrigerated for a single period of up to 4 days at room temperature, not above 30°C. Discard the pre-filled syringe or SensoReady pen after 4 days if left unrefrigerated.

12 SPECIAL HANDLING INSTRUCTIONS

Following administration of COSENTYX (secukinumab) using the pre-filled syringe or the SensoReady Pen, the syringe or pen should be disposed of in a puncture-resistant container for syringes and needles. Patients or caregivers should be instructed in the technique as well as proper syringe and needle disposal, and not to reuse these items.

Keep out of reach from children.

Incompatibilities

Solution for injection in pre-filled syringe and SensoReady pen: These medicinal products must not be mixed with other medicinal products.

Powder for solution for injection: COSENTYX should not be mixed with any medication or diluents other than sterile water for injection.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: COSENTYX®

Chemical name: Secukinumab

Molecular formula and molecular mass: Secukinumab is a fully human IgG1 monoclonal anti-IL-17A antibody with a molecular mass of 147,944 Daltons when deglycosylated. Secukinumab is produced in a recombinant Chinese Hamster Ovary (CHO) cell line.

Structural formula: Secukinumab is an antibody that contains two heavy chains and two light chains. Both heavy chains contain oligosaccharide chains linked to the protein at Asn307.

Physicochemical properties: Secukinumab drug substance is a colorless to slightly yellow aqueous solution. The pH of the aqueous solution of secukinumab drug substance is in the range of 5.5 – 6.1.

Pharmaceutical standard: House Standard

Product Characteristics:

COSENTYX (secukinumab) is supplied as:

•75mg/0.5mL Solution for injection in pre-filled syringe consisting of a sterile solution in a single use Pre-Filled Syringe (PFS) with a staked 27 gauge fixed ½ inch needle with plunger stopper and rigid needle shield. The syringe is fitted with a passive safety guard.

•150 mg/1mL Solution for injection in pre-filled syringe consisting of a sterile solution in a single use Pre-Filled Syringe (PFS) with a staked 27 gauge fixed ½ inch needle with plunger stopper and rigid needle shield. The syringe is fitted with a passive safety guard.

•150 mg/1mL Solution for injection in pre-filled SensoReady® pen consisting of a sterile solution in a single use Pre-Filled Syringe (PFS) with a 27 gauge fixed ½ inch needle with plunger stopper and rigid needle shield assembled into a pen of a triangular shape with a removable rubber cap

•Powder for solution in a single-use (type 1) glass vial with a coated stopper*. Each vial of powder for solution for subcutaneous injection contains 150 mg of COSENTYX when reconstituted with 1 mL water for injection.

*single-use vial not available in Canada

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

14.1.1 Plaque psoriasis

Adult patients

The safety and efficacy of COSENTYX were assessed in four randomized, double-blind, placebo-controlled phase III studies in a total of 2,403 patients 18 years of age and older with plaque psoriasis who had a minimum body surface area involvement of 10%, and Psoriasis Area and Severity Index (PASI) score greater than or equal to 12, and who were candidates for phototherapy or systemic

therapy [ERASURE, FIXTURE, FEATURE, JUNCTURE]. The efficacy and safety of COSENTYX 150 mg and 300 mg were evaluated versus either placebo or etanercept.

In addition, the safety and efficacy of COSENTYX was evaluated in 205 patients with moderate to severe palmoplantar (palms and soles) plaque psoriasis (GESTURE), and in 198 patients with moderate to severe plaque psoriasis with significant nail involvement (TRANSFIGURE).

Study demographics and trial design

Of the 2,403 patients who were included in the placebo-controlled Studies 1 to 4 (see Table 7), 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. These characteristics (PASI, IGA mod 2011, and DLQI) were measured at baseline and throughout the study.

Table 7 - Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Mean age (Range)	Gender
Study 1 (ERASURE)	Randomized, double-blind, placebo-controlled, multicenter	Secukinumab 150 mg or 300 mg, or placebo; SC once a week at baseline and Weeks 1, 2, 3, then q month starting at Week 4 until Week 48 Secukinumab 150 mg: N=245 Secukinumab 300 mg: N=245 Placebo: N=248	N=738	45.1 (19-83)	M=509 F=229
Study 2 (FIXTURE)	Randomized, double-blind, placebo-controlled, active-comparator controlled, multicenter	Secukinumab 150 mg or 300 mg or placebo, SC once a week at baseline and Weeks 1, 2, 3, then q month starting at Week 4 until Week 48 Etanercept 50 mg, SC twice a week until Week 12, then weekly from Week 12 through Week 51 Secukinumab 150 mg: N=327 Secukinumab 300 mg: N=327 Etanercept 50 mg: N=326 Placebo: N=326	N=1,306	44.4 (18-82)	M=929 F=377

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Mean age (Range)	Gender
Study 3 (FEATURE)	Randomized, double-blind, controlled, multicenter, with prefilled syringe	Secukinumab 150 mg or 300 mg, or placebo; SC once a week at baseline and Weeks 1, 2, 3, then q month starting at Week 4 until Week 12 Secukinumab 150 mg: N=59 Secukinumab 300 mg: N=59 Placebo: N=59	N=177	45.9 (18-77)	M=117 F=60
Study 4 (JUNCTURE)	Randomized, double-blind, controlled, multicenter, with SensoReady pen	Secukinumab 150 mg or 300 mg, or placebo; SC once a week at baseline and Weeks 1, 2, 3, then q month starting at Week 4 until Week 12 Secukinumab 150 mg: N=61 Secukinumab 300 mg: N=60 Placebo: N=61	N=182	44.7 (18-83)	M=125 F=57
Study 5 (TRANSFIGURE)	Randomized, double-blind, placebo-controlled, multicenter	Secukinumab 150 mg or 300 mg SC once weekly at baseline and Weeks 1, 2, 3, then q month starting at Week 4 until Week 128 or placebo SC once weekly at baseline and Weeks 1, 2, 3, 4, 8 followed by 150 mg or 300 mg SC once weekly at Week 16 to Week 20 and then q month starting at Week 24 until Week 128	N=198	44.1 (19-74)	M=160 F=38
Study 6 (GESTURE)	Randomized, double-blind, placebo-controlled, multicenter	Secukinumab 150 mg or 300 mg SC once weekly at baseline and Weeks 1, 2, 3, then q month starting at week 4 until Week 128 or placebo SC once weekly at baseline and Weeks 1, 2, 3, 4, 8 followed by 150 mg or 300 mg SC once weekly at Week 16 to Week 20 and then q month starting at Week 24 until Week 128	N=205	50.7 (19-80)	M=112 F=93

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Mean age (Range)	Gender
Study 7 (SCALP)	Randomized, double-blind, placebo-controlled, parallel-group, multicenter	Secukinumab 300 mg SC once weekly at baseline and Weeks 1, 2, 3, 4, 8, 12, 16, and 20 or placebo SC once weekly at baseline and Weeks 1, 2, 3, 4, 8	N=102	41.9 (18-69)	M=48 F=54

Table 8 - Baseline Disease Characteristics in ERASURE, FIXTURE, FEATURE, JUNCTURE for COSENTYX and Placebo

	Secukinumab 150 mg N=692	Secukinumab 300 mg N=691	Placebo N=692
Median PASI	19.2	19.8	19.4
PASI > 20, n (%)	324 (46.8)	337 (48.8)	327 (47.3)
IGA of severe, n (%)	253 (36.6)	255 (36.9)	268 (38.7)
Psoriatic arthritis present, n (%)	118 (17.1)	126 (18.2)	134 (19.4)
Prior exposure to systemic therapy, n (%)	447 (64.6)	438 (63.4)	420 (60.7)
Failed to respond to systemic therapy, n (%)	343 (49.6)	325 (47.0)	317 (45.8)
Prior exposure to biologic therapy, n (%)	161 (23.3)	146 (21.1)	147 (21.2)
Failed to respond to biologic therapy, n (%)	69 (10.0)	50 (7.2)	56 (8.1)
Prior exposure to systemic therapy excluding biologics, n (%)	393 (56.8)	373 (54.0)	363 (52.5)
Failed to respond to systemic therapy excluding biologics, n (%)	318 (46.0)	303 (43.8)	294 (42.5)

Note: The baseline disease characteristics from the etanercept arm in the FIXTURE study (not shown in table) were consistent with the other treatment groups.

The co-primary endpoints in the placebo and active controlled studies were the proportion of patients who achieved a PASI 75 response and IGA mod 2011 'clear' or 'almost clear' response versus placebo at Week 12 (see Table 8).

The PASI is a composite score that takes into consideration both the fraction of body surface area affected and the nature and severity of psoriatic changes within the affected regions (induration, erythema and scaling). 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. Based on the Phase III data in secukinumab, IGA mod 2011 'clear' or 'almost clear' response correlates to a PASI response of around PASI 90, rather than with a PASI 75 response. This may be due to the strict definition of "almost clear" on the IGA mod 2011 scale which, for example, does not allow for any thickening of the skin.

Pediatric patients

Severe plaque psoriasis

As presented in Table 9, in a randomized, double-blind, placebo and etanercept-controlled study was conducted in pediatric patients aged 6 to less than 18 years of age with severe plaque psoriasis, as defined by a PASI score ≥20, an IGA mod 2011 score of 4, and BSA involvement of ≥10%, who were candidates for systemic therapy.

Table 9 - Summary of patient demographics for Study A2310

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Mean age (Range)	Gender
Study A2310	Multicenter, randomized, double-blind, parallel group, placebo- and active (etanercept)-controlled study.	Secukinumab low dose (75 mg for body weight <50 kg or 150 mg for body weight ≥50 kg), secukinumab high dose (75 mg for body weight <25 kg, 150 mg for body weight ≥25 kg and <50 kg, or 300 mg for body weight ≥50 kg), or placebo, SC at Weeks 0, 1, 2, 3, and 4 followed by the same dose every 4 weeks, or etanercept (0.8 mg/kg weekly, up to a maximum of 50 mg).	N=162	13.5 (6-17)	M= 65 F= 97

Study A2310 evaluated 162 patients who were randomized to receive either low dose of COSENTYX, high dose of COSENTYX placebo or etanercept (see Table 9 for dosing regimens). Approximately 43% had prior exposure to phototherapy, 53% to conventional systemic therapy, 2% had prior exposure to biologics, and 9% had concomitant psoriatic arthritis. Patient distribution by weight and age at randomisation is described in Table 10.

Table 10 - Patient distribution by weight and age for pediatric psoriasis in Study A2310

Randomisation strata	Description	Secukinumab low dose n=40	Secukinumab high dose n=40	Placebo n=41	Etanercept n=41	Total N=162
Age	6-<12 years	8	9	10	10	37
	≥12-<18 years	32	31	31	31	125
Weight	<25 kg	2	3	3	4	12
	≥25-<50 kg	17	15	17	16	65
	≥50 kg	21	22	21	21	85

Patients randomized to receive placebo who were non-responders at Week 12 were switched to either the secukinumab low or high dose group (dose based on body weight group) and received study drug at Weeks 12, 13, 14, and 15, followed by the same dose every 4 weeks starting at Week 16. All patients were followed for efficacy and safety during the 52 weeks following the first dose.

As presented in Table 11, an open-label, two-arm, parallel-group, multicentre phase III study enrolled 84 pediatric patients 6 to less than 18 years of age with moderate to severe plaque psoriasis (as defined by a PASI score ≥12, an IGA mod 2011 score of ≥3, and involving ≥10% of the body surface area) who were candidates for systemic therapy. All patients were followed for efficacy and safety for at least 24 weeks following first administration.

Table 11 Summary of patient demographics for Study A2311

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Mean age (Range)	Gender
Study A2311	Multicenter, randomized, open label, two-arm, parallel group study.	Secukinumab low dose (75 mg for body weight <50 kg or 150 mg for body weight ≥50 kg), secukinumab high dose (75 mg for body weight <25 kg, 150 mg for body weight ≥25 kg and <50 kg, or 300 mg for body weight ≥50 kg) SC at Weeks 0, 1, 2, 3, and 4 followed by the same dose every 4 weeks.	N=84	12.6 (6-17)	M= 39 F= 45

14.1.2 Psoriatic arthritis

The safety and efficacy of COSENTYX were assessed in 1,999 patients in three randomized, double-blind, placebo-controlled phase III studies in adult patients, age 18 years and older 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 in these studies had a diagnosis of PsA of at least five years. The majority of patients also had active psoriasis skin lesions or a documented history of psoriasis. Over 61% and 43% of the PsA patients had enthesitis and dactylitis at baseline.

PsA1 Study (FUTURE 1) evaluated 606 patients, of whom 60.7% had concomitant MTX. Patients with each subtype of PsA were enrolled, including polyarticular arthritis with no evidence of rheumatoid nodules (76.7%), spondylitis with peripheral arthritis (18.5%), asymmetric peripheral arthritis (60.2%), distal interphalangeal involvement (59.6%) and arthritis mutilans (7.9%). 29% (N=178) of patients were previously treated with an anti-TNF-alpha agent and discontinued the anti-TNF-alpha agent for either lack of efficacy or intolerance. 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 receiving placebo were re-randomized to receive COSENTYX (either 75 mg or 150 mg every 4 weeks) at Week 16 or Week 24 based on responder status (≥ 20% improvement from baseline in both tender and swollen joint counts).

PsA2 Study (FUTURE 2) evaluated 397 patients, of whom 46.6% had concomitant MTX. Patients with each subtype of PsA were enrolled, including polyarticular arthritis with no evidence of rheumatoid nodules (85.9%), spondylitis with peripheral arthritis (21.7%), asymmetric peripheral arthritis (64.0%), distal interphalangeal involvement (57.9%) and arthritis mutilans (6.3%). 35% (N=139) of patients were previously treated with an anti-TNF-alpha agent and discontinued the anti-TNF-alpha agent for either lack of efficacy or intolerance. Patients randomized to COSENTYX received 75 mg, 150 mg or 300 mg s.c. at Weeks 0, 1, 2, 3, and 4 followed by the same dose every month. Patients receiving placebo were re-randomized to receive COSENTYX (either 150 mg or 300 mg every 4 weeks) at Week 16 or Week 24 based on responder status (≥ 20% improvement from baseline in both tender and swollen joint counts).

The two studies had the same primary endpoint: the percentage of patients achieving at least a 20% improvement in the American College of Rheumatology (ACR 20) criteria at Week 24. The key secondary endpoints were PASI 75, PASI 90, DAS28-CRP, SF-36, HAQ-DI, ACR 50, presence of dactylitis, and presence of enthesitis. Structural damage was also followed radiographically in the PsA1 Study by measuring the mean change in modified Total Sharp score (mTSS).

PsA3 Study (FUTURE 5) evaluated 996 patients, of whom 50.1% had concomitant MTX treatment. Patients with each subtype of PsA were enrolled, including polyarticular arthritis with no evidence of rheumatoid nodules (78.7%), spondylitis with peripheral arthritis (19.8%), asymmetric peripheral arthritis (65%), distal interphalangeal involvement (56.7%) and arthritis mutilans (6.8%). Patients were randomized to receive COSENTYX 150 mg, 300 mg, or placebo s.c. at Weeks 0, 1, 2, 3 and 4 followed by the same dose every month, or a once monthly injection of COSENTYX 150 mg. Patients treated with placebo received Cosentyx, either 150 mg or 300 mg, s.c., per baseline randomization, at Week 16 or Week 24 based upon responder status. The primary endpoint was ACR 20 response at Week 16. Structural damage was followed radiographically in the PsA3 study by measuring the key secondary endpoint of change from baseline in modified Total Sharp Score (mTSS) at Week 24. The other key secondary endpoints were PASI 75, PASI 90, DAS28-CRP, SF-36, HAQ-DI, ACR 50, presence of dactylitis, and presence of enthesitis.

The evidence indicates that there are no differences in ACR20 responses with the intravenous loading dose regimen compared to the subcutaneous (SC) loading dose regimen. COSENTYX is NOT recommended for use with an intravenous (IV) loading dose (see **4 DOSAGE AND ADMINISTRATION**).

Axial manifestations in psoriatic arthritis

A randomized, double-blind, placebo-controlled study (MAXIMISE) assessed the efficacy of secukinumab in 485 PsA patients with axial manifestations (axPsA) who were naive to biologic treatment and responded inadequately to NSAIDs. The clinical diagnosis of axPsA was based on the presence of active spinal disease defined by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4, spinal pain Visual Analogue Scale (VAS) ≥ 40, and inadequate response to ≥ 2 NSAIDs over a period of 4 weeks. The mean time since first diagnosis of axPsA was 3 years. Patients randomized to COSENTYX received 150 mg or 300 mg s.c. at Weeks 0, 1, 2, 3, and 4 followed by the same dose every month. Patients were allowed to continue pre-study NSAIDs, methotrexate (MTX), and corticosteroids at a stable dose from baseline through to the end of study. The primary variable of at least 20% improvement in Assessment of SpondyloArthritis international Society (ASAS) criteria at Week 12.

Table 12 - Summary of trial design and patient demographics for clinical trials in Psoriatic Arthritis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Mean age (Range)	Gender
Study 1 (FUTURE 1)	Randomized, double-blind, placebo-controlled, multicenter	Secukinumab IV loading dose (10 mg/kg) or PBO at Wks 0, 2, 4 followed by 75 mg s.c., 150 mg s.c., or PBO[a] q month. Secukinumab 75 mg: N=202 Secukinumab 150 mg: N=202 Placebo: N=202	N=606	49.0 (20-77)	M= 276 (45.5%) F= 330 (54.5%)
Study 2 (FUTURE 2)	Randomized, double-blind, placebo-controlled, multicenter	Secukinumab SC loading dose of 75 mg, 150 mg, 300 mg or PBO at Wks 0, 1, 2, 3, 4 followed by 75 mg s.c., 150 mg s.c., 300 mg s.c., or PBO[b] q month. Secukinumab 75 mg: N=99 Secukinumab 150 mg: N=100 Secukinumab 300 mg: N=100 Placebo: N=98	N=397	48.0 (20-77)	M= 192 (48.4%) F= 205 (51.6%)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Mean age (Range)	Gender
Study 3 (FUTURE 5)	Randomized, double-blind, placebo-controlled, multicenter	Secukinumab 150 mg s.c. q4w from Wk 0 to Wk 24 + PBO s.c. at Wks 1, 2 and 3; then q4w from Wk 4 to Wk 24 (N=222) Secukinumab 150 mg s.c. + PBO at Wks 0, 1, 2, and 3; then q4w from Wk 4 to Week 24 (secukinumab) (N=220) Secukinumab 300 mg s.c. at Wks 0, 1, 2, and 3, then q4w from Wk 4 to Wk 24 (N=222) PBO s.c. at Wks 0, 1, 2, and 3; then q4w from Wk 4 to 12 or Wk 20 (N=332)	N=996	48.8 (19-81)	M= 500 (50.2%) F= 496 (49.8%)
Study 4 (MAXIMISE)	Randomized, double-blind, placebo-controlled, multicenter	Secukinumab 150 mg + PBO s.c. at Baseline, Week 1, 2, 3 and 4, then 4 weeks later at Week 8; then q4w from Week 12 to Week 52. Secukinumab 300 mg s.c. at Baseline, Week 1, 2, 3 and 4, then 4 weeks later at Week 8; then q4w from Week 12 to Week 52. PBO s.c. at Baseline, Week 1, 2, 3 and 4, then 4 weeks later at Week 8; then Secukinumab 150 mg + PBO s.c. q4w from Week 12 to Week 52 OR Secukinumab 300 mg q4w from Week 12 to Week 52.	N=485	46.5 (18-78)	M= 240 (49.4%) F= 245 (50.6%)

[a] PBO non-responders (< 20% improvement from baseline in tender or swollen joint counts) were re-randomized 1:1 at Wk 16 to receive either secukinumab 75 mg or 150 mg s.c. every 4 Wks; PBO responders at Wk 16 were re-randomized 1:1 at Wk 24 to receive either secukinumab 75 mg or 150 mg s.c. every 4 Wks.

[b] PBO non-responders (< 20% improvement from baseline in tender or swollen joint counts) were re-randomized 1:1 at Wk 16 to receive either secukinumab 150 mg or 300 mg s.c. every 4 Wks; PBO responders at Wk 16 were re-randomized 1:1 at Wk 24 to receive either secukinumab 150 mg or 300 mg every 4 Wks.

14.1.3 Axial spondyloarthritis (axSpA)

Ankylosing spondylitis (AS, radiographic axial spondyloarthritis)

The safety and efficacy of COSENTYX were assessed in 816 patients in three randomized, double-blind, placebo-controlled phase III studies in adult patients (mean age: 42 yrs, range: 18-77 yrs.) with active ankylosing spondylitis (AS) with a BASDAI ≥ 4 despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or disease-modifying anti-rheumatic drug (DMARD) therapy. Patients in the AS1 Study and AS2 Study had a diagnosis of AS for a median of 2.7 to 5.8 years.

AS1 Study (MEASURE 1) evaluated 371 patients, of whom 14.8% and 33.4% used concomitant MTX or sulfasalazine, respectively. 27.0% of patients enrolled in the study were previously treated with an anti-TNF-alpha agent who either discontinued due to lack of efficacy or intolerance. 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. Patients receiving placebo were re-randomized to receive COSENTYX (either 75 mg or 150 mg every 4 weeks) at Week 16 or Week 24 based on ASAS 20 response.

AS2 Study (MEASURE 2) evaluated 219 patients, of whom 11.9% and 14.2% used concomitant MTX or sulfasalazine, respectively. 38.8% of patients enrolled in the study were previously treated with an anti-TNF-alpha agent who either discontinued due to lack of efficacy or intolerance. Patients randomized to COSENTYX received 75 mg or 150 mg s.c. at Weeks 0, 1, 2, 3, and 4 followed by the same dose every month. At Week 16, patients who were randomized to placebo at baseline were re-randomized to receive COSENTYX (either 75 mg or 150 mg) s.c. every month. The two studies had the same primary endpoint: the percentage of patients achieving at least a 20% improvement in ASAS 20 criteria at Week 16. The secondary endpoints were ASAS 40, hsCRP, ASAS 5/6, total BASDAI, SF-36 PCS, ASQoL, and ASAS partial remission.

AS3 Study (MEASURE 3) evaluated 226 patients, of whom 13.3% and 23.5% used concomitant MTX or sulfasalazine, respectively. Patients randomized to COSENTYX received 10 mg/kg, i.v. at Weeks 0, 2, and 4, followed by either 150 mg or 300 mg s.c. every month. At Week 16, patients who were randomized to placebo at baseline were re-randomized to receive COSENTYX (either 150 mg or 300 mg) s.c. every month. The primary endpoint was ASAS20 at Week 16. Patients were blinded to the treatment regimen up to Week 52, and the study continued to Week 156.

The evidence indicates that there are no differences in ASAS 20 responses with the intravenous loading dose regimen compared to the subcutaneous (SC) loading dose regimen. COSENTYX is NOT recommended for use with an intravenous (IV) loading dose (see **4 DOSAGE AND ADMINISTRATION)**.

Table 13 - Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Mean age (Range)	Gender
AS1 Study (MEASURE 1)	Randomized, double-blind, placebo-controlled, multicenter	Secukinumab iv loading dose 10 mg/kg or PBO Wks 0, 2, 4 followed by 75 mg sc, 150 mg sc, or PBO[a, b] q month Secukinumab 75 mg: N=124 Secukinumab 150 mg: N=125 Placebo: N=122	N=371	41.8 (18-76)	M= 257 (69%) F= 114 (31%)
AS2 Study (MEASURE 2)	Randomized, double-blind, placebo-controlled, multicenter	Secukinumab sc loading dose of 75 mg, 150 mg, or PBO Wks 0, 1, 2, 3 followed by 75 mg sc, 150 mg sc, or PBO[c] q month Secukinumab 75 mg: N=73 Secukinumab 150 mg: N=72 Placebo: N=74	N=219	43.3 (19-77)	M= 153 (70%) F= 66 (30%)
AS3 Study (MEASURE 3)	Randomized, double-blind, double-dummy, placebo-controlled, parallel group, multicenter	Secukinumab iv loading dose 10 mg/kg at Weeks 0, 2, 4 or PBO iv Maintenance dose: 150 mg and 300 mg administered sc q4wk from Week 8 or PBO sc Secukinumab 150 mg: N=74 Secukinumab 300 mg: N=76 Placebo: N=76	N=226	42.5 (20-73)	M=136 (60%) F=90 (40%)

[a] PBO non-responders (not achieving ASAS 20) were re-randomized 1:1 at Wk 16 to receive either secukinumab 75 or 150 mg sc every 4 Wks

[b] PBO responders (achieving ≥ ASAS 20) were re-randomized 1:1 at Wk 16 to receive either secukinumab 75 or 150 mg sc every 4 Wks starting at Wk 24

[c] PBO patients were re-randomized 1:1 at Wk 16 to receive either secukinumab 75 or 150 mg sc every 4 Wks

[d] PBO patients were re-randomized 1:1 at Wk 16 to receive either secukinumab 150 mg or 300 mg sc every 4 Wks

14.1.4 Non-radiographic axial spondyloarthritis (nr-axSpA)

The safety and efficacy of COSENTYX were assessed in 555 patients in one randomized, double-blind, placebo-controlled phase III study consisting of a 2-year core phase and a 2-year extension phase in patients with active non-radiographic axial spondyloarthritis (nr-axSpA). All patients fulfilled the ASAS classification criteria for axial spondyloarthritis (axSpA) with no radiographic evidence of changes in the

sacroiliac joints that would meet the modified New York criteria for ankylosing spondylitis (AS). Patients enrolled had active disease, defined as a BASDAI ≥4, total back pain VAS of ≥40 (on a scale of 0 to 100 mm), despite current or previous non-steroidal anti-inflammatory drug (NSAID) therapy and increased C-reactive protein (CRP) and/or evidence of sacroiliitis on Magnetic Resonance Imaging (MRI). Patients in this study had a diagnosis of axSpA for a mean of 2.1 to 3.0 years and 54% of the study participants were female.

In Nr-axSpA 1 Study (PREVENT), 57.6% of patients had increased CRP, 72.2% had evidence of sacroiliitis on MRI and 29.9% had both increased CRP and evidence of sacroiliitis on MRI. Overall, 9.7% of patients were previously treated with an anti-TNF-alpha agent and discontinued the anti-TNF-alpha agent for either lack of efficacy or intolerance (anti-TNF-alpha-IR patients). Additionally, 9.9% and 14.8% used concomitant MTX or sulfasalazine, respectively.

Patients were treated with COSENYX 150 mg subcutaneous treatment with load (Weeks 0, 1, 2, 3, and 4) or without load (Weeks 0 and 4) followed by the same dose every 4 weeks or placebo. In the double-blind period, patients received either placebo or COSENTYX for 52 weeks. Starting Week 16, dose adjustment or addition of concomitant NSAIDs and DMARDs was permitted. Starting at Week 20, patients were allowed to switch to open-label COSENTYX 150 mg monthly or other biologic at the discretion of the investigator and patient. There were 2 primary endpoints which assessed at least 40% improvement in ASAS40 at Week 16 and Week 52 in the anti-TNF-naïve population.

Table 14 - Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Mean age (Range)	Gender
Nr-axSpA 1 Study (PREVENT)	Randomized, double-blind, placebo-controlled, multicenter	Secukinumab s.c. loading dose of 150 mg Wks 0, 1, 2, 3 followed by 150 mg s.c. q month Secukinumab 150 mg s.c. q month (with PBO weeks 1, 2, 3), or PBO Wks 0, 1, 2, 3 followed by PBO q month Secukinumab 150 mg Load: N=185 Secukinumab 150 mg No Load: N=184 Placebo: N=186	N=555	39.4 (18-80)	M= 255 (45.9%) F= 300 (54.1%)

14.2 Study Results

14.2.1 Plaque psoriasis

Adult patients

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

and sustained to Week 52.

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

Efficacy measures at Week 12

In the ERASURE and the FIXTURE studies, compared with placebo, significantly greater proportions of patients randomized to 150 mg or 300 mg secukinumab achieved a clear or almost clear IGA mod 2011 score, and significantly greater proportions of patients randomized to 150 mg or 300 mg secukinumab were PASI 90 and PASI 100 responders at Week 12 (Table 15). Superiority versus placebo was demonstrated at both the 300 mg and 150 mg secukinumab doses in these studies.

Table 15 - Summary of PASI 75/90 & IGA mod 2011 'Clear' or 'Almost Clear' Clinical Response at Week 12 in Psoriasis Studies ERASURE and FIXTURE (FAS)

	ERASURE			FIXTURE			
	Placebo	COSENTYX		Placebo	COSENTYX		Etanercept
		150 mg	300 mg		150 mg	300 mg	
Number of patients	246	244	245	324	327	323	323
PASI 75 response n (%)	11 (4.5%)	174 (71.6%)*	200 (81.6%)*	16 (4.9%)	219 (67.0%)^*	249 (77.1%)^*	142 (44.0%)
IGA mod 2011 "clear" or "almost clear" response n (%)	6 (2.40%)	125 (51.2%)*	160 (65.3%)*	9 (2.8%)	167 (51.1%)^*	202 (62.5%)^*	88 (27.2%)
PASI 90 response n (%)	3 (1.2%)	95 (39.1%)*	145 (59.2%)*	5 (1.5%)	137 (41.9%)*	175 (54.2%)*	67 (20.7%)

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

^ p values versus etanercept: p=0.0250

Note: p values reflected in the table are only those that correspond to hypotheses pre-specified in the testing strategy

In the FIXTURE study, 24.1% and 14.4% of patients receiving secukinumab 300 mg and 150 mg, respectively, achieved a PASI 100 response at Week 12 compared with 0% of patients receiving placebo and 4.3% of the patients receiving Etanercept. In the ERASURE study, 28.6% and 12.8% of patients receiving secukinumab 300 mg and 150 mg, respectively, achieved a PASI 100 response at Week 12 compared with 0.8% of patients receiving placebo.

In the FEATURE study, 69.5% and 75.9% of patients receiving secukinumab 150 mg and 300 mg, respectively, achieved a PASI 75 response at Week 12 compared with 0% of patients receiving placebo. In the JUNCTURE study, 71.7% and 86.7% of patients receiving secukinumab 150 mg and 300 mg, respectively, achieved a PASI 75 response at Week 12 compared with 3.3% of patients receiving placebo.

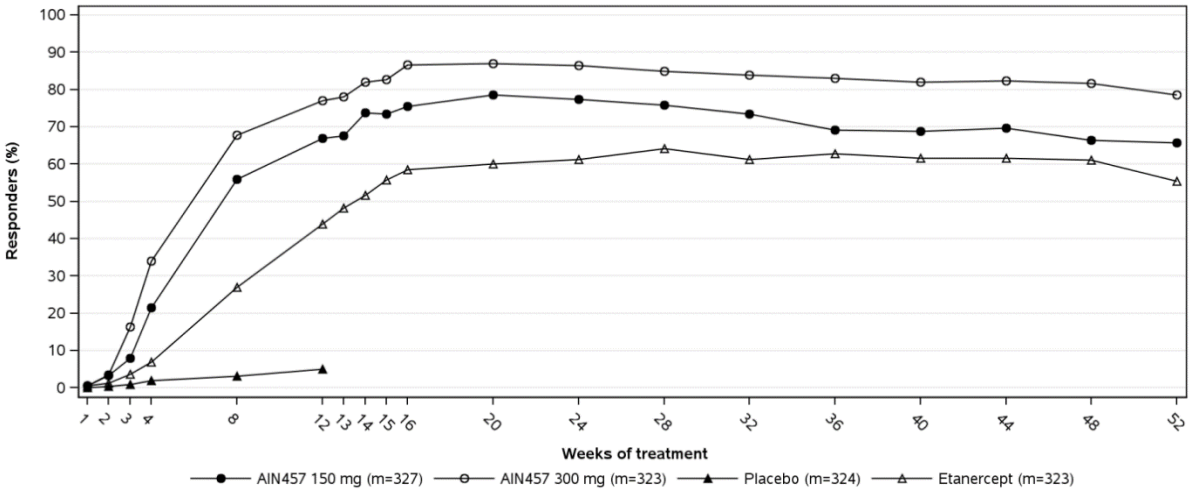
In FEATURE, 52.5% and 69.0% of patients receiving 150 mg or 300 mg secukinumab, respectively, achieved IGA mod 2011 score of a cleared or almost clear compared with 2.8% of the placebo patients at Week 12. In JUNCTURE, 53.3% and 73.3% of patients receiving 150 mg or 300 mg secukinumab,

respectively, achieved IGA mod 2011 score of a cleared or almost clear compared with 2.8% of the placebo patients at Week 12.

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

With continued treatment over 52 weeks response was maintained as outlined for PASI 75 response from the FIXTURE study (see Figure 1) which shows PASI 75 response over time. In addition, subjects in FIXTURE who were PASI 75 responders maintained their responses in 84% (210/249) of subjects treated with COSENTYX 300 mg and in 82% (180/219) of subjects treated with COSENTYX 150 mg. Similarly, subjects in ERASURE who were PASI 75 responders at Week 12 maintained their responses in 81% (161/200) of the subjects treated with COSENTYX 300 mg and in 72% (126/174) of subjects treated with COSENTYX 150 mg. FIXTURE subjects who were clear or almost clear on the IGA also maintained their responses in 80% (161/202) of subjects treated with COSENTYX 300 mg and in 68% (113/167) of subjects treated with COSENTYX 150 mg. ERASURE subjects who were clear or almost clear on the IGA at Week 12 also maintained their responses in 74% (119/160) of subjects treated with COSENTYX 300 mg and in 59% (74/125) of subjects treated with COSENTYX 150 mg.

Figure 1 - Time course of PASI 75 responders (non-responder imputation) over entire treatment – FIXTURE Study



m = number of subjects evaluable

Among subjects who chose to participate (40%) in using the Psoriasis Symptom Diary, significant improvements in signs and symptoms of itching, pain and scaling at Week 12 were reported in COSENTYX – treated groups compared to placebo (ERASURE and FIXTURE).

Improvements at Week 12 from baseline compared to placebo (ERASURE, FIXTURE) and etanercept (FIXTURE) were demonstrated in the DLQI, these improvements were maintained for 52 weeks.

Other Clinical Trials

Effect in difficult-to-treat forms of psoriasis

TRANSFIGURE was a randomized, double-blind, placebo-controlled, parallel group, multicenter phase III

study. Patients were adults with chronic moderate to severe plaque type psoriasis for at least 6 months prior to randomization including significant nail involvement defined by fingernail NAPSI ≥ 16 and number of fingernails involved ≥ 4 and a PASI score ≥ 12 and BSA ≥ 10%. Patients had to be candidates for systemic therapy defined as having psoriasis considered inadequately controlled by topical treatment and/or phototherapy and/or previous systemic therapy. Patients were randomized in a 1:1:1 ratio to receive COSENTYX 300 mg (N=66), 150 mg (N=67) or placebo (N=65). Randomization was stratified by body weight at Baseline Visit (< 90 kg or ≥ 90 kg). Dosing was by subcutaneous injection once weekly for 5 weeks (at Baseline, Weeks 1, 2, 3, and 4) followed by dosing every 4 weeks, starting at Week 8. The primary endpoint was percentage change from baseline at Week 16 in NAPSI score. The results, adjusted mean changes from baseline -46.1% for COSENTYX 300 mg vs. -11.7% for placebo (difference in adjusted means -34.4% [95% CI -45.2, -23.5]; p<0.0001), were statistically significant. At Week 16, all placebo patients were re-randomized to COSENTYX 150 mg or 300 mg and the study continued to 132 weeks.

GESTURE was a randomized, double-blind, placebo-controlled, parallel group, multicenter phase III study. Patients were adults with chronic moderate to severe plaque type psoriasis for at least 6 months including at baseline significant involvement of palms and soles as defined by a Palmoplantar Investigator's Global Assessment (ppIGA) score of ≥ 3 (on a 5-point scale) and at least 1 extra psoriasis plaque on the skin. Patients were candidates for systemic therapy defined as having psoriasis considered inadequately controlled by topical treatment (including super potent topical corticosteroid) and/or phototherapy and/or previous systemic therapy. Patients were randomized 1:1:1 to receive COSENTYX 300 mg (N=69), COSENTYX 150 mg (N=68) or placebo (N=68). Randomization was stratified by body weight at Baseline Visit (< 90 kg or ≥ 90 kg). Dosing was by subcutaneous injection once weekly for 5 weeks (at Baseline, Weeks 1, 2, 3, and 4) followed by dosing every 4 weeks, starting at Week 8. The primary endpoint was ppIGA score of 0 (clear) or 1 (almost clear/minimal) response at Week 16 (to be considered a ppIGA responder at Week 16, a patient had a ppIGA score of 0 or 1 at the Week 16 visit and a reduction of at least 2 points on the ppIGA scale from baseline). The ppIGA scale was based on the IGA modified version 2011 specifically applied to the palms and soles; the ppIGA is a non-validated tool for the measurement of palmoplantar psoriasis severity. Superior efficacy was observed for COSENTYX 300 mg vs. placebo with respect to ppIGA 0 or 1 response at Week 16 (33.3% vs. 1.5%, respectively; p<0.0001). At Week 16 and at Week 80, patients treated with placebo who were not ppIGA 0 or 1 responders were re-randomized, to receive COSENTYX 150 mg or 300 mg. Patients in the COSENTYX treatment groups remained in the same groups. The study continued to 132 weeks.

In a randomized, double-blind, placebo-controlled, multicenter study (SCALP), COSENTYX was evaluated in 102 patients with moderate to severe scalp psoriasis, defined as having a Psoriasis Scalp Severity Index (PSSI) score of greater than or equal to 12, an IGA mod 2011 scalp only score of 3 or greater, and at least 30% of the scalp affected. In this study, 62% of patients had at least 50% or more of scalp surface area affected. The proportions of subjects achieving a PSSI 90 response at Week 12 were 52.9% and 2.0% for the COSENTYX 300 mg and the placebo groups (p<0.001), respectively. The proportions of subjects achieving an IGA scalp only score of 0 or 1 (clear or almost clear) at Week 12 were 56.9% and 5.9% for the COSENTYX 300 mg and the placebo groups (p<0.001), respectively.

Pediatric patients

Study A2310

The co-primary endpoints at Week 12 were the proportion of patients treated with a low and high dose of COSENTYX who achieved a PASI 75 response and IGA mod 2011 'clear' or 'almost clear' (0 or 1) response versus placebo. The key secondary endpoint at Week 12 was the proportion of patients who achieved a PASI 90 response.

At Week 12, the efficacy of both the low and the high dose of secukinumab was comparable for the co-primary endpoints. The risk ratio estimates in favour of both secukinumab doses were statistically significant for both the PASI 75 and IGA mod 2011 0 or 1 responses (see Table 16).

Table 16 - Summary of Clinical Response in Severe Pediatric Psoriasis at Weeks 12*

Response criterion	Treatment comparison 'test' vs. 'control'	'test' n**/m (%)	'control' n**/m (%)	Risk ratio estimate (95% CI)	p-value***
			At week 12		
PASI 75	Secukinumab Low dose vs. Placebo	32/40 (80.1)	6/41(14.9)	5.37 (2.52, 11.44)	<.0001
	Secukinumab High dose vs. Placebo	32/40 (80.2)	6/41(14.9)	5.38 (2.53, 11.45)	<.0001
	Secukinumab Low dose vs. Etanercept	32/40 (80.1)	27/41 (65.7)	1.22 (0.92, 1.62)	
	Secukinumab High dose vs. Etanercept	32/40 (80.2)	27/41 (65.7)	1.22 (0.92, 1.62)	
IGA 0/1	Secukinumab Low dose vs. Placebo	28/40 (69.8)	3/41 (6.3)	11.34 (3.06, 42.02)	<.0001
	Secukinumab High dose vs. Placebo	25/40(62.6)	3/41(6.3)	10.17 (2.72, 37.97)	<.0001
	Secukinumab Low dose vs. Etanercept	28/40 (69.8)	15/41 (36.3)	1.93 (1.20, 3.08)	
	Secukinumab High dose vs. Etanercept	25/40(62.6)	15/41 (36.3)	1.73 (1.06, 2.80)	
PASI 90	Secukinumab Low dose vs. Placebo	28/40(71.1)	1/41(2.5)	28.55 (4.08, 199.83)	<.0001
	Secukinumab High dose vs. Placebo	28/40(69.3)	1/41(2.5)	27.82 (3.97, 194.83)	<.0001
	Secukinumab Low dose vs. Etanercept	28/40(71.1)	13/41 (31.4)	2.27 (1.36, 3.77)	
	Secukinumab High dose vs. Etanercept	28/40(69.3)	13/41 (31.4)	2.21 (1.33, 3.68)	

** multiple imputation was used to handle missing values*

*** n is the rounded mean number of responders for 100 imputations, m = number of subjects evaluable.*

**** The family-wise type I error was set to 2.5% (one-sided) and each hypothesis of secukinumab Low or High dose compared to Placebo was tested sequentially at 1.25% with respect to the co-primary and key secondary endpoints, and p-value is from an exact logistic regression model with treatment group, baseline body-weight category and age category as factors.*

Patients were followed for efficacy and safety up to 52 weeks following the first dose. Results for the co-primary endpoints and key secondary endpoint at Week 52 were consistent with those observed at Week 12. The safety profiles of the low dose and the high dose were comparable.

At Week 24, the PASI 75 response was 94.9% for COSENTYX low dose and 91.0% for COSENTYX high dose. At the same time point, the IGA 0 or 1 response was 89.6% for COSENTYX low dose and 78.3% for COSENTYX high dose. PASI 90 response at Week 24 was 84.4% for COSENTYX low dose and 80.2% for COSENTYX high dose. By week 52 the PASI 75 response was 89.8% for COSENTYX low dose and 91.2% for COSENTYX high dose. At the same time point, the IGA 0 or 1 response was 74.5% for COSENTYX low dose and 78.1% for COSENTYX high dose. PASI 90 response at Week 52 was 76.5% for COSENTYX low dose and 82.6% for COSENTYX high dose.

Pediatric patients treated with COSENTYX reported an improvement in health-related quality of life as measured by a CDLQI (Children's Dermatology Life Quality Index) score of 0 or 1 (indicating no impairment) compared to placebo at Week 12 (COSENTYX low dose 44.7%, COSENTYX high dose 50%, placebo 15%).

Study A2311

The co-primary endpoints were the proportion of patients who achieved a reduction in PASI score of at least 75% (PASI 75) and IGA mod 2011 'clear' or 'almost clear' (0 or 1) with at least a 2 point improvement from baseline to Week 12. Key secondary endpoint included PASI 90 response at Week 12.

At Week 12, the efficacy of both the low and the high dose of secukinumab was comparable for the co-primary endpoints (see Table 17).

Patients were followed for efficacy for 24 weeks following first administration. Results for the co-primary endpoints and key secondary endpoint at Week 24 were consistent with those observed at Week 12. The safety profiles of the low dose and the high dose were comparable.

Table 17 Summary of clinical response in moderate to severe pediatric psoriasis at Weeks 12*

	Week 12	
	Secukinumab low dose	**Secukinumab high dose**
Number of patients	42	42
PASI 75 response n (%)	39 (92.9%)	39 (92.9%)
IGA mod 2011 'clear' or 'almost clear' response n (%)	33 (78.6%)	35 (83.3%)
PASI 90 response n (%)	29 (69.0%)	32 (76.2%)
** non-responder imputation was used to handle missing values*		

14.2.2 Psoriatic arthritis

Clinical response

Signs and symptoms

Patients treated with COSENTYX 150 mg and 300 mg subcutaneous (SC) dosing demonstrated greater improvements in ACR 20 and ACR 50 response compared to placebo at Week 24 (see Table 18).

Table 18 - Clinical response in Study PsA2 at Week 24

	Placebo (N=98)	COSENTYX 150 mg (N=100)	COSENTYX 300 mg (N=100)
ACR 20 response % (n)	15% (15)	51% (51)	54% (54)
Difference from placebo (95% CI)	-	36% (24%, 48%)	39% (27%, 51%)
p-value[a]	-	p<0.0001	p<0.0001
ACR 50 response % (n)	7% (7)	35% (35)	35% (35)
Difference from placebo (95% CI)	-	28%[b] (18%, 38%)	28% [b] (17%, 38%)
ACR 70 response % (n)	1% (1)	21% (21)	20% (20)
Difference from placebo (95% CI)	-	20% [b] (12%, 28%)	19% [b] (11%, 27%)

ACR: American College of Rheumatology

[a] p-value is based on the logistic regression with treatment and TNF-alpha inhibitor status as factors and baseline weight as a covariate. Type 1 error rate controlled using a hierarchical testing strategy.

[b] 95% confidence intervals for ACR 50 and ACR 70 are not adjusted for multiplicity testing.

Patients who met escape criteria (less than 20% improvement in tender or swollen joint counts) at Week 16 were considered non-responders at Week 24.

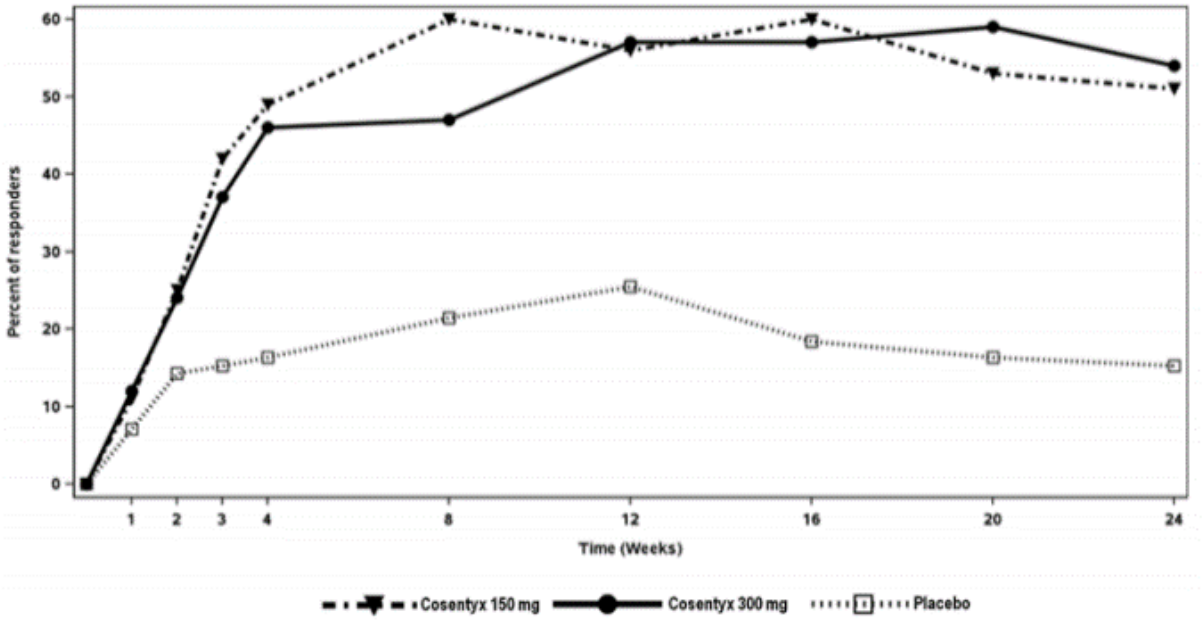
Premature discontinuation from the placebo-controlled portion period (24 weeks) for any reason: placebo 10.2% (10/98), COSENTYX 150 mg 5% (5/100) and COSENTYX 300 mg 3% (3/100). All patients who prematurely discontinued, for any reason, were considered non-responders for ACR 20, ACR 50, and ACR 70.

Concomitant methotrexate usage: placebo 51% (50/98), COSENTYX 150 mg 44% (44/100) and COSENTYX 300 mg 44% (44/100).

The onset of action of COSENTYX occurred as early as Week 2 and was maintained up to Week 52.

The percentage of patients achieving ACR 20 response, by visit, up to Week 24 is shown in Figure 2.

Figure 2 - Percent of patients achieving ACR 20 response through Week 24 in Study PsA2



Patients who met escape criteria (less than 20% improvement in tender or swollen joint counts) at Week 16 were considered non-responders at Week 24.

The results of the components of the ACR response criteria are shown in Table 17.

Table 19 - Mean change from baseline in ACR components in Study PsA2 at Week 24

	COSENTYX 150 mg (N=100)		**COSENTYX 300 mg (N=100)**		**Placebo (N=98)**	
	Baseline Mean	Change from baseline at Week 24 Mean (SE)	Baseline Mean	Change from baseline at Week 24 Mean (SE)	Baseline Mean	Change from baseline at Week 24 Mean (SE)
Number of swollen joints (Scale 0 to 76)	11.9	-6.32[d] (0.618)	11.2	-7.28[d] (0.619)	12.1	-5.14[d] (0.867)
Number of tender joints	24.1	-11.42[d] (1.25)	20.2	-10.84[d] (1.25)	23.4	-4.28[d] (1.74)

	COSENTYX 150 mg (N=100)		COSENTYX 300 mg (N=100)		Placebo (N=98)	
	Baseline Mean	Change from baseline at Week 24 Mean (SE)	Baseline Mean	Change from baseline at Week 24 Mean (SE)	Baseline Mean	Change from baseline at Week 24 Mean (SE)
(Scale 0 to 78)						
Patient's assessment of pain[a]	58.9	-23.39[d] (2.25)	57.7	-22.35[d] (2.26)	55.4	-11.71[d] (3.18)
Patient global assessment[a]	62.0	-25.78[d] (2.19)	60.7	-26.70[d] (2.21)	57.6	-10.14[d] (3.07)
Physician global assessment[a]	56.7	-32.97[d] (1.82)	55.0	-38.52[d] (1.840)	55.0	-25.23[d] (2.526)
Disability Index (HAQ)[b]	1.22	-0.48[d] (0.05)	1.28	-0.56[d] (0.05)	1.17	-0.31[d] (0.06)
CRP (mg/L)[c]	14.42	-8.82 (27.30)[e]	11.08	-7.00 (14.76)[e]	8.17	-2.42 (8.79)[e]

[a] Visual analog scale; 0=best, 100=worst

[b] Disability index of the Health Assessment Questionnaire (HAQ); 0 = best, 3 = worst; measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.

[c] Mean change based upon observed data at Week 24; placebo patients include PBO non-responders (less than 20% improvement in tender or swollen joint counts) who began receiving secukinumab at Week 16.

[d] (LS) mean treatment change from baseline

[e] Standard deviation

Of patients who received COSENTYX 150 mg, 300 mg or placebo, 65% (N=193/298) were anti-TNF-alpha-naïve patients and 35% (N=105/298) were anti-TNF-alpha inadequate responder (IR) patients.

For anti-TNF-alpha-naïve patients, ACR 20 responses at Week 24 were 63.5% (N=40/63), 58.2% (N=39/67) and 15.9% (N=10/63) for COSENTYX 150 mg, 300 mg, and placebo, respectively.

For anti-TNF-alpha-IR patients, ACR 20 responses at Week 24 were 29.7% (N=11/37), 45.5% (N=15/33) and 14.3% (N=5/35) in for COSENTYX 150 mg, 300 mg and placebo, respectively.

Patients treated with COSENTYX 150 mg and 300 mg subcutaneous (SC) dosing demonstrated greater improvements in ACR 20 and ACR 50 compared to placebo at Week 16 (see Table 20). Improvement was maintained to Week 24.

Table 20 - Clinical response in Study PsA3 at Week 16

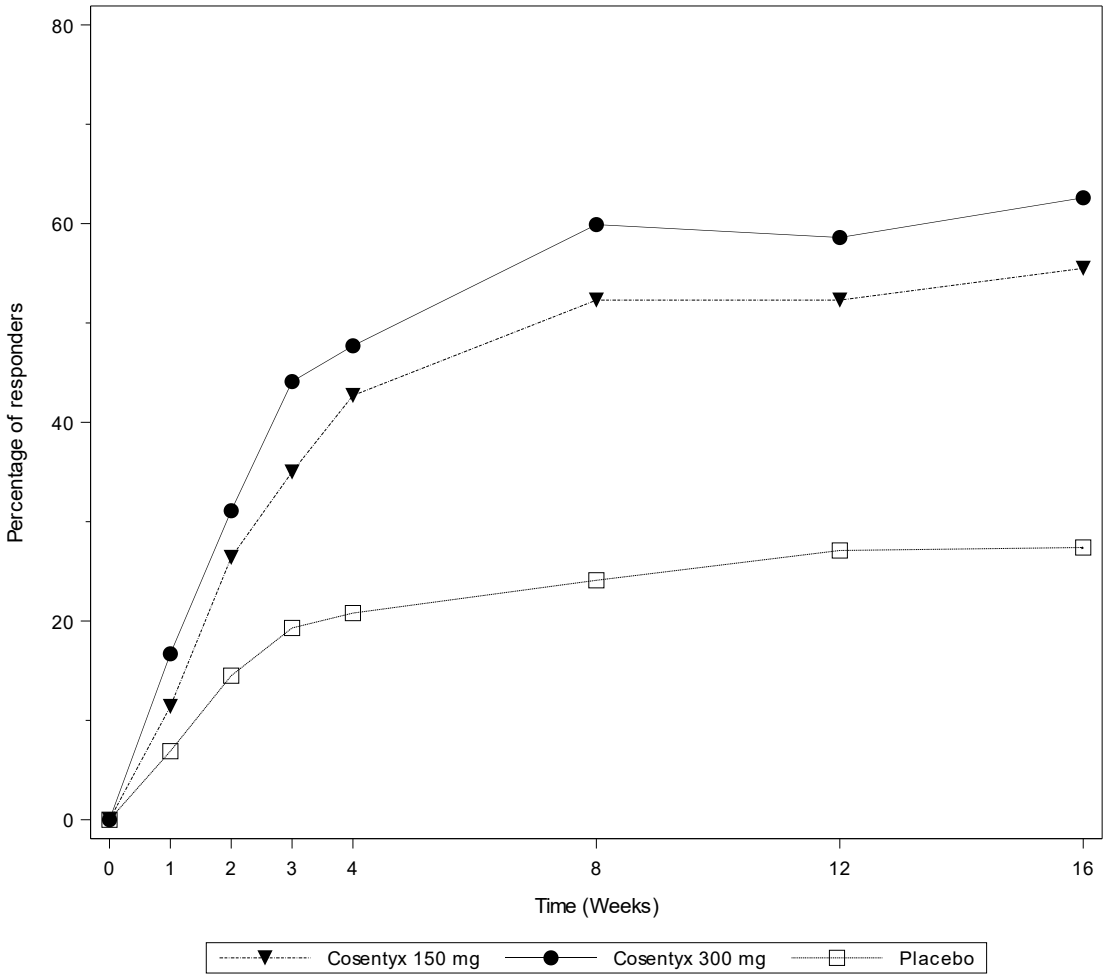
	Placebo (N=332)	**COSENTYX 150 mg (N=220)**	**COSENTYX 300 mg (N=222)**
Week 16			
ACR 20 response % (n)	27.4 (91)	55.5 (122)	62.6 (139)
Difference from placebo (95% CI)	-	28.0% (19.9%, 36.2%)	35.2% (27.2%, 43.2%)
p-value[a]	-	p<0.0001	p<0.0001
ACR 50 response % (n)	8.1 (27)	35.9 (79)	39.6 (88)
Difference from placebo (95% CI)	-	27.8% (20.8%, 34.8%)	31.5% (24.4%, 38.6%)

ACR: American College of Rheumatology

[a] p-value is based on the logistic regression with treatment and TNF-alpha inhibitor status as factors and baseline weight as a covariate. Type 1 error rate controlled using a hierarchical testing strategy

The percentage of patients achieving ACR 20 response, by visit, up to Week 16 is shown in Figure 3.

Figure 3 - Percent of patients achieving ACR 20 response through Week 16 in Study PsA3



The results of the components of the ACR response criteria are shown in Table 21.

Table 21 - Mean change from baseline in ACR components in Study PsA3 at Week 16

	COSENTYX 150 mg (N=220)		**COSENTYX 300 mg (N=222)**		**Placebo (N=332)**	
	Baseline	Change from Baseline	Baseline	Change from Baseline	Baseline	Change from Baseline
		Week 16		Week 16		Week 16
	Mean	Mean (SE)	Mean	Mean (SE)	Mean	Mean (SE)

Number of swollen joints (Scale 0 to 76)	12.1	-6.66 (0.450)	10.0	-7.16 (0.449)	11.7	-4.54 (0.375)
Number of tender joints (Scale 0 to 78)	21.2	-9.75 (0.818)	19.8	-10.76 (0.816)	21.2	-5.61 (0.680)
Patient's assessment of pain[a]	56.5	-18.03 (1.603)	52.8	-20.79 (1.594)	53.6	-6.50 (1.337)
Patient global assessment[a]	53.9	-13.90 (1.638)	55.0	-17.84 (1.630)	52.5	-5.62 (1.369)
Physician global assessment[a]	57.7	-30.50 (1.464)	55.4	-34.40 (1.460)	54.3	-15.38 (1.209)
Disability Index (HAQ)[b]	1.27	-0.44 (0.035)	1.21	-0.55 (0.035)	1.26	-0.21 (0.029)
CRP (mg/L)[c]	13.60	-8.87 (20.63)[d]	9.92 (17.50)[d]	-5.70 (16.32)[d]	13.09 (27.32)[d]	-2.05 (20.64)[d]

[a] Visual analog scale; 0=best, 100=worst

[b] Disability index of the Health Assessment Questionnaire (HAQ); 0 = best, 3 = worst; measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.

[c] Mean change based upon observed data at Week 24; placebo patients include PBO non-responders (less than 20% improvement in tender or swollen joint counts) who began receiving secukinumab at Week 16.

[d] Standard deviation

Radiographic Response

In PsA3 Study, inhibition of progression of structural damage was assessed radiographically and expressed by the modified Total Sharp Score (mTSS) and its components, the Erosion Score (ES) and the Joint Space Narrowing Score (JSN), at Week 24 compared to baseline. Radiographs of hands, wrists, and feet were obtained at baseline, Week 16 and/or Week 24 and scored independently by at least two readers who were blinded to treatment group and visit number. COSENTYX 150 mg and 300 mg treatment inhibited the rate of progression of peripheral joint damage compared with placebo treatment as measured by the change from baseline in mTSS at Week 24 (see Table 22).

Table 22 - Rate of Change per 24 Weeks in Modified Total Sharp Score

Treatment	n	Rate of Change per 24 weeks	Difference From Placebo (95% CI)
Secukinumab 150 mg No Load (N = 222)	210	-0.09	-0.58 (-0.92, -0.24)
Secukinumab 150 mg With Load (N = 220)	213	0.14	-0.34 (-0.68, 0.00)
Secukinumab 300 mg With Load (N = 222)	217	0.03	-0.45 (-0.79, -0.12)
Placebo (N = 332)	301	0.48	

N – number of subjects randomized
n – number of subjects included in the analysis
CI – confidence interval

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

Patient Reported Outcomes

In PsA2 Study, the mean change from baseline in the Disease Activity Index Score 28 using C-reactive protein (DAS28-CRP) at Week 24 was -1.58 and -0.96 in patients treated with COSENTYX 150 mg and placebo, respectively.

In patients with coexisting plaque psoriasis (≥ 3% skin involvement with psoriasis at baseline), the proportion of patients who responded based on Psoriasis Area Severity Index 75 (PASI 75) were 48% (N=28/58) and 16% (N=7/43) in the COSENTYX 150 mg and placebo groups, respectively.

In PsA2 Study, the mean change from baseline by Week 24 in Health Assessment Questionnaire-Disability Index (HAQ-DI) was -0.48 vs. -0.31 in patients treated with COSENTYX 150 mg and patients treated with placebo, respectively. The proportion of patients who achieved at least -0.3 improvement in HAQ-DI score from baseline was 46% (N=46/100) in COSENTYX 150 mg group, compared with 16.3% (N=16/99) in the placebo group.

COSENTYX-treated patients reported improvements in health-related quality of life as measured by the SF-36 Physical Component Summary at Week 24 as compared to placebo.

Axial manifestations in psoriatic arthritis

The primary variable of at least a 20% improvement in Assessment of SpondyloArthritis International Society (ASAS 20) criteria at week 12 was met. Treatment with secukinumab 150 mg or 300 mg compared to placebo resulted in clinically meaningful improvement in signs and symptoms (including greater decreases from baseline in spinal pain) and improvement in physical function (see Table 23).

Table 23 - Clinical response on MAXIMISE Study at Week 12

	Placebo (n=164)	**150 mg (n=157)**	**300 mg (n=164)**
ASAS 20 response, % (95% CI)	31.2 (24.6, 38.7)	66.3* (58.4, 73.3)	62.9* (55.2, 70)

ASAS 40 response, % (95% CI)	12.2 (7.8, 18.4)	39.5 (32.1, 47.4)	43.6 (36.2, 51.3)
BASDAI 50, % (95% CI)	9.8 (5.9, 15.6)	32.7 (25.8, 40.5)	37.4 (30.1, 45.4)
Spinal pain, VAS (95% CI)	-13.6 (-17.2, -10)	-28.5 (-32.2, -24.8)	-26.5 (-30.1, -22.9)
Physical function, HAQDI (95% CI)	-0.155 (-0.224, -0.086)	-0.330 (-0.401, -0.259)	-0.389 (-0.458, -0.320)

** p<0.0001; ASAS: Assessment of SpondyloArthritis International Society Criteria; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; VAS: Visual Analog Scale; HAQDI: Health Assessment Questionnaire – Disability Index*

Improvement in ASAS 20 and ASAS 40 for both secukinumab doses were observed by Week 4 and were maintained up to 52 weeks.

14.2.3 Axial spondyloarthritis (axSpA)

Ankylosing spondylitis (AS, radiographic axial spondyloarthritis)

Clinical response

Signs and symptoms

Patients treated with COSENTYX 150 mg demonstrated greater improvements in ASAS 20 and ASAS 40 responses compared to placebo at Week 16. Responses were observed in patients regardless of concomitant therapies or prior anti-TNF-alpha exposure status.

In AS2 Study, treatment with COSENTYX 150 mg resulted in greater improvement in ASAS 20 and ASAS 40 compared with placebo at Week 16 (see Table 24).

Table 24 - Efficacy Results for AS2 Study at Week 16

	COSENTYX 150 mg (N=72)	**Placebo (N=74)**	**Difference from placebo (95% CI)**	**p-value**
ASAS 20 response % (n)	61% (44)	28% (21)	33 (18, 48)	p=0.0001[a]
ASAS 40 response % (n)	36% (26)	11% (8)	25 (12, 38)	p=0.0008[a]

ASAS: Assessment of SpondyloArthritis International Society Criteria.

[a] p-value is based on the logistic regression with treatment and TNF-alpha inhibitor status as factors and baseline weight as a covariate. All p-values adjusted for multiplicity of testing based on pre-defined hierarchy.

Premature discontinuation from the placebo-controlled period (16 weeks) for any reason: placebo 11% (8/74) and COSENTYX 150 mg 8% (6/72). All patients who prematurely discontinued, for any reason, were considered non-responders for ASAS 20 and ASAS 40 response endpoints.

The mean change in BASDAI score, a composite index representing the disease activity in AS patients, from baseline at Week 16 was 2.19 vs. 0.85 in COSENTYX 150 mg-treated patients and placebo-treated patients, respectively.

The results of the main components of the ASAS 20 response criteria are shown in Table 25.

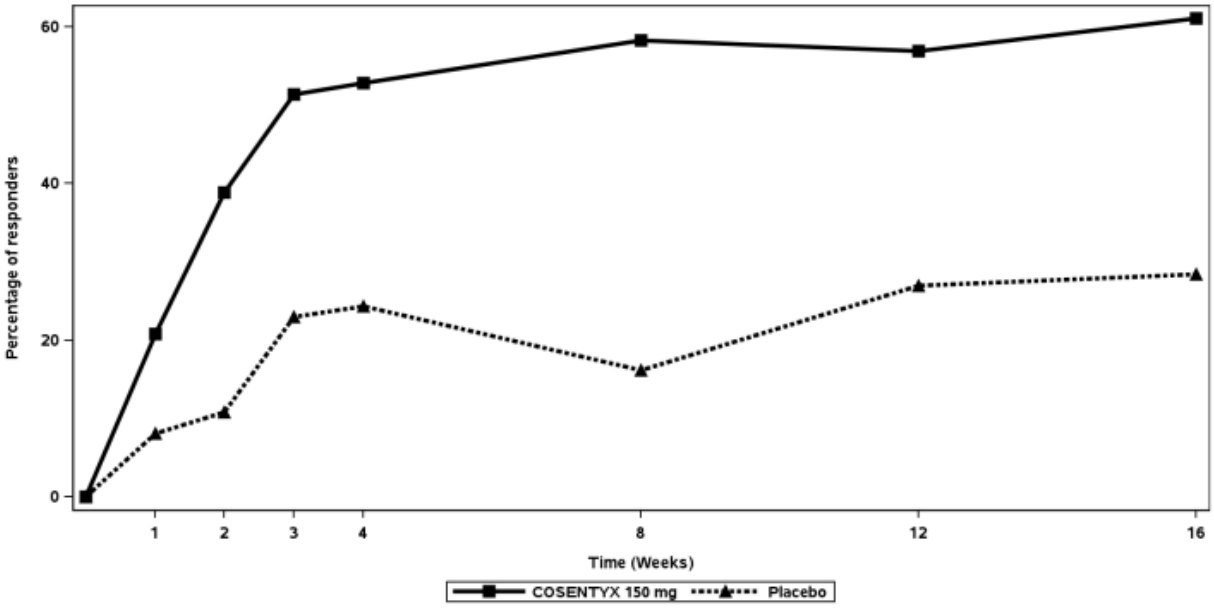
Table 25 - Main components of the ASAS 20 response criteria at baseline and Week 16 in AS2 Study (mean score and SD)

	COSENTYX 150 mg (N=72)			**Placebo (N=74)**		
ASAS 20 Response criteria	**Baseline**	**Week16**	**Change from baseline at Week 16**	**Baseline**	**Week16**	**Change from baseline at Week 16**
-Patient global assessment (0-10) [1]	6.7 (1.7)	3.8 (2.4)	-3.0 (2.6)	7.0 (1.6)	5.5 (2.2)	-1.5 (2.5)
-Total spinal pain (0-10)	6.6 (1.7)	3.7 (2.5)	-2.9 (2.5)	6.9 (1.9)	5.7 (2.3)	-1.2 (2.6)
-BASFI (0-10) [2]	6.2 (2.1)	3.8 (2.6)	-2.3 (2.2)	6.1 (2.0)	5.3 (2.6)	-0.8 (1.9)
-Inflammation (0-10) [3]	6.5 (2.1)	4.0 (2.5)	-2.5 (2.9)	6.5 (2.1)	5.7 (2.4)	-0.8 (2.3)

[1] Percent of subjects with at least a 20% and 10 unit improvement measured on a Visual Analog Scale (VAS) with 0= none, 10= severe
[2] Bath Ankylosing Spondylitis Functional Index
[3] Inflammation is the mean of two patient-reported stiffness self-assessment in BASDAI

The percentage of patients achieving an ASAS 20 response by visit up to Week 16 is shown in Figure 4, with separation compared to placebo occurring as early as Week 1.

Figure 4 - ASAS 20 responses in AS2 Study over time up to Week 16



ASAS 20 responses at Week 16 were 68.2% vs. 31.1% in anti-TNF-alpha-naïve patients and 50.0% vs. 24.1% in anti-TNF-alpha-IR patients for COSENTYX 150 mg and placebo, respectively.

Spinal mobility was assessed by BASMI. The mean change from baseline in BASMI score at Week 16 was -0.51 vs. -0.22 in COSENTYX 150 mg-treated patients and placebo-treated patients, respectively.

In AS2 Study, among 72 patients initially randomised to COSENTYX 150 mg, 61 (84.7%) patients were still on treatment at Week 52. Among these patients, the ASAS 20 and ASAS 40 responses were achieved by 45 (73.8%) and 35 (57.4%) subjects respectively.

The mean change from baseline by Week 16 in Ankylosing Spondylitis Quality of Life (ASQoL) was -4.00 vs. -1.37 in patients treated with COSENTYX 150 mg and patients treated with placebo, respectively. Patients treated with COSENTYX reported improvements in the SF-36 Physical Component Summary (PCS) Score at Week 16 compared to placebo.

In AS3 Study, treatment with COSENTYX 150 mg and COSENTYX 300 mg resulted in greater improvements in ASAS 20 and ASAS 40 compared with placebo at Week 16 (see Table 26).

Table 26 - Efficacy Results for AS3 Study at Week 16

	COSENTYX 150 mg (N=74)	**COSENTYX 300 mg (N=76)**	**Placebo (N=76)**	**Difference from placebo (95% CI); p-value**	
				COSENTYX 150 mg	**COSENTYX 300 mg**
ASAS 20 response % (n)	58% (43)	61% (46)	37% (28)	21 (6, 37); p=0.0102[a]	24 (9, 39); p=0.0075[a]
ASAS 40 response %	41% (30)	42% (32)	21% (16)	20 (5, 34);	21 (7, 36);

(n)				p=0.0102[a]	p=0.0102[a]

ASAS: Assessment of SpondyloArthritis International Society Criteria.

[a] p-value is based on the logistic regression with treatment and TNF-alpha inhibitor status as factors and baseline weight as a covariate. All p-values adjusted for multiplicity of testing based on pre-defined hierarchy.

Premature discontinuation from the placebo-controlled period (16 weeks) for any reason: placebo 3.9% (3/76), COSENTYX 150 mg 0% (0/74) and COSENTYX 300 mg 1.3% (1/76). All patients who prematurely discontinued, for any reason, were considered non-responders for ASAS 20 and ASAS 40 response endpoints.

14.2.4 Non-radiographic axial spondyloarthritis (nr-axSpA)

Clinical response

In Nr-axSpA 1 Study, treatment with COSENTYX 150 mg resulted in significant improvements in the measure of disease activity compared to placebo at Week 16 and Week 52 (Table 27)

Table 27 - Summary of Clinical Response in Nr-axSpA 1 Study at Week 16 and Week 52

Number of subjects with ASAS40 response (%)	COSENTYX 150 mg with load (n= 185)	COSENTYX 150 mg without load (n= 184)	Placebo (n= 186)	Difference from placebo (95% CI)	
				COSENTYX 150 mg with load	COSENTYX 150 mg without load
Week 16	74 (40)	75 (41)	52 (28)	12 (2, 22)	13 (3, 22)
Week 52	62 (34)	70 (38)	36 (19)	14 (5, 23)	19 (10, 28)

Difference in proportions with 95% CI based on normal approximation.

Signs and symptoms

In Nr-axSpA 1 Study, treatment with COSENTYX 150 mg resulted in significant improvements in the measures of disease activity compared to placebo at Week 16 and Week 52. These measures include ASAS 40, ASAS 5/6, BASDAI, BASDAI 50, high-sensitivity CRP (hsCRP), ASAS 20 response, ASAS partial remission compared to placebo (see Table 28). Efficacy for all these endpoints was maintained up to Week 52.

Table 28 - Clinical response in Nr-axSpA 1 Study at Week 16

Outcome (p-value vs placebo)	Placebo	COSENTYX 150 mg[1]	Difference from placebo (95% CI)
Number of TNF-naive patients randomized	**171**	**164**	
ASAS 40 response, %	29.2%	41.5%	12.3 (2.5, 22.8)*
Total number of patients randomized	**186**	**185**	
ASAS 40 response, %	28.0%	40.0%	12.7 (3.0, 22.4)*
ASAS 5/6, %	23.7%	40.0%	17.1 (7.4, 26.7)*
BASDAI, LS mean change from baseline score	-1.46	-2.35	-0.89 (-1.39, -0.38)*
BASDAI 50, %	21.0%	37.3%	18.5 (8.7, 27.4)*
hsCRP, (post-BSL/BSL ratio)	0.91	0.64	0.70 (0.58, 0.84)*
ASAS 20 response, %	45.7%	56.8%	11.7 (1.7, 23.0)*
ASAS partial remission, %	7.0%	21.6%	14.6 (7.5, 21.7)*

[1]secukinumab 150 mg s.c. at weeks 0, 1, 2, 3, and 4 followed by the same dose every month

All p-values adjusted for multiplicity of testing based on pre-defined hierarchy

Non-responder imputation used for missing binary endpoints, mixed models with repeated measures applied to continuous endpoints

Model Based Treatment Difference

**p <0.05 versus placebo*

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

The results of the main components of the ASAS 40 response criteria for all patients randomized are shown in Table 29. Responses were sustained up to Week 52.

Table 29 - Main components of the ASAS40 response criteria and other measures of disease activity in nr-axSpA patients at baseline and Week 16 in Nr-axSpA 1 Study

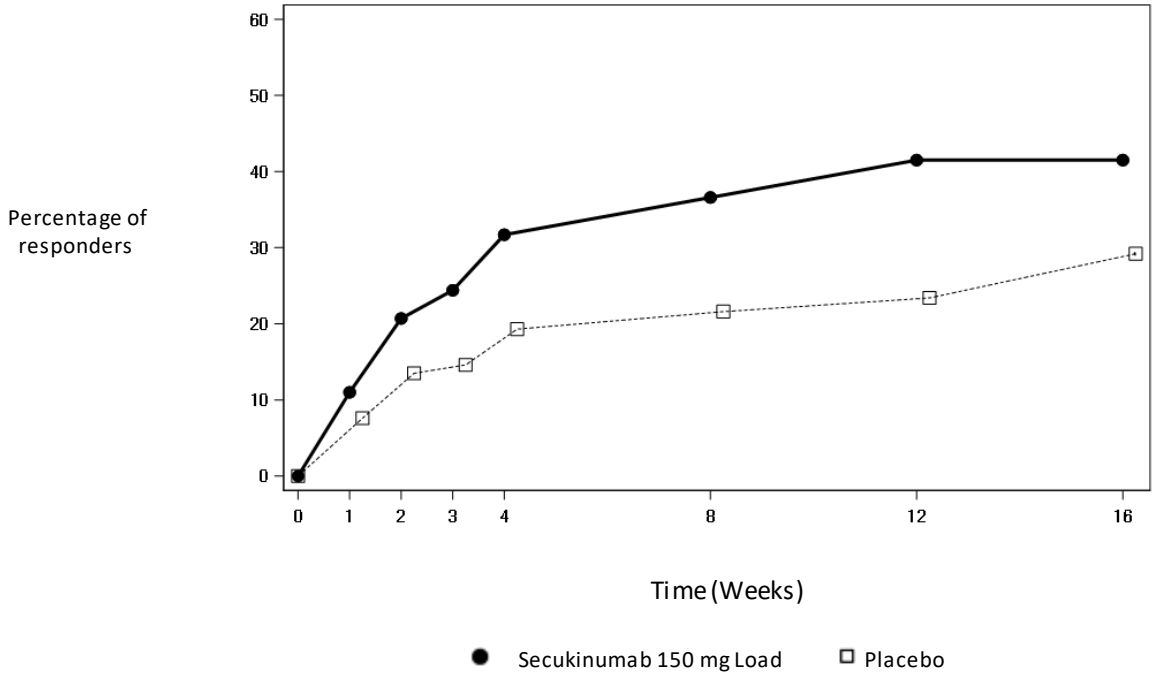
	Placebo (N = 186)	COSENTYX 150 mg[1] (N = 185)

	Baseline	Week 16 change from baseline	Baseline	Week 16 change from baseline
ASAS40 Response criteria				
-Patient global assessment of Disease Activity (0 to 100 mm)	68.8	-13.78	72.6	-24.10
-Total back pain (0 to 100 mm)	70.9	-15.64	73.3	-24.96
-BASFI (0 to 10)	5.893	-1.01	6.244	-1.75
-Inflammation (0 to 10)	6.588	-1.71	7.206	-2.76
hsCRP (mg/L) Mean Change at Week 16	10.76	-2.42	13.17	-7.90
BASDAI (0 to 10)	6.760	-1.46	7.082	-2.35
- Spinal pain	7.52	-2.03	7.76	-3.00
- Peripheral pain and swelling (0 to 10)	6.13	-1.60	6.29	-2.26
BASMI	2.765	-0.13	2.923	-0.26

[1]*secukinumab 150 mg s.c. at weeks 0, 1, 2, 3, and 4 followed by the same dose every month*

The percentage of patients achieving an ASAS 40 response in anti-TNF-alpha naïve patients by visit is shown in Figure 5.

Figure 5 - ASAS 40 responses in anti-TNF-alpha naïve patients in Nr-axSpA 1 Study over time up to Week 16



ASAS 40 responses were also improved at Week 16 in anti-TNF-alpha-IR patients for COSENTYX 150 mg compared with placebo.

Physical function and health-related quality of life

Patients treated with COSENTYX 150 mg showed improvements by Week 16 compared to placebo-treated patients in physical function as assessed by the BASFI (Week 16: -1.75 vs -1.01). They also showed improvements compared to placebo-treated patients by Week 16 in health-related quality of life as measured by ASQoL (LS mean change: Week 16: -3.45 vs -1.84) and SF-36 Physical Component Summary (SF-36 PCS) (LS mean change: Week 16: 5.71 vs 2.93) These improvements were sustained up to Week 52.

Spinal mobility

Spinal mobility was assessed by BASMI up to Week 16. Numerically greater improvements were demonstrated in patients treated with COSENTYX compared with placebo-treated patients at Weeks 4, 8, 12 and 16.

Reduction of inflammation in magnetic resonance imaging (MRI)

Objective signs of inflammation were assessed by MRI at baseline and Week 16 and expressed as change from baseline in Berlin SI-joint edema score for sacroiliac joints. Mean change from baseline to Week 16 was statistically significantly greater for secukinumab 150 mg compared to placebo (−1.68 vs. −0.39 , $p < 0.05$).

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Single-dose Toxicity
Single subcutaneous injection of secukinumab to the monkey at doses of 15 or 150 mg/kg followed by a 7- or 28-day observation period was well tolerated systemically and at the injection sites. The highest dose of 150 mg/kg administered, was concluded as the NOAEL.

Repeat-dose Toxicity
Secukinumab was well tolerated following weekly IV doses of up to 150 mg/kg for up to 26 weeks and SC doses up to 150 mg/kg for 13 weeks. There was no evidence of treatment-related adverse findings in immunotoxicity (including infections or hypersensitivity reactions) and safety pharmacology evaluations. Immunogenicity was detected in one animal given 150 mg/kg/week subcutaneously for 13 weeks. Serum concentrations that are well tolerated in animals for 13 weeks of s.c. dosing are in excess of at least 110-fold (Cmax) and 120-fold (Cav) the serum concentrations in psoriasis patients at maintenance therapy, treated with a clinical dose of 300 mg s.c. q4 weeks.

Table 30 - Sub-Chronic and Chronic Toxicology (Pivotal studies)

Study Type	Species	Route	No. of animals/ group	Doses (Mg/kg/week)	Findings
13 week	Cynomolgus monkey	subcutaneous	3m 3f 2m 2f recovery	15, 50, 150	No adverse signs of toxicity NOAEL = 150 mg/kg/week
4 week	Cynomolgus monkey	intravenous	3m 3f 2m 2f recovery	10, 30, 100	No adverse signs of toxicity NOAEL = 150 mg/kg/week
4 week	Cynomolgus monkey	intravenous	3m 3f 2m 2f recovery	15, 50, 150	No adverse signs of toxicity NOAEL = 150 mg/kg/week
26 week	Cynomolgus monkey	intravenous	4m 4f 2m 2f recovery	15, 50, 150	No adverse signs of toxicity NOAEL = 150mg/kg/week

Carcinogenicity: Carcinogenicity studies have not been conducted for secukinumab

Genotoxicity: Genotoxicity studies have not been conducted for secukinumab.

Reproductive and Developmental Toxicology: In an embryo fetal development study in cynomolgus monkeys secukinumab was neither teratogen nor embryotoxic at doses up to 150 mg/kg/week. The mouse surrogate antibody BZN035, a murine anti-murine IL-17A antibody, caused no adverse findings on reproduction or development.

Table 31 - Reproductive Toxicology (pivotal studies)

Study Type	Species	Route	No. of animals/ group	Doses (Mg/kg/week)	Findings
Fertility and early embryonic development study	Mice	subcutaneous	24m 24f	15, 50, 150	BZN035 was neither teratogen nor embryotoxic. BZN035 did not affect fertility of the adult mice nor the development of the pups exposed via the treated mother. NOEL = 150 mg/kg/week
Embryo fetal development study	Cynomolgus monkey	subcutaneous	16f	15, 50, 150	Secukinumab was neither teratogen nor embryotoxic. NOAEL = 150 mg/kg/week
Pre- and postnatal development study	Mice	subcutaneous	24f	15, 50, 150	BZN035 did not affect pregnancy or delivery; or morphological, functional and immunological developmental parameters of offspring. NOAEL = 150 mg/kg/week

Special Toxicology: No non-specific tissue binding was observed when secukinumab was applied to normal human or cynomolgus monkey tissues.

Juvenile Toxicity: Juvenile toxicity studies have not been conducted with secukinumab.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr COSENTYX®

Secukinumab

Read this carefully before you start taking **COSENTYX®** and each time you get a refill. This Patient Medication Information is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **COSENTYX**.

What is COSENTYX used for?

COSENTYX is used for the treatment of the following inflammatory diseases:

- **Plaque psoriasis**
- **Psoriatic arthritis**
- **Axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis**

Plaque psoriasis

COSENTYX is used to treat a skin condition called 'plaque psoriasis'. Plaque psoriasis causes inflammation affecting the skin. COSENTYX will reduce the inflammation and other symptoms of the disease.

Adult

COSENTYX is used in adults with moderate to severe plaque psoriasis.

Pediatrics

COSENTYX is used in patients 6 years and older with moderate to severe plaque psoriasis. Psoriasis can cause raised, thick, red and scaly patches ("psoriatic lesions") that can appear anywhere on your body.

Psoriatic arthritis

COSENTYX is used in adults with active psoriatic arthritis and can be used alone or with another medicine called methotrexate. You may first be given other medicines for this disease. If you do not respond well enough to these medicines, you will be given COSENTYX.

The condition is an inflammatory disease of the joints, often accompanied by psoriasis.

Axial spondyloarthritis (axSpA)

COSENTYX is used to treat conditions called 'ankylosing spondylitis' and 'non-radiographic axial spondyloarthritis'. These are inflammatory disease primarily affecting the spine, which causes inflammation of the spinal joints.

COSENTYX is used in adults with active ankylosing spondylitis and active non-radiographic axial spondyloarthritis.

You (or your child) may first be given other medicines for this disease. If you do not respond well enough to these medicines, you (or your child) will be given COSENTYX.

How does COSENTYX work?

COSENTYX contains the active substance secukinumab. Secukinumab is a fully-human monoclonal antibody. Monoclonal antibodies are proteins that recognize and bind specifically to certain proteins in the body.

COSENTYX belongs to a group of medicines called interleukin (IL) inhibitors. This medicine works by neutralising the activity of a protein called IL-17A, which is present at increased levels in diseases such as psoriasis, psoriatic arthritis and axial spondyloarthritis (including both ankylosing spondylitis and non-radiographic axial spondyloarthritis). COSENTYX helps reduce the signs and symptoms of psoriasis such as pain, itching, and scaly patches. In addition, COSENTYX helps reduce the signs and symptoms of psoriatic arthritis and axial spondyloarthritis (including both ankylosing spondylitis and non-radiographic axial spondyloarthritis).
If you have any questions about how COSENTYX works or why this medicine has been prescribed for you, ask your doctor, pharmacist or healthcare provider.

What are the ingredients in COSENTYX?

Medicinal ingredients: Secukinumab

Non-medicinal ingredients: **Solution for injection:** L-histidine/histidinehydrochloride monohydrate, L-methionine, polysorbate 80, Trehalose dehydrate, water for injection.

Powder for solution for injection*: Sucrose, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, water for injection

COSENTYX comes in the following dosage forms:

Solution for injection in a pre-filled syringe (75 mg/0.5 mL) or pre-filled syringe (150 mg/mL) or pre-filled SensoReady® pen (150 mg/mL) or single-use vial (lyophilized powder for solution for injection) (150mg)*.

*single-use vial not available in Canada

Do not use COSENTYX if:

- **If you (or your child) had a severe allergic** reaction to secukinumab or any of the other ingredients of COSENTYX.
- If you think you (or your child) may be allergic, ask your doctor for advice before using COSENTYX.
- Do not take COSENTYX if you (or your child) have any signs of infection or an active tuberculosis infection unless you are instructed to by your healthcare provider.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take COSENTYX. Talk about any health conditions or problems you may have, including if you:

- you (or your child) currently have an infection or if you have long-term or repeated infections.
- you (or your child) have tuberculosis. Your doctor should check for tuberculosis before starting treatment.

- you (or your child) ever had an allergic reaction to latex. The needle cap on the COSENTYX SensoReady pen and pre-filled syringe contains a derivative of latex.
- you (or your child) have ever been diagnosed with inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis). Your doctor should check for signs and symptoms of inflammatory bowel disease.
- you (or your child) had a recent vaccination or if you (or your child) will receive a vaccination during treatment with COSENTYX.

Other warnings you should know about:

COSENTYX is a medicine that affects the immune system.

COSENTYX may increase the risk of having serious side effects such as infections.

You (or your child) have worsening symptoms or develop new symptoms of stomach pain or diarrhea.

Signs or symptoms of a potentially serious infection. These may include:

- fever, flu-like symptoms, muscle aches, night sweats
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water

Signs or symptoms of an allergic reaction. These may include:

- chest tightness, difficulty breathing or swallowing
- low blood pressure, which can cause dizziness or light-headedness
- swelling of the face, lips, mouth or throat

Do not use COSENTYX if you (or your child) have any signs of infections or an allergic reaction unless you are instructed to by your healthcare provider.

Children and adolescents (below the age of 18 years)

COSENTYX is not recommended for children under 6 years of age with plaque psoriasis because it has not been studied in this age group.

COSENTYX is not recommended for children and adolescents (under 18 years of age) in other indications because it has not been studied in this age group.

Pregnancy and breast-feeding

Talk to your doctor before using COSENTYX:

- If you (or your child) are pregnant, think that you may be pregnant or are planning to have a baby.
- COSENTYX is not recommended during pregnancy unless the benefits clearly outweigh the potential risks.
- If you (or your child) are breast-feeding or plan to breast-feed.
- It is not known if COSENTYX passes into your breast milk.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with COSENTYX:

Tell your doctor or pharmacist:

- If you (or your child) are taking, have recently taken or might take any other medicines.
- If you (or your child) have recently had or are going to have a vaccination. You should not receive certain types of vaccines (live vaccines) while using COSENTYX.

How to take COSENTYX:

Your healthcare provider will prescribe the dose of COSENTYX that is right for you (or your child).

- If the prescribed dose is **75 mg**, administer **1 injection** of COSENTYX 75 mg/0.5mL for each dose.
- If the prescribed dose is **150 mg**, administer **1 injection** of COSENTYX 150 mg/1mL for each dose.
- If the prescribed dose is **300 mg**, administer **2 injections** of COSENTYX 150 mg/1mL for each dose.

Always use COSENTYX as your doctor has told you. You should check with your doctor, nurse or pharmacist if you are not sure.

COSENTYX is administered via injection under the skin ('subcutaneously').

You and your doctor should decide if you should inject COSENTYX yourself.

It is important not to try to inject yourself (or your child) until you have been trained by your doctor, nurse or pharmacist. A caregiver may also give you your COSENTYX injection after proper training.

Usual dose:

Your doctor will decide how much COSENTYX you (or your child) need.

Plaque psoriasis

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

In children 6 years and older, the recommended dose is based on body weight and is given by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3, and 4 followed by monthly maintenance dosing.

For children receiving the 75 mg dose, the 75 mg/0.5mL pre-filled syringe should be used.

Psoriatic arthritis

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

For psoriatic arthritis patients with coexistent moderate to severe plaque psoriasis, use the dosing and administration recommendations for plaque psoriasis.

For patients who did not respond well to medicines called tumor necrosis factor (TNF) blockers or continues to have active psoriatic arthritis, the 300 mg dose may be given.

Axial spondyloarthritis (axSpA)

Ankylosing spondylitis

The recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3, and 4 followed by monthly maintenance dosing. Based on your response, the doctor may increase your dose to 300 mg. Each 300 mg dose is given as two subcutaneous injections of 150 mg.

Non-radiographic axial spondyloarthritis

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

This is a long-term treatment. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.

Overdose:

If you accidentally injected more COSENTYX or sooner than according to your doctor's prescription, inform your doctor.

If you think you, or a person you are caring for, have taken too much COSENTYX, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

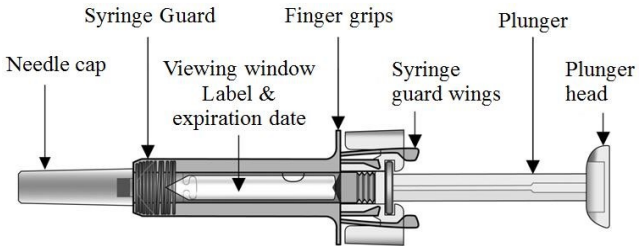
If you have forgotten to inject a dose of COSENTYX, inject the next dose as soon as you remember. Then talk to your doctor to discuss when you should inject the next dose.

COSENTYX solution for injection is a clear liquid. Its color may vary from colorless to slightly yellow. COSENTYX is available in packs containing 1 or 2 pre-filled syringe(s) or SensoReady pens.

Instructions for use of the COSENTYX 150 mg pre-filled syringe

Read ALL the way through these instructions before injecting. It is important not to try to inject yourself or a person in your care until you have been trained by your doctor, nurse or pharmacist. The box contains 1 or 2 COSENTYX prefilled syringe(s) individually sealed in a plastic blister.

Your COSENTYX pre-filled syringe



After the medication has been injected the syringe guard will be activated to cover the needle. This COSENTYX pre-filled syringe is intended to aid in the protection of healthcare professionals, patients who self-inject doctor prescribed medications and individuals that assist self-injecting patients from accidental needle sticks.

What you additionally need for your injection:

- Alcohol swab
- Cotton ball or gauze
- Sharps disposal container

Important safety information

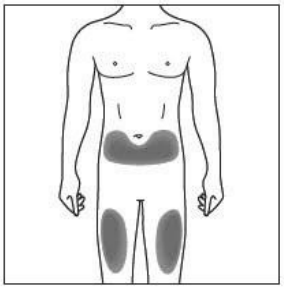
Caution: Keep the COSENTYX pre-filled syringe out of the reach of children.

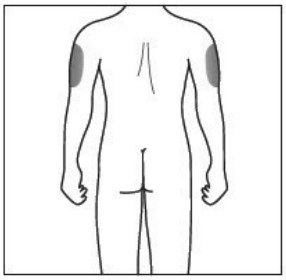
1. The needle cap of the syringe may contain dry rubber (latex), which should not be handled by persons sensitive to this substance.
2. Do not open the sealed outer box until you are ready to use the COSENTYX pre-filled syringe.
3. Do not use the COSENTYX pre-filled syringe if either the seal on the outer box or the seal of the blister are broken, as it may not be safe for you to use.
4. Never leave the COSENTYX pre-filled syringe lying around where others might tamper with it.
5. Do not shake the COSENTYX pre-filled syringe.
6. Be careful not to touch the syringe guard wings before use. By touching them, the syringe guard may be activated too early.
7. Do not remove the needle cap until just before you give the injection.
8. The COSENTYX pre-filled syringe cannot be re-used. Dispose of the used COSENTYX pre-filled syringe immediately after use in a sharps container.

Storage of the COSENTYX 150 mg pre-filled syringe

1. Store the COSENTYX pre-filled syringe sealed in its outer box to protect it from light. Store in the refrigerator between 2°C and 8°C. DO NOT FREEZE.
2. Remember to take the COSENTYX pre-filled syringe out of the refrigerator and allow it to reach room temperature before preparing it for injection (15 to 30 minutes).
3. Do not use the COSENTYX pre-filled syringe after the expiration date shown on the outer box or syringe label. If it has expired, return the entire pack to the pharmacy.

The injection site





The injection site is the place on the body where you are going to use the COSENTYX pre-filled syringe.

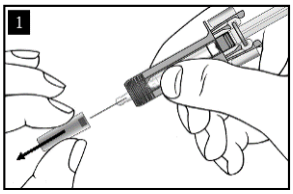
- The recommended site is the front of your thighs. You may also use the lower abdomen, but **not** the area 2 inches around the navel (belly button). If a caregiver is giving you the injection, the outer upper arms may also be used.
- Choose a different site each time you give yourself an injection.
- Do not inject into areas where the skin is tender, bruised, red, scaly or hard. Avoid areas with scars or stretch marks.

Preparing the COSENTYX 150 mg pre-filled syringe ready for use

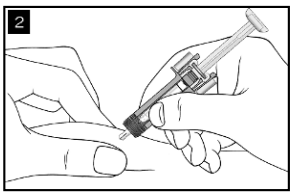
Note: for a 150 mg dose, prepare 1 pre-filled syringe and inject the content. For a 300 mg dose, prepare 2 pre-filled syringes and inject the content of both.

1. Take the box containing the COSENTYX pre-filled syringe out of the refrigerator and leave it **unopened** for about 15 to 30 minutes so that it reaches room temperature.
2. When you are ready to use the COSENTYX pre-filled syringe, wash your hands thoroughly with soap and water.
3. Clean the injection site with an alcohol swab.
4. Remove the COSENTYX pre-filled syringe from the outer box and take it out of the blister.
5. Inspect the COSENTYX pre-filled syringe. The liquid should be clear. Its color may vary from colorless to slightly yellow. You may see a small air bubble, which is normal. DO NOT USE if the liquid contains easily visible particles, is cloudy or is distinctly brown. DO NOT USE if the COSENTYX pre-filled syringe is broken. In all these cases, return the entire product pack to the pharmacy.

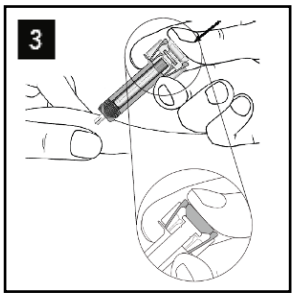
How to use the COSENTYX 150 mg pre-filled syringe



Carefully remove the needle cap from the COSENTYX pre-filled syringe. Discard the needle cap. You may see a drop of liquid at the end of the needle. This is normal.

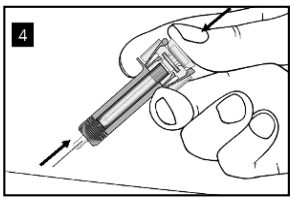


Gently pinch the skin at the injection site and insert the needle as shown. Push the needle all the way in to ensure that the medication can be fully administered.

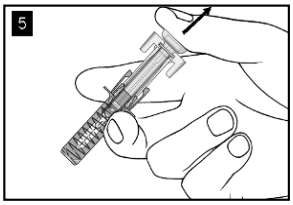


Holding the COSENTYX pre-filled syringe as shown, **slowly** depress the plunger **as far as it will go** so that the plunger head is completely between the syringe guard wings.

Keep the plunger pressed fully down while you hold the syringe in place for 5 seconds.



Keep the plunger fully depressed while you carefully lift the needle straight out from the injection site.



Slowly release the plunger and allow the syringe guard to automatically cover the exposed needle.

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

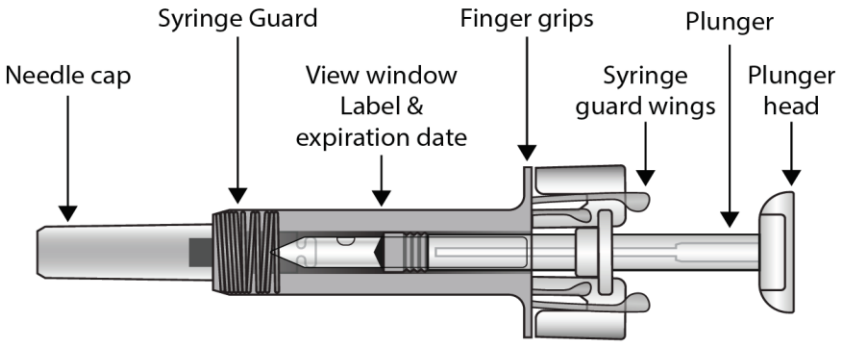
Disposal instructions

Dispose of the used COSENTYX pre-filled syringe in a sharps container (closable, puncture resistant container). For the safety and health of you and others, needles and used syringes **must never** be re-used.

Instructions for use of the 75 mg COSENTYX pre-filled syringe

Read ALL the way through these instructions before injecting. It is important not to try to inject yourself until you or a person in your care have been trained by your doctor, nurse or pharmacist. The box contains one COSENTYX 75 mg pre-filled syringe individually sealed in a plastic blister.

Your COSENTYX 75 mg pre-filled syringe



After the medication has been injected the syringe guard will be activated to cover the needle. This COSENTYX pre-filled syringe is intended to aid in the protection of healthcare professionals, patients who self inject doctor prescribed medications, and individuals who assist self injecting patients from accidental needle sticks.

What you additionally need for your injection:

- Alcohol swab
- Cotton ball or gauze
- Sharps disposal container

Important safety information

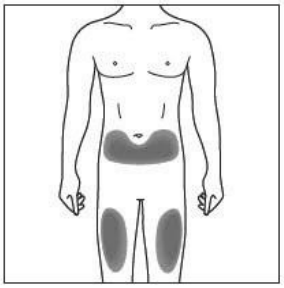
Caution: Keep the COSENTYX pre-filled syringe out of the reach of children.

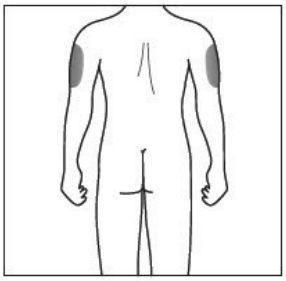
1. The needle cap of the syringe contains dry rubber (latex), which should not be handled by persons sensitive to this substance.
2. Do not open the sealed outer box until you are ready to use the COSENTYX pre-filled syringe.
3. Do not use the COSENTYX pre-filled syringe if either the seal on the outer box or the seal of the blister are broken, as it may not be safe for you to use.
4. Never leave the COSENTYX pre-filled syringe lying around where others might tamper with it.
5. Do not shake the COSENTYX pre-filled syringe.
6. Be careful not to touch the syringe guard wings before use. By touching them, the syringe guard may be activated too early.
7. Do not remove the needle cap until just before you give the injection.
8. The COSENTYX pre-filled syringe cannot be re-used. Dispose of the used COSENTYX pre-filled syringe immediately after use in a sharps container.

Storage of the COSENTYX 75 mg pre-filled syringe

1. Store the COSENTYX pre-filled syringe sealed in its outer box to protect it from light. Store in the refrigerator between 2°C and 8°C. DO NOT FREEZE.
2. Do not use the COSENTYX pre-filled syringe after the expiration date shown on the outer box or syringe label. If it has expired, return the entire pack to the pharmacy.

The injection site





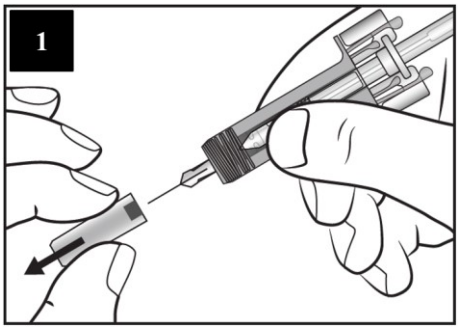
The injection site is the place on the body where you are going to use the COSENTYX pre-filled syringe.

- The recommended site is the front of your thighs. You may also use the lower abdomen, but not the area 2 inches (5 cm) around the navel (belly button). If a caregiver is giving you the injection, the outer upper arms may also be used.
- Choose a different site each time you give yourself an injection.
- Do not inject into areas where the skin is tender, bruised, red, scaly or hard. Avoid areas with scars or stretch marks.

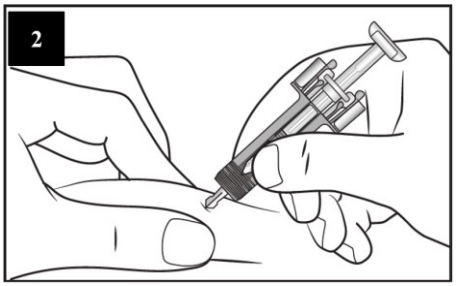
Preparing the COSENTYX 75 mg pre-filled syringe ready for use

1. Take the box containing the COSENTYX pre-filled syringe out of the refrigerator and leave it **unopened** for about 15 to 30 minutes so that it reaches room temperature.
2. When you are ready to use the COSENTYX pre-filled syringe, wash your hands thoroughly with soap and water.
3. Clean the injection site with an alcohol swab.
4. Remove the COSENTYX pre-filled syringe from the outer box and take it out of the blister.
5. Inspect the COSENTYX pre-filled syringe. The liquid should be clear. Its color may vary from colorless to slightly yellow. You may see a small air bubble, which is normal. DO NOT USE if the liquid contains easily visible particles, is cloudy or is distinctly brown. DO NOT USE if the COSENTYX pre-filled syringe is broken. In all these cases, return the entire product pack to the pharmacy.

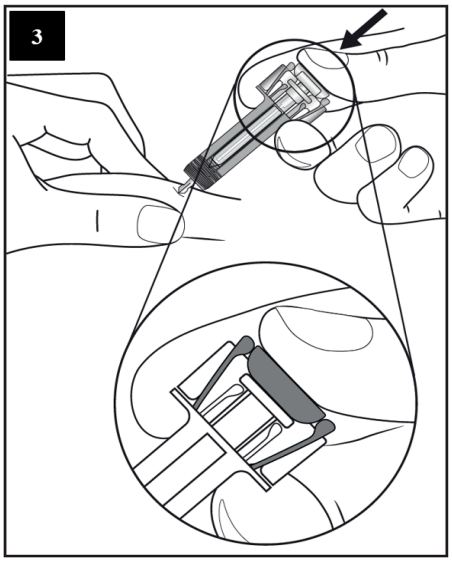
How to use the COSENTYX 75 mg pre-filled syringe



Carefully remove the needle cap from the COSENTYX pre-filled syringe. Discard the needle cap. You may see a drop of liquid at the end of the needle. This is normal.

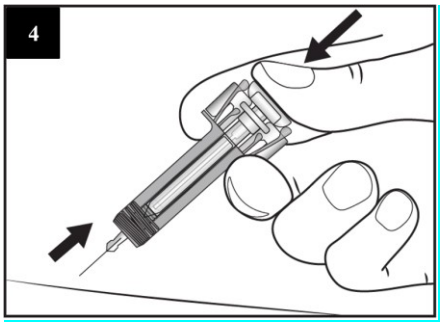


Gently pinch the skin at the injection site and insert the needle as shown. Push the needle all the way in to ensure that the medication can be fully administered.

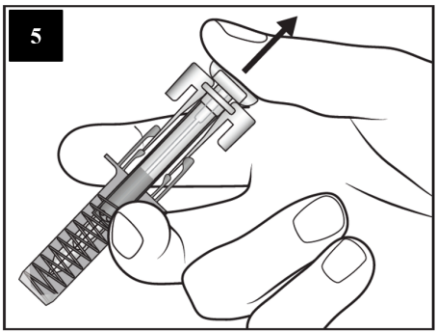


Holding the COSENTYX pre-filled syringe as shown, **slowly** depress the plunger **as far as it will go** so that the plunger head is completely between the syringe guard wings.

Keep the plunger pressed fully down while you hold the syringe in place for 5 seconds.



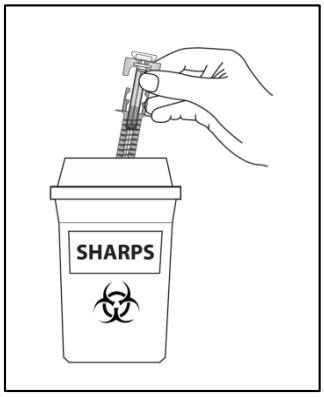
Keep the plunger fully depressed while you carefully lift the needle straight out from the injection site.



Slowly release the plunger and allow the syringe guard to automatically cover the exposed needle.

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

Disposal instructions



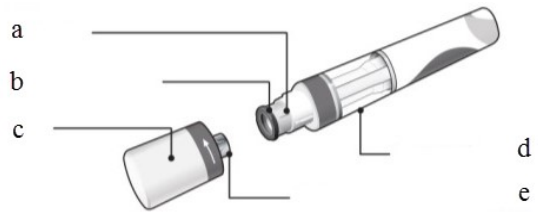
Dispose of the used COSENTYX pre-filled syringe in a sharps container (closable, puncture resistant container). For the safety and health of you and others, needles and used syringes **must never** be re-used.

Instructions for use of COSENTYX SensoReady pen 150 mg

Read ALL the way through these instructions before injecting.

These instructions are to help you to inject correctly using the COSENTYX SensoReady pen.

It is important not to try to inject yourself or a person in your care until you have been trained by your doctor, nurse or pharmacist.



a. Needle
b. Needle guard
c. Cap
d. Inspection window
e. Internal needle cover

COSENTYX SensoReady pen shown with the cap removed. **Do not** remove the cap until you are ready to inject.

Store your boxed COSENTYX SensoReady pen in a **refrigerator** between 2°C and 8°C and **out of the reach of children**.

Do not **freeze** the COSENTYX SensoReady pen.

Do not **shake** the COSENTYX SensoReady pen.

Do not use the COSENTYX SensoReady pen if it has been **dropped** with the cap removed.

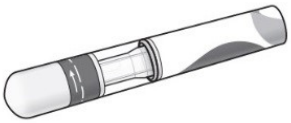
For a more comfortable injection, take the COSENTYX SensoReady pen out of the refrigerator **15 to 30 minutes before injecting** to allow it to reach room temperature.

What you need for your injection:

Included in the carton:

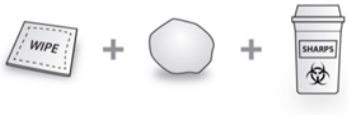
- A new and unused COSENTYX SensoReady pen.

  1 pen is needed for a 150 mg dose and 2 pens are needed for a 300 mg dose.

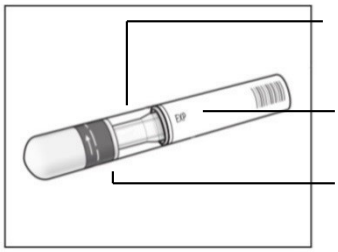


Not Included in the carton:

- Alcohol swab
- Cotton ball or gauze
- Sharps disposal container

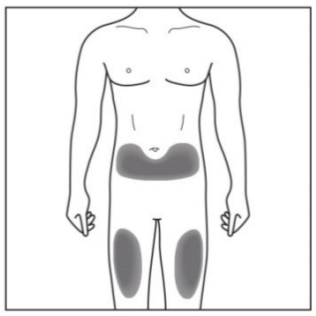


Before your injection



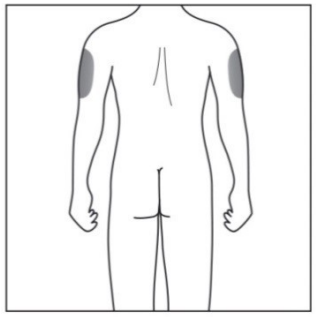
1/ Important safety checks before you inject:

- The liquid should be clear. Its color may vary from colorless to slightly yellow.
- **Do not use** if the liquid contains easily visible particles, is cloudy or is distinctly brown. You may see a small air bubble, which is normal.
- **Do not use** your COSENTYX SensoReady pen if the **expiration date** has passed.
- **Do not use** if the **safety seal** has been broken.
- Contact your pharmacist if the COSENTYX SensoReady pen fails any of these checks.



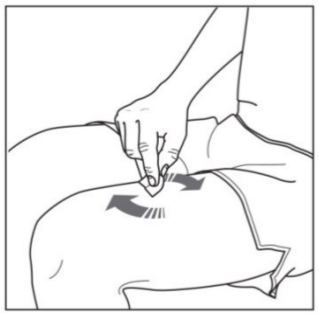
2a/ Choose your injection site:

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



2b/ Caregivers and Healthcare Professionals Only:

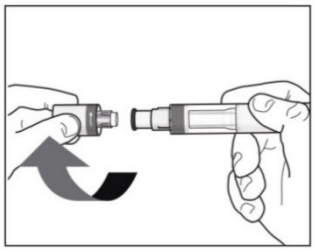
If a **caregiver** or **healthcare professional** is giving you your injection, they may also inject into your outer upper arm.



3/ Cleaning your injection site:

- Wash your hands with hot soapy water.
- Using a circular motion, clean the injection site with the alcohol swab. Leave it to dry before injecting.
- Do not touch the cleaned area again before injecting.

Your injection

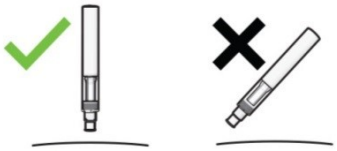


4/ Removing the cap:

- Only remove the cap when you are ready to use the COSENTYX SensoReady pen.
- Twist off the cap in the direction of the arrows.
- Once removed, throw away the cap. **Do not try to re-attach the cap.**
- Use the COSENTYX SensoReady pen within 5 minutes of removing the cap.

5/ Holding your COSENTYX SensoReady pen:

- Hold the COSENTYX SensoReady pen at 90° to the cleaned injection site.



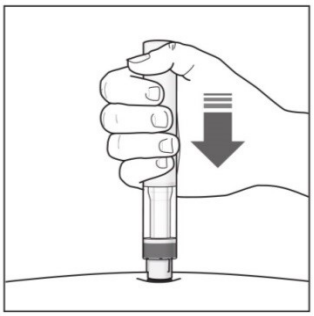
Correct Incorrect

YOU MUST READ THIS BEFORE INJECTING.

During the injection you will hear **2 loud clicks**.

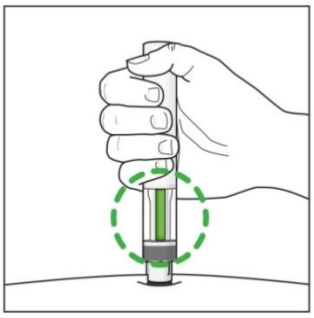
The **1st click** indicates that the injection has started. Several seconds later a **2nd click** will indicate that the injection is **almost** finished.

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



6/ Starting your Injection:

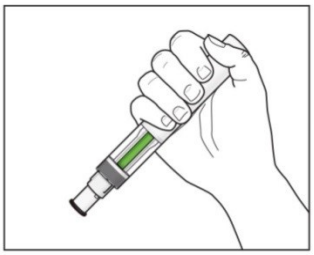
- Press the COSENTYX SensoReady pen firmly against the skin to start the injection.
- **The 1st click** indicates the injection has started.
- **Keep holding** the COSENTYX SensoReady pen firmly against your skin.
- The **green indicator** shows the progress of the injection.



7/ Completing your injection:

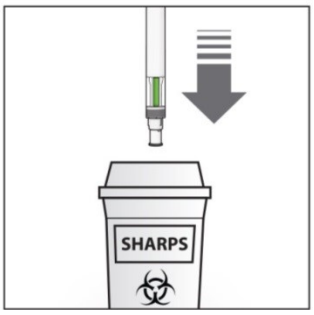
- Listen for the **2nd click**. This indicates the injection is **almost** complete.
- Check the **green indicator** fills the window and has stopped moving.
- The COSENTYX SensoReady pen can now be removed.

After your injection



8/ Check the green indicator fills the window:

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



9/ Disposing of your COSENTYX SensoReady pen:

- Dispose of the used COSENTYX SensoReady pen in a sharps disposal container (i.e. a puncture-resistant closable container, or similar).
- Never try to reuse your COSENTYX SensoReady pen.

Instructions for use of COSENTYX powder for solution for injection*

*single-use vial not available in Canada

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

Store the vial of 150 mg powder for solution for injection of COSENTYX in the refrigerator between 2°C to 8°C.

The single-use vial contains 150 mg of COSENTYX for reconstitution with sterile water for injection (SWFI). Do not use the vial after the expiry date shown on the outer box or vial. If it has expired, return the entire pack to the pharmacy.

The preparation of the solution for subcutaneous injection shall be done without interruption ensuring that aseptic technique is used. The preparation time from piercing the stopper until end of reconstitution on average takes 20 minutes and should not exceed 90 minutes.

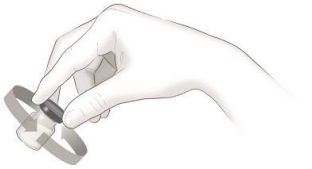
To prepare COSENTYX 150 mg powder for solution for injection please adhere to the following instructions:

Instructions for reconstitution of COSENTYX 150 mg powder for solution for injection:

1. Bring the vial of COSENTYX 150 mg powder for solution for injection to room temperature and ensure sterile water for injection (SWFI) is at room temperature.
2. Withdraw slightly more than 1.0 mL sterile water for injection (SWFI) into a 1 mL graduated disposable syringe and adjust to 1.0 mL.
3. Remove the plastic cap from the vial.
4. Insert the syringe needle into the vial containing the lyophilized cake of COSENTYX through the center of the rubber stopper and reconstitute the cake by slowly injecting 1.0 mL of SWFI into the vial. The stream of SWFI should be directed onto the lyophilized cake.

5. Tilt the vial to an angle of approx. 45° and gently rotate between the fingertips for approx. 1 minute. Do not shake or invert the vial.

6. Keep the vial standing at room temperature for a minimum of 10 minutes to allow for dissolution. Note that foaming of the solution may occur.
7. Tilt the vial to an angle of approx. 45° and gently rotate between the fingertips for approx. 1 minute. Do not shake or invert the vial.



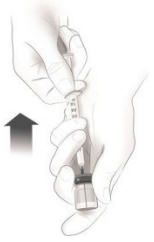
8. Allow the vial to stand undisturbed at room temperature for approximately 5 minutes. The resulting solution should be clear. Its color may vary from colorless to slightly yellow. Do not use if the lyophilized powder has not fully dissolved or if the liquid contains easily visible particles, is cloudy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

9. Prepare the required number of vials (1 vial for the 75 mg dose, 1 vial for the 150 mg dose, 2 vials for the 300 mg dose).

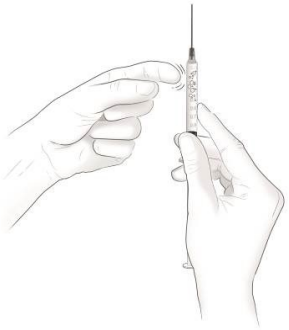
After preparation, the solution for subcutaneous injection can be used immediately or can be stored at 2°C to 8°C for up to 24 hours. Do not freeze. After storage at 2°C to 8°C, the solution should be allowed to come to room temperature for approximately 20 minutes before administration. The solution should be administered within 1 hour after removal from the 2°C to 8°C storage.

Instructions for administration of COSENTYX solution

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

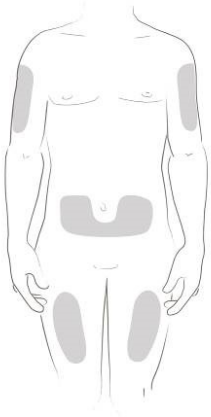


2. For the 150mg and 300 mg doses, carefully withdraw slightly more than 1.0 mL of the solution for subcutaneous injection from the vial into a 1 mL graduated disposable syringe using a suitable needle (e.g. 21G x 2”). This needle will only be used for withdrawing COSENTYX into the disposable syringe. Prepare the required number of syringes (2 syringes for the 300 mg dose). For a child receiving the 75 mg dose, carefully withdraw slightly more than 0.5 mL of the solution for subcutaneous injection and discard the rest immediately.
3. With the needle pointing upward, gently tap the syringe to move any air bubbles to the top.



4. Replace the attached needle with a 27G x ½” needle.

5. Expel the air bubbles. For the 150 mg dose, and advance the plunger to the 1.0 mL mark. For the 75 mg dose, advance the plunger to the 0.5 mL mark.
6. Clean the injection site with an alcohol swab.
7. Inject the COSENTYX solution subcutaneously into the front of thighs, lower abdomen (but **not** the area 2 inches (5 centimeters) around the navel (belly button) or outer upper arms. Choose a different site each time an injection is administered. Do not inject into areas where the skin is tender, bruised, red, scaly or hard. Avoid areas with scars or stretch marks.



8. Any remaining solution in the vial must not be used and should be discarded in accordance with local requirements. Vials are for single use only. Dispose of the used syringe in a sharps container (closable, puncture resistant container). For the safety and health of you and others, needles and used syringes **must never** be re-used.

What are possible side effects from using COSENTYX?

These are not all the possible side effects you may have when taking COSENTYX. If you experience any side effects not listed here, tell your healthcare professional.

As with all medicines, patients treated with COSENTYX may experience side effects.

STOP using COSENTYX and seek medical help immediately if you experience any of the following, which are signs of an allergic reaction:

- difficulty breathing or swallowing
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps

Possible side effects

Side effects include the following listed below. Most of the side effects are mild to moderate. If these side effects become severe, please tell your doctor, pharmacist or healthcare provider.

Some side effects are very common *(These side effects may affect more than 1 in 10 people)*

- Upper respiratory tract infections with symptoms such as sore throat and stuffy nose (nasopharyngitis, rhinitis)

Some side effects are common *(These side effects may affect up to 1 in every 10 people)*

- Cold sores (oral herpes)
- Diarrhea
- Itchy rash (urticaria)
- Runny nose (rhinorrhea)

Some side effects are uncommon *(These side effects may affect up to 1 in every 100 people)*

- Oral thrush (oral candidiasis)
- Signs of low levels of white blood cells such as fever, sore throat or mouth ulcers due to infections (neutropenia)
- Athlete's foot (tinea pedis)
- Discharge from the eye with itching, redness and swelling (conjunctivitis)
- Nausea, diarrhea, vomiting, abdominal pain and fever (symptoms of inflammatory bowel disease)

Not known (*frequency cannot be estimated from available data)*

- Fungal infections of the skin and mucous membranes (thrush)

If you notice any side effects not listed in this Patient Medication Information, please inform your doctor or pharmacist.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Serious allergic reactions		√	√
Serious infections		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store COSENTYX pre-filled syringe or SensoReady pen sealed in its box to protect from light.
- Store in the refrigerator between 2°C and 8°C. DO NOT FREEZE.
- Do not shake.
- If necessary, the pre-filled syringe and the SensoReady pen may be stored unrefrigerated for a single period of up to 4 days at room temperature, not above 30°C. Discard the pre-filled syringe or SensoReady pen after 4 days if left unrefrigerated.

Do not use COSENTYX pre-filled syringe or SensoReady pen:

- After the expiration date shown on the outer box or the label on the syringe or the SensoReady pen.
- If the liquid contains easily visible particles, is cloudy or is distinctly brown.

Any unused product or waste material should be disposed of in accordance with local requirements. Ask your pharmacist how to dispose of medicines you no longer use.

Keep out of reach and sight of children.

If you want more information about COSENTYX:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.novartis.ca, or by calling 1-800-363-8883 number.

This Patient Medication Information was prepared by Novartis Pharmaceuticals Canada Inc.

Last Revised: APR 08, 2022

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