PRODUCT MONOGRAPH

PrCOSENTYX®

(Secukinumab)

Solution for injection
Powder for solution for injection*

150 mg/1.0 mL

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.

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous injection (s.c.)	Sterile solution for injection in pre-filled syringe, SensoReady® pen (150 mg/1 mL) or single-use vial (lyophilized powder)*	None *For a complete listing, see Dosage Forms, Composition and Packaging section.*

*single-use vial supplied as lyophilized powder not available in Canada

DESCRIPTION

COSENTYX (Secukinumab) is a fully human IgG1κ monoclonal antibody with a molecular mass of 147,944 Daltons when deglycosylated.

Secukinumab selectively binds and neutralizes the proinflammatory cytokine interleukin-17A (IL-17A). Secukinumab works by targeting IL-17A and inhibiting its interaction with the IL-17 receptor, which is expressed on various cell types including keratinocytes and synoviocytes.

COSENTYX is supplied as a sterile solution in a single-use pre-filled SensoReady pen with a 27 gauge fixed ½ inch needle or a single-use pre-filled syringe with a 27 gauge fixed ½ inch needle.

COSENTYX is also supplied as a powder for solution for subcutaneous injection in a single-use glass vial*. The vial is stoppered with a coated stopper.

COSENTYX does not contain preservatives.

INDICATIONS AND CLINICAL USE

Plaque psoriasis

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

Psoriatic arthritis

COSENTYX is indicated for the treatment of adult patients with active psoriatic arthritis when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. COSENTYX can be used alone or in combination with methotrexate (see **CLINICAL TRIALS, Psoriatic arthritis**).

Ankylosing spondylitis

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

CONTRAINDICATIONS

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

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 **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.

Gastrointestinal

Inflammatory Bowel Disease

Caution should be exercised, when prescribing COSENTYX to patients with inflammatory bowel disease as exacerbations of inflammatory bowel disease, in some cases serious, were observed in clinical studies in both COSENTYX and placebo groups. In addition, new onset inflammatory bowel disease cases occurred in clinical trials with COSENTYX (see **ADVERSE REACTIONS**). Patients who are treated with COSENTYX and have inflammatory bowel disease should be followed closely.

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.

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 **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 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.

Special Populations

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 **TOXICOLOGY**). COSENTYX should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Nursing Women
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.

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.

Pediatrics (< 18 years of age)
Safety and effectiveness of COSENTYX in pediatric patients have not been evaluated.

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 974 psoriatic arthritis patients exposed to COSENTYX in clinical studies, a total of 85 patients were 65 years of age or older and 4 patients were 75 years of age or older.

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

Although limited in patient number, no differences in safety and efficacy were observed between older and younger patients (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most frequently reported adverse drug reactions 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 2.8% in the COSENTYX arms and 5.1% in the placebo arm in the ankylosing spondylitis studies.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

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

Adverse drug reactions in plaque psoriasis

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 1 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 1 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 300 mg (N=690) n (%)	COSENTYX 150 mg (N=692) n (%)	Placebo (N=694) n (%)	Etanercept* N=323 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 (0.0)
Pharyngitis	8 (1.2)	7 (1.0)	0 (0)	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

Adverse drug reactions in psoriatic arthritis

COSENTYX was studied in two placebo-controlled psoriatic arthritis trials with 1,003 patients (703 patients on COSENTYX and 300 patients on placebo) for a total exposure of 1,061 patient-years of study exposure (median duration of exposure for secukinumab-treated patients: 456 days

in PsA1 Study and 245 days in PsA2 Study). The 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 2 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 2 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 (%)**	**10mg/kg 75 mg N=202 n (%)**	**10mg/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

Adverse drug reactions in ankylosing spondylitis

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

Of the 394 patients who received COSENTYX, 145 patients received a subcutaneous load of COSENTYX (AS1 Study) and 249 received an intravenous loading dose of secukinumab (AS2 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 (66% and 59%, respectively), driven primarily by AEs in the infections and infestations SOC (mainly nasopharyngitis).

Table 3 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) and AS2 (MEASURE 2).

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

	COSENTYX (AS2)		**COSENTYX (AS1)**		**Placebo**
	75 mg N=73 n (%)	**150 mg N=72 n (%)**	**10mg/kg 75 mg N=124 n (%)**	**10mg/kg 75 mg N=125 n (%)**	**N=196 n (%**
Adverse Reactions					
Infections and Infestations					
Nasopharyngitis	6 (8.2)	8 (11.1)	13 (10.5)	17 (13.6)	12 (6.1)
Upper respiratory tract infection	4 (5.5)	1 (1.4)	4 (3.2)	1 (0.8)	4 (2.0)
Pharyngitis	0	0	2 (1.6)	3 (2.4)	1 (0.5)
Oral herpes	0	2 (2.8)	2 (1.6)	1 (0.8)	0

Infections

In the placebo-controlled period of clinical studies in plaque psoriasis (a total of 1382 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 **WARNINGS AND PRECAUTIONS**).

Over the entire treatment period (a total of 3430 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 **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 (31%) compared to the placebo group (18%) in the 16-week placebo-controlled period with 0.3% serious infections in the COSENTYX groups. Over the entire treatment period, infections were reported in 68% of patients treated with COSENTYX, with 1.1% cases of serious infections (see **WARNINGS AND PRECAUTIONS, Infections**).

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

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

Hypersensitivity Reactions

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

Immunogenicity

In psoriasis, psoriatic arthritis and ankylosing spondylitis clinical studies, less than 1% of patients treated with COSENTYX developed antibodies to secukinumab up to 52 weeks of treatment. About half of the treatment emergent anti-drug antibodies were 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 **WARNINGS AND PRECAUTIONS, Inflammatory Bowel Disease**).

Among the 571 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 (0.7 per 100 patient-years) and 3 ulcerative colitis (0.4 per 100 patient-years)). During the placebo-controlled 16-week period, there were 2 Crohn's disease exacerbations and 1 new onset ulcerative colitis case that was a serious adverse event in patients treated with COSENTYX compared to none of the patients treated with placebo. During the remainder of the study when all patients received COSENTYX, 1 patient developed Crohn's disease, 2 patients had Crohn's exacerbations, 1 patient developed ulcerative colitis, and 1 patient had an ulcerative colitis exacerbation (see **WARNINGS AND PRECAUTIONS, Inflammatory Bowel Disease**).

Less Common Clinical Trial Adverse Drug Reactions (<1%)

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 and ankylosing spondylitis.

Post-Market Adverse Drug Reactions

There are no new post-marketing adverse drug reactions for COSENTYX at this time.

DRUG INTERACTIONS

No drug interaction studies have been performed in humans with COSENTYX.

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

In a study, after *meningococcal* and inactivated *influenza* vaccinations, a similar proportion of 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.

A direct impact of IL-17A on the expression and activity of cytochrome P450 (CYP450) enzymes has not been reported. Since the formation of CYP450 enzymes can be regulated by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation, COSENTYX could alter the formation of CYP450 enzymes by reducing mRNA levels of IL-6 through IL-17A neutralization. Therefore, for patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index (e.g. warfarin), monitoring for therapeutic effect and dosage modification of the CYP450 substrate may be considered.

DOSAGE AND ADMINISTRATION

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 **WARNINGS AND PRECAUTIONS**).

Recommended Dose and Dosage Adjustment

Plaque psoriasis

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

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

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

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

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

Special populations:

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

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

Geriatric patients (65 years of age or older)
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 974 psoriatic arthritis patients exposed to COSENTYX in clinical studies, a total of 85 patients were 65 years of age or older and 4 patients were 75 years of age or older.

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

Although limited in patient number, no differences in safety and efficacy were observed between older and younger patients (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

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 if a physician determines that it is appropriate. However, the physician should ensure appropriate follow-up of patients. Patients should be instructed to inject the full amount of COSENTYX according to the instructions provided in the package leaflet. Comprehensive instructions for administration are given in the package leaflet.

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

*single-use vial not available in Canada

Full instructions for use are provided in **SPECIAL HANDLING INSTRUCTIONS**.

OVERDOSAGE

Doses up to 30 mg/kg (i.e. approximately 2,000 to 3,000 mg) have been administered intravenously in clinical studies without dose-limiting toxicity. In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

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 and ankylosing spondylitis. 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. The frequency of IL-17 producing cells was higher in the subchondral bone marrow of facet joints from patients with ankylosing spondylitis. Secukinumab inhibits the release of proinflammatory cytokines and chemokines.

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 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 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.

Pharmacokinetics

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

Absorption

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

Following subcutaneous administration of 150 or 300 mg every 4 weeks, 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, 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 subjects with plaque psoriasis in a small crossover pharmacokinetic study.

Distribution

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

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

Metabolism

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

Excretion

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 plaque psoriasis patients following intravenous administration. Secukinumab clearance increase as body weight increases.

Dose Linearity
Secukinumab exhibited dose-proportional pharmacokinetics in subjects with psoriasis over a dose range from 25 mg to 300 mg following subcutaneous administrations.

Special Populations and Conditions

Pediatrics (< 18 years of age)
Specific studies of COSENTYX in pediatric patients have not been conducted.

Geriatrics (≥ 65 years of age)
Of the 3,430 plaque psoriasis patients exposed to COSENTYX in clinical studies, a total of 230 were 65 years of age or older and 32 patients were 75 years of age or older.

Of the 974 psoriatic arthritis patients exposed to COSENTYX in clinical studies, a total of 85 patients were 65 years of age or older and 4 patients were 75 years of age or older.

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

Based on population PK analysis, clearance in elderly patients and patients less than 65 years of age was similar.

Gender
The impact of gender differences on exposure is considered to be not clinically relevant.

Race
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.

STORAGE AND STABILITY

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.

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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

COSENTYX (secukinumab) is supplied as:

- 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.

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

Each pre-filled syringe or SensoReady pen contains 150 mg secukinumab.

COSENTYX pre-filled syringe or SensoReady pen contain the following inactive ingredients: Trehalose dehydrate, L-histidine/histidine hydrochloride monohydrate, L-methionine, polysorbate 80, water for injection.

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.

COSENTYX powder for solution for subcutaneous injection in a vial contains the following inactive ingredients**:** Sucrose, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, water for injection.

COSENTYX is provided in 150 mg dosage per unit and is dispensed in the following formats;

- in a carton containing one (1) pre-filled glass syringe,
- in a carton containing two (2) pre-filled glass syringes,
- one (1) pre-filled SensoReady pen,

- two (2) pre-filled SensoReady pens or
- single use vial*

COSENTYX does not contain preservatives.

*single-use vial not available in Canada

PART II: SCIENTIFIC INFORMATION

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.
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.
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.

Product characteristics:

COSENTYX (secukinumab) is supplied as:

- 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

CLINICAL TRIALS

Plaque psoriasis

The safety and efficacy of COSENTYX were assessed in four randomized, double-blind, placebo-controlled phase 3 studies in a total of 2403 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.

Study demographics and trial design

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

Table 4 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=1306	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

Table 5 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 6).

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**.**

Study results

The 300 mg dose provided improved skin clearance across efficacy endpoints of PASI 75/90/100, and IGA mod 2011 ‘clear’ or ‘almost clear’ responses across all studies with peak effects seen at week 16 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 6). Superiority versus placebo was demonstrated at both the 300 mg and 150 mg secukinumab doses in these studies.

Table 6 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.

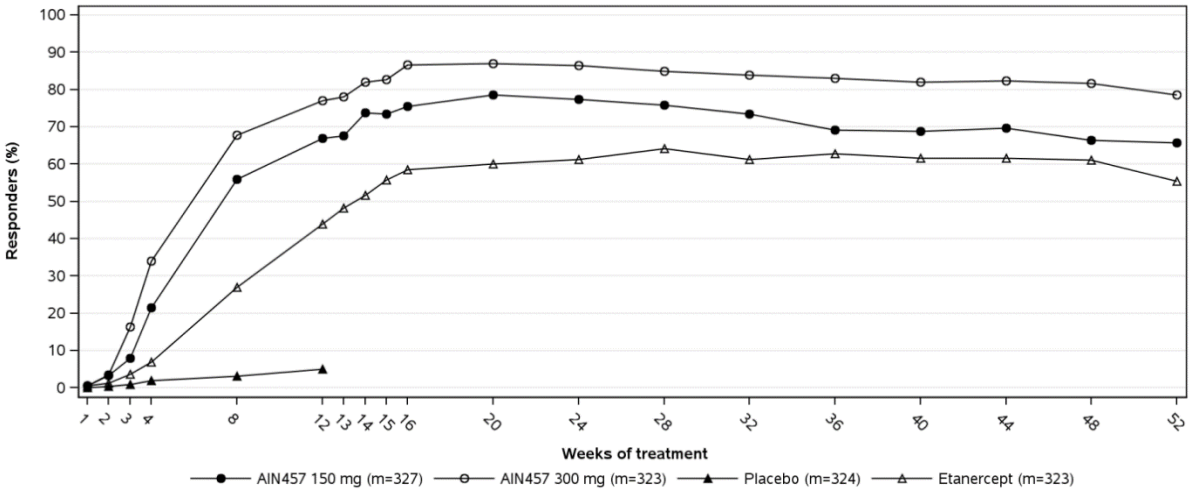
In the FEATURE study, 69.5% and 75.9% of patients receiving secukinumab 150 mg and 300 mg, respectively, achieved a PASI 75 response at Week 12 compared with 0% of patients receiving placebo. In the JUNCTURE study, 71.7% and 86.7% of patients receiving secukinumab 150 mg and 300 mg, respectively, achieved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

Psoriatic arthritis

The safety and efficacy of COSENTYX were assessed in 1,003 patients in two randomized, double-blind, placebo-controlled phase III studies in 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 62% and 47% of the PsA patients had enthesitis and dactylitis at baseline, respectively.

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-TNFα agent and discontinued the anti-TNFα 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-TNFα agent and discontinued the anti-TNFα 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, and 3, followed by the same dose every month starting at Week 4. 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).

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 **DOSAGE AND ADMINISTRATION**).

Table 7 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 sc, 150 mg sc, 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 75mg,150 mg, 300 mg or PBO at Wks 0, 1, 2, 3, 4 followed by 75 mg sc, 150 mg sc, 300 mg sc, 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%)

[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 sc 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 sc 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 sc 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.

Study results

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 8).

Table 8 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 TNFα 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.

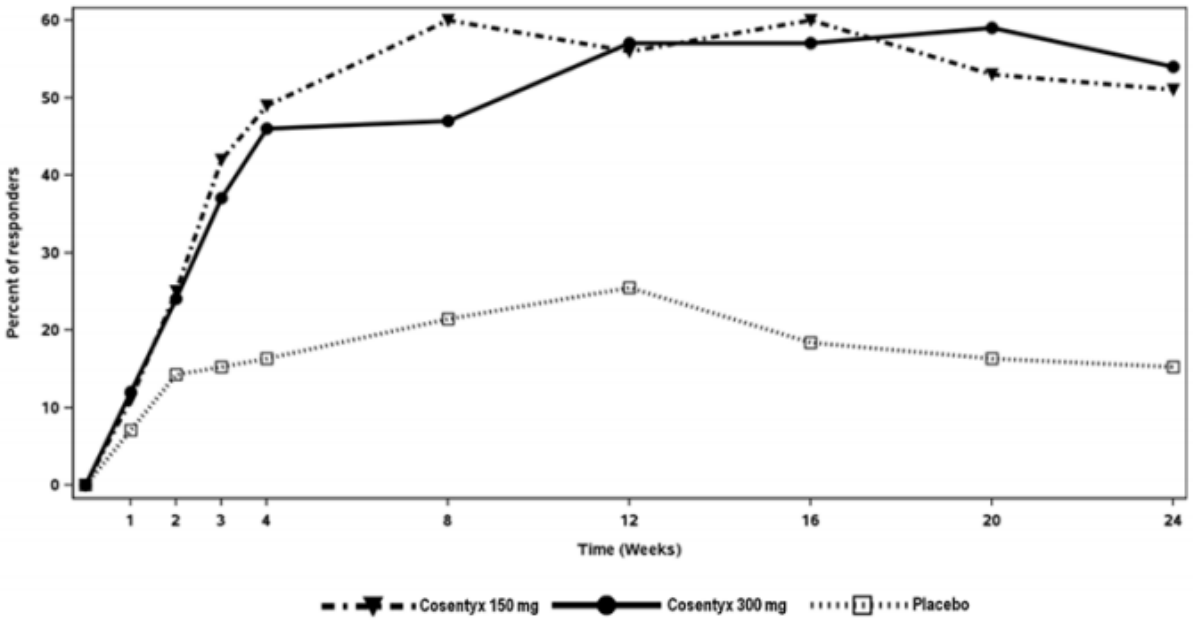
Premature discontinuation from the placebo-controlled portion period (24 weeks) for any reason: placebo 10.2% (10/98), COSENTYX 150 mg 5% (5/100) and COSENTYX 300 mg 3% (3/100). All patients who prematurely discontinued, for any reason, were considered non-responders for ACR 20, ACR 50, and ACR 70.

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.

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 9.

Table 9 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 (Scale 0 to 78)	24.1	-11.42[d] (1.25)	20.2	-10.84[d] (1.25)	23.4	-4.28[d] (1.74)
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-TNFα-naïve patients and 35% (n=105/298) were anti-TNFα inadequate responder (IR) patients.

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

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

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% (28/58) and 16% (7/43) in the COSENTYX 150 mg and placebo groups, respectively.

In PsA2 Study, the mean change from baseline by Week 24 in Heath 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.

Ankylosing spondylitis

The safety and efficacy of COSENTYX were assessed in 590 patients in two 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 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or disease-modifying anti-rheumatic drug (DMARD) therapy. Patients in these studies had a diagnosis of AS for a median of 2.7 to 5.8 years.

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-TNFα 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-TNFα 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, and 3, followed by the same dose every month starting at Week 4. 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 Assessment of Spondyloarthritis International

Society (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.

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 **DOSAGE AND ADMINISTRATION)**.

Table 10 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%)

[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

Study results

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-TNFα 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 11).

Table 11 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 12.

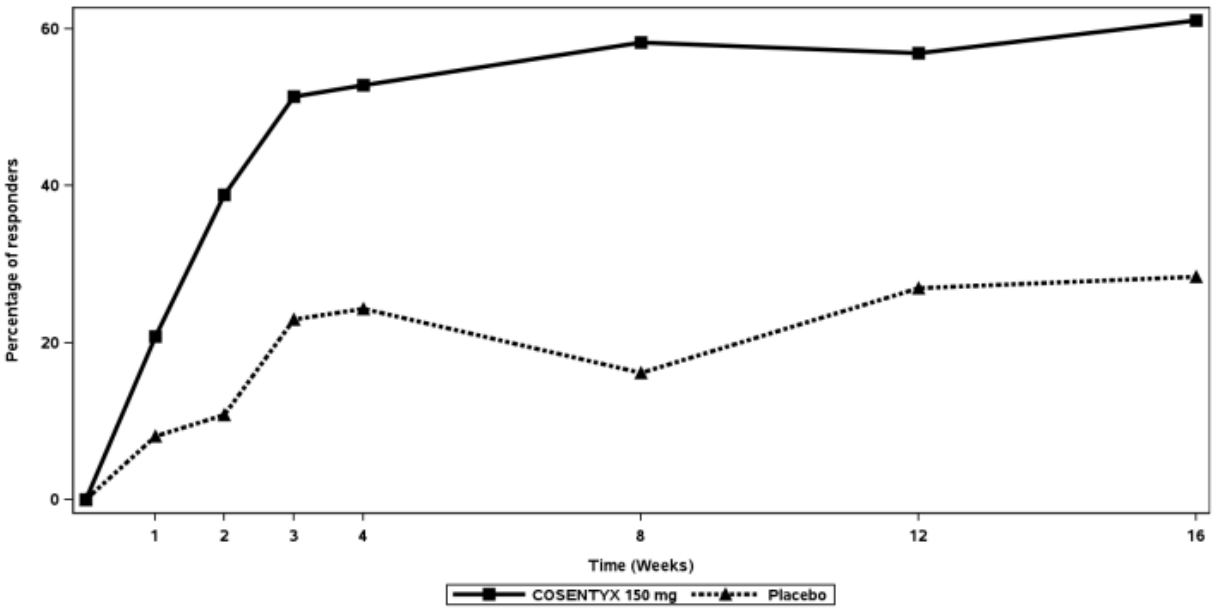
Table 12 Main components of the ASAS 20 response criteria at baseline and Week 16 in AS2 Study (mean score and SD)

	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 3, with separation compared to placebo occurring as early as Week 1.

Figure 3 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-TNFα-naïve patients and 50.0% vs. 24.1% in anti-TNFα-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.

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 13 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

Genotoxicity
Genotoxicity studies have not been conducted for secukinumab.

Carcinogenicity
Carcinogenicity studies have not been conducted for secukinumab.

Reproductive toxicity
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 14 Reproductive Toxicology (pivotal studies)

Study Type	Species	Route	No. of animals/ group	Doses (Mg/kg/week)	Findings

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	16 f	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

Other toxicity studies

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

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PART III: CONSUMER INFORMATION

[Pr]COSENTYX®
(Secukinumab)

This leaflet is part III of a three-part "Product Monograph" published when COSENTYX was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about COSENTYX. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

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

- Plaque psoriasis
- Psoriatic arthritis
- Ankylosing spondylitis

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.

COSENTYX is used in adults 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.

Ankylosing spondylitis

COSENTYX is used to treat a condition called 'ankylosing spondylitis'. The condition is an inflammatory disease primarily affecting the spine, which causes inflammation of the spinal joints.

COSENTYX is used in adults with active ankylosing spondylitis.

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.

What it does:

COSENTYX contains the active substance secukinumab. Secukinumab is a fully-human monoclonal antibody. Monoclonal antibodies are proteins that recognise 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 ankylosing spondylitis. 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 ankylosing spondylitis.

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.

When it should not be used:

Do not use COSENTYX

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

What the medicinal ingredient is:

Secukinumab

What the important nonmedicinal ingredients are:

Trehalose dehydrate, L-histidine/histidine hydrochloride monohydrate, L-methionine, polysorbate 80, water for injection

What dosage forms it comes in:

Solution for injection in a pre-filled syringe or pre-filled SensoReady® pen or single-use vial (lyophilized powder)*.

*single-use vial not available in Canada

WARNINGS AND PRECAUTIONS

COSENTYX is a medicine that affects your immune system.

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

BEFORE you use COSENTYX talk to your doctor or pharmacist if:

- you currently have an infection or if you have long-term or repeated infections.
- you have tuberculosis. Your doctor should check you for tuberculosis before starting treatment.
- you 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 have Crohn's disease or ulcerative colitis.
- you had a recent vaccination or if you will receive a vaccination during treatment with COSENTYX.

Tell your doctor or pharmacist immediately if you get any of these symptoms during treatment with COSENTYX:

You 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 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 and adolescents (under 18 years of age) because it has not been studied in this age group.

Pregnancy and breast-feeding

Talk to your doctor before using COSENTYX:

- If you 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 are breast-feeding or plan to breast-feed.
- It is not known if COSENTYX passes into your breast milk.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist:

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

PROPER USE OF THIS MEDICATION

Your healthcare provider will prescribe the dose of COSENTYX that is right for you.

- If your prescribed dose of COSENTYX is 150 mg, administer 1 injection of COSENTYX for each dose.
- If your prescribed dose of COSENTYX is 300 mg, administer 2 injections 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 your skin ('subcutaneously').

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

It is important not to try to inject yourself 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 need.

Plaque psoriasis

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

Psoriatic arthritis

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

For 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 and continues to have active psoriatic arthritis, the 300 mg dose may be given.

Ankylosing spondylitis

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

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.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

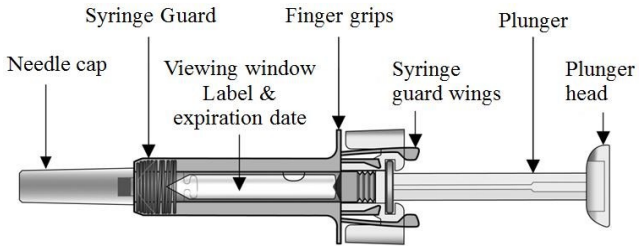
If you have forgotten to inject a dose of COSENTYX, inject the next dose as soon as you remember. Then talk to your doctor to discuss when you should inject the next dose.

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 pre-filled syringe

Read ALL the way through these instructions before injecting. It is important not to try to inject yourself 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

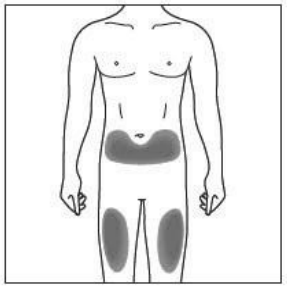
Caution: Keep the COSENTYX pre-filled syringe out of the reach of children.

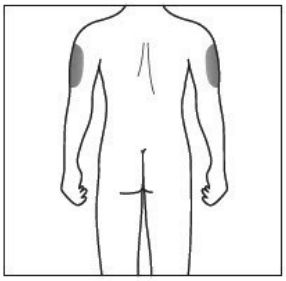
1. The needle cap of the syringe may contain dry rubber (latex), which should not be handled by persons sensitive to this substance.
2. Do not open the sealed outer box until you are ready to use the COSENTYX pre-filled syringe.
3. Do not use the COSENTYX pre-filled syringe if either the seal on the 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 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.

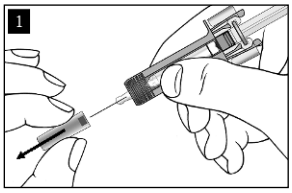
Preparing the COSENTYX pre-filled syringe ready for use

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

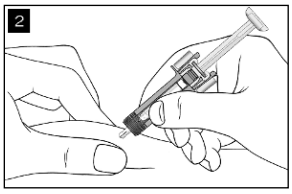
blister.

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.

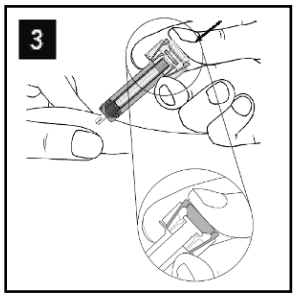
How to use the COSENTYX pre-filled syringe



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.

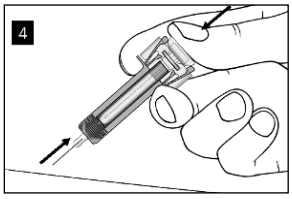


Gently pinch the skin at the injection site and insert the needle as shown. Push the needle all the way in to ensure that the medication can be fully administered.

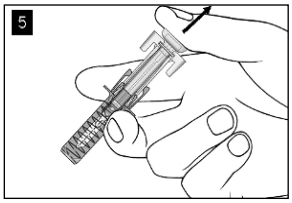


Holding the COSENTYX pre-filled syringe as shown, **slowly** depress the plunger **as far as it will go** so that the plunger head is completely between the syringe guard wings.

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 injections 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

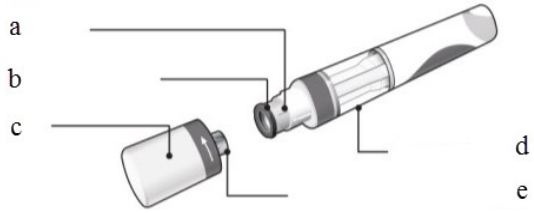
Dispose of the used COSENTYX pre-filled syringe in a sharps container (closable, puncture resistant container). For the safety and health of you and others, needles and used syringes **must never** be re-used.

Instructions for use of COSENTYX SensoReady pen

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 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.

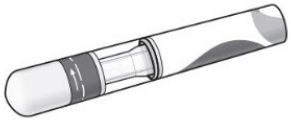
Do not use the COSENTYX SensoReady pen if it has been **dropped** with the cap removed.

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:

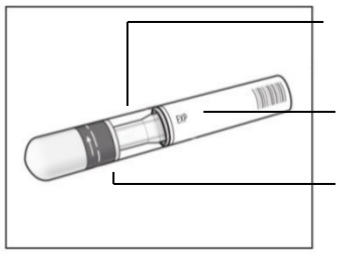
- A new and unused COSENTYX SensoReady pen.



Not Included in the carton:

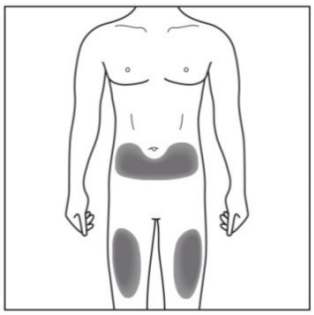
- Alcohol swab.
- Cotton ball or gauze.
- Sharps disposal container.

Before your injection



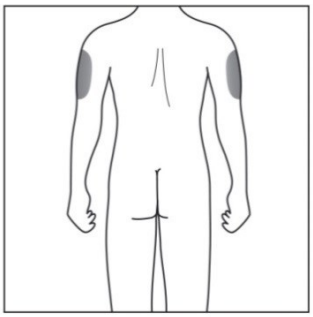
1/ Important safety checks before you inject:

- 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.



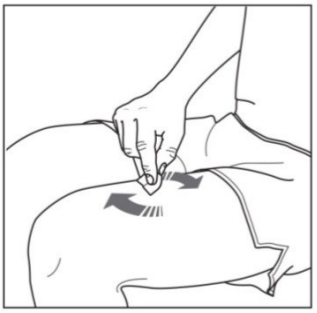
2a/ Choose your injection site:

- 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:

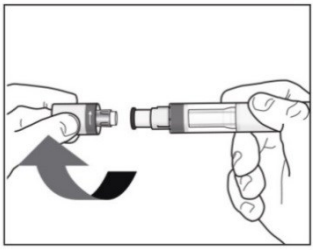
If a **caregiver** or **healthcare professional** is giving you your injection, they may also inject into your outer upper arm.



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

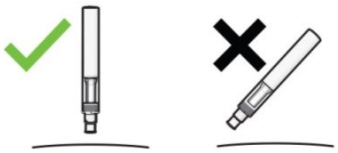


4/ Removing the cap:

- 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 degrees to the cleaned injection site.



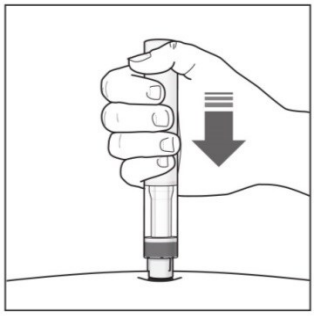
Correct Incorrect

YOU MUST READ THIS BEFORE INJECTING.

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

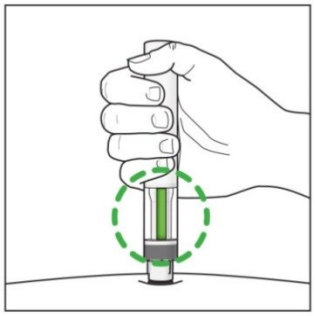
The **1st click** indicates that the injection has started. Several seconds later a **2nd click** will indicate that the injection is **almost** finished.

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:

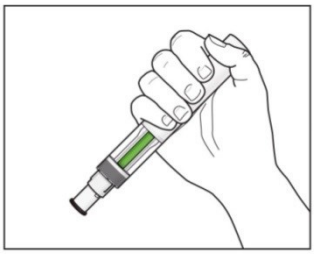
- Press the COSENTYX SensoReady pen firmly against the skin to start the injection.
- **The 1st click** indicates the injection has started.
- **Keep holding** the COSENTYX SensoReady pen firmly against your skin.
- The **green indicator** shows the progress of the injection.



7/ Completing your injection:

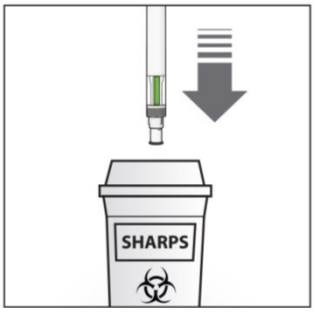
- Listen for the **2nd click**. This indicates the injection is **almost** complete.
- Check the **green indicator** fills the window and has stopped moving.
- The COSENTYX SensoReady pen can now be removed.

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.

<u>Instructions for use of COSENTYX powder for solution for injection*</u>

*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.

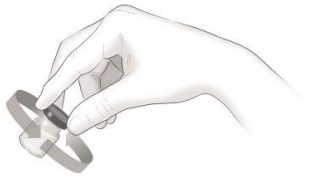
The preparation of the solution for subcutaneous injection shall be done without interruption ensuring that aseptic technique is used. The preparation time from piercing the stopper until end of reconstitution on average takes 20 minutes and should not exceed 90 minutes.

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

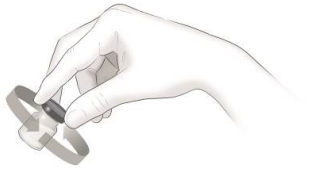
Instructions for reconstitution of COSENTYX 150 mg powder for solution for injection:

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.

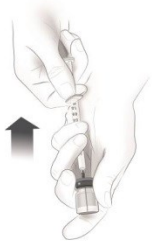


8. Allow the vial to stand undisturbed at room temperature for approximately 5 minutes. The resulting solution should be clear. Its color may vary from colorless to slightly yellow. Do not use if the lyophilized powder has not fully dissolved or if the liquid contains easily visible particles, is cloudy or is distinctly brown.
9. Prepare the required number of vials (2 vials for the 300 mg dose).

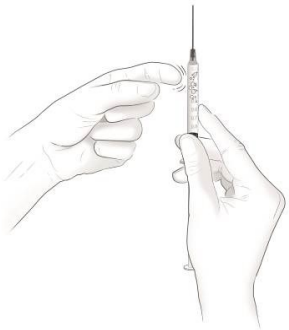
After preparation, the solution for subcutaneous injection can be used immediately or can be stored at 2°C to 8 °C for up to 24 hours. Do not freeze. After storage at 2°C to 8 °C, the solution should be allowed to come to room temperature for approximately 20 minutes before administration. The solution 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 degrees and position the needle tip at the very bottom of the solution in the vial when drawing the solution into the syringe. DO NOT invert the vial.

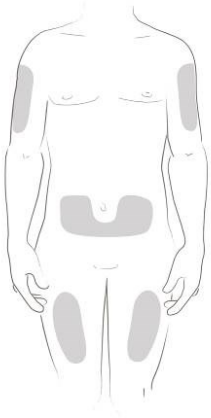


2. Carefully withdraw slightly more than 1.0 mL of the solution for subcutaneous injection from the vial into a 1 mL graduated disposable syringe using a suitable needle (e.g. 21G x 2”). This needle will only be used for withdrawing COSENTYX into the disposable syringe. Prepare the required number of syringes (2 syringes for the 300 mg dose).
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 and advance the plunger to the 1.0 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 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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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)

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

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rare	Serious allergic reactions		√	√

This is not a complete list of side effects. For any unexpected effects while taking COSENTYX, contact your doctor or pharmacist.

HOW TO STORE IT

- Keep this medicine out of the sight and reach of children.
- 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

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.
- Ask your pharmacist how to dispose of medicines no longer required.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.novartis.ca
or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc., at:
1-800-363-8883

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