CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

SECUKINUMAB
(Cosentyx — Novartis Pharmaceuticals Canada Inc.)
Indication: Psoriatic Arthritis

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that secukinumab be reimbursed for the treatment of adult patients with active psoriatic arthritis (PsA), used alone or in combination with methotrexate, when the response to previous disease-modifying antirheumatic drugs (DMARDs) therapy has been inadequate, if the following condition is met:

Condition
- The annual drug plan cost for the treatment of PsA with secukinumab should not exceed the annual drug plan cost of treating PsA with the least costly biologic reimbursed.

Reasons for the Recommendation:
1. Two randomized controlled trials (RCTs) — FUTURE 1 (N = 606), FUTURE 2 (N = 397) — conducted in adult patients with active PsA demonstrated that secukinumab 150 mg was superior to placebo for the proportion of patients achieving an American College of Rheumatology (ACR20) response at weeks 16 and 24.
2. In the absence of head-to-head comparisons, a manufacturer-submitted network meta-analysis (NMA) indicated that secukinumab was superior to placebo but not statistically significantly different when compared with etanercept, infliximab, adalimumab, golimumab, ustekinumab, certolizumab, and apremilast for ACR20 response at weeks 12 to 16. The NMA did not assess comparative safety. Hence, there is no evidence that secukinumab provides superior efficacy or safety compared with other biologics currently reimbursed by participating drug plans for the treatment of PsA.
3. At the submitted price [redacted] per 150 mg/mL for a pre-filled syringe), the annual cost of secukinumab 150 mg (first year: [redacted], subsequent years: [redacted] to [redacted]) is less than that of anti-tumour necrosis factor (TNF) alpha biologic drugs and apremilast. At the recommended dose, the annual cost of secukinumab 300 mg (first year: [redacted]; subsequent years: [redacted] to [redacted]) is less than that of infliximab (Remicade) but more costly than other anti-TNF alpha biologic drugs and apremilast in the first year.

Of Note:
CDEC noted that subgroup analyses among patients who were TNF alpha inhibitor inadequate responders in FUTURE 2 suggested that a statistically significantly greater proportion of

patients in only the secukinumab 300 mg treatment group achieved an ACR20 response at weeks 16 and 24 compared with placebo. Secukinumab 300 mg is a Health Canada–approved dose for the treatment of this subgroup of patients with PsA.

Background:
Secukinumab is indicated for the treatment of the following: alone or in combination with methotrexate for adult patients with active PsA when the response to previous DMARD therapy has been inadequate; adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy; and moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. For patients with PsA, the recommended dose is 150 mg by subcutaneous (SC) injection, with initial dosing at weeks 0, 1, 2, and 3, followed by monthly maintenance dosing starting at week 4; for PsA patients with coexistent moderate to severe plaque psoriasis, the dosing and administration recommendations for plaque psoriasis are to be used (300 mg by SC injection, with initial dosing at weeks 0, 1, 2, and 3, followed by monthly maintenance dosing starting at week 4). If a patient is a TNF alpha inhibitor inadequate responder and continues to have active PsA, the 300 mg dose should be considered. Secukinumab is available as a 150 mg/1 mL solution for SC injection in pre-filled syringes or pens. Each 300 mg dose is given as two SC injections of 150 mg.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs and pivotal studies of secukinumab for the treatment of PsA, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients living with PsA.

Patient Input Information:
Five patient groups responded to the CDR call for patient input: the Canadian Arthritis Patient Alliance, Arthritis Consumer Experts, the Canadian Spondylitis Association, and a combined submission from the Canadian Skin Patient Alliance and the Arthritis Society. The following is a summary of information provided:

- Individuals living with PsA experience joint pain, stiffness, fatigue, and loss of function. Some patients have difficulty sitting, using the stairs, bending to pick up objects, and getting in and out of the bathtub. Daily living activities such as vacuuming, cleaning, doing the dishes, and grocery shopping become challenging for some patients, causing them to require help from caregivers. Patients also experience skin sensitivity, redness, flaking, and pain from the plaque psoriasis.
- The impact of the disease goes beyond affecting patients' physical well-being, with some patients likely to stop engaging in social and creative activities because they have limited time and energy, and increased pain. Furthermore, the acute awareness of skin lesions has a psychological impact.
- Current therapy includes biologic drugs, conventional DMARDs, and nonsteroidal anti-inflammatory drugs. Patients are challenged by the heterogeneity of response to treatments and the waning effectiveness of therapies experienced by some individuals. Patients indicated that a large array of treatment options is needed to ensure that they always have access to effective therapies. Many patients indicated that treatments are often inconvenient and ineffective in treating their symptoms.

- PsA patients have concerns about adverse effects over a prolonged period of drug use (which may include heartburn, dizziness, and increased blood sugar levels), cost, scheduling issues for infusions and phototherapy, and the need to take time off work or find someone to deal with both treatment and family commitments.

Clinical Trials

The CDR systematic review included two pivotal, phase 3, double-blind, placebo-controlled RCTs (FUTURE 1 [N = 606] and FUTURE 2 [N = 397]). The FUTURE 1 study was a three-arm superiority study that evaluated the efficacy and safety of secukinumab 150 mg or secukinumab 75 mg SC every four weeks compared with placebo; the FUTURE 2 study was a four-arm superiority trial that evaluated the efficacy and safety of secukinumab 300 mg SC, secukinumab 150 mg SC, or secukinumab 75 mg SC every four weeks compared with placebo. Both studies included patients with symptoms of moderate to severe PsA for at least six months. Twenty-nine per cent of patients included in FUTURE 1 were TNF alpha inhibitor inadequate responders and 37% of patients included in FUTURE 2 study were TNF alpha inhibitor inadequate responders. At week 16 (visit 8), patients were classified as responders (≥ 20% improvement from baseline in both tender and swollen joint counts) or non-responders. In FUTURE 1, patients in the placebo group who were responders remained on placebo until week 24. At week 24, these patients were re-randomized (1:1) to receive either secukinumab 75 mg or 150 mg every four weeks. Patients in the placebo group who were non-responders were re-randomized (1:1) at week 16 to receive either secukinumab 75 mg or 150 mg every four weeks. In FUTURE 2, patients in the placebo group who were non-responders were re-randomized to receive secukinumab 150 mg SC or 300 mg SC (1:1) every four weeks; patients in the placebo group who were responders continued to receive placebo every four weeks until week 24. At week 24, these patients were re-randomized to receive secukinumab 150 mg SC or 300 mg SC (1:1) every four weeks regardless of responder status. In FUTURE 2, investigators and patients remained dose-blinded until after the week 52 analysis.

In accordance with dosing recommendations in the product monograph, CDEC deliberations focused on the results reported for the secukinumab 150 mg and 300 mg dosage regimens.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- ACR responses
- Minimal disease activity (MDA)
- Disease Activity Score (DAS) 28 and C-reactive protein
- Health assessment questionnaire–disability index (HAQ-DI)
- Short Form (36) Health Survey (SF-36)
- Psoriatic Arthritis Quality of Life instrument (PsAQoL)
- Dermatology Life Quality Index (DLQI)
- Patient's assessment of pain
- Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) Work Productivity and Activity Impairment – General Health (WPAI-GH)
- Leeds Dactylitis Index (LDI)
- van der Heijde modified total Sharp score (vdH-mTSS)
- Psoriasis Area and Severity Index (PASI)
- Modified Nail Psoriasis Severity Index (mNAPSI)

- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The primary efficacy end point in both included studies was the proportion of patients in each treatment group who achieved an ACR20 response at week 24.

Efficacy

- In FUTURE 2, both secukinumab treatment groups were statistically significantly superior to placebo for an ACR20 response at week 24 (54% for secukinumab 300 mg versus 15% for placebo, odds ratio [95% confidence interval (CI)] = 6.81 [3.42 to 13.56], $P < 0.0001$; 51% for secukinumab 150 mg versus 15% for placebo, odds ratio [95% CI] = 6.52 [3.25 to 13.08], $P < 0.0001$). A statistically significantly greater proportion of TNF alpha inhibitor–naive patients in the secukinumab 150 mg treatment group achieved an ACR20 response at weeks 16 and 24 compared with placebo ([redacted] for secukinumab 150 mg versus [redacted] for placebo, *P* [redacted] at week 16, and 63% for secukinumab 150 mg versus 16% for placebo, $P < 0.0001$ at week 24). A statistically significantly greater proportion of TNF alpha inhibitor– inadequate responder patients in the secukinumab 300 mg treatment group achieved an ACR20 response at weeks 16 and 24 compared with placebo ([redacted] for secukinumab 300 mg versus [redacted] for placebo, *P* = [redacted] at week 16, and 45% for secukinumab 300 mg versus 14% for placebo, $P = 0.0077$ at week 24).
- In FUTURE 1, a statistically significantly greater proportion of patients in the secukinumab 150 mg treatment group achieved an ACR20 response at weeks 16 and 24 compared with placebo ([redacted] for secukinumab 150 mg versus [redacted] for placebo, *P* [redacted] at week 16, and 50% for secukinumab 150 mg versus 17.3% for placebo, $P < 0.0001$ at week 24). A statistically significantly greater proportion of TNF alpha inhibitor–naive patients in the secukinumab 150 mg treatment group achieved an ACR20 response at weeks 16 and 24 compared with placebo ([redacted] for secukinumab 150 mg versus [redacted] for placebo, *P* [redacted] at week 16, and 54.5% for secukinumab 150 mg versus 17.5% for placebo, $P < 0.0001$ at week 24).
- In FUTURE 2, a statistically significantly greater reduction from baseline in the HAQ-DI score was achieved in patients in the secukinumab 300 mg treatment group compared with placebo at week 24; however, the secukinumab 150 mg treatment group did not achieve a statistically significantly greater reduction from baseline in the HAQ-DI score at week 24. In FUTURE 1, the proportion of patients achieving HAQ-DI improvements of at least 0.30 points at weeks 16 and 24 was statistically significant in favour of the secukinumab 150 mg treatment group in comparison with the placebo treatment group.
- In both FUTURE 1 and FUTURE 2, secukinumab resulted in a complete resolution of dactylitis and enthesitis in a larger proportion of patients versus placebo. Whereas claims of statistical significance between groups could not be assessed because of the statistical analysis hierarchy failing at a higher order comparison, these results were considered to be clinically meaningful.
- In general, secukinumab appeared to improve health-related quality of life versus placebo in a clinically meaningful way, as assessed by the SF-36, PsAQoL, and DLQI instruments.
- Likewise, secukinumab generally appeared to improve PsA-related symptoms, such as pain (measured with the patient's assessment of pain instrument) and fatigue (measured with the FACIT-Fatigue instrument), as compared with placebo. The changes in the patient's assessment of pain score from baseline between groups were clinically significant in both trials, whereas the difference in change from baseline between treatment groups and placebo for FACIT-Fatigue were clinically significant in the FUTURE 2 only.

- Radiographic change was only assessed in FUTURE 1 using vdH-mTSS. The mean change from baseline in vdH-mTSS was statistically significantly lower in the secukinumab 150 mg versus placebo group, but the results have uncertain clinical significance given that the difference between the secukinumab 150 mg treatment group and placebo is 0.47 on a scale that ranges from 0 to 528 and was assessed following 24 weeks of treatment.

Harms (Safety and Tolerability)

- By week 16, in FUTURE 2, adverse events were reported in 56% of patients in the secukinumab 300 mg group, 57% in the secukinumab 150 mg group, and 58% in the placebo group. In FUTURE 1, the overall incidence of adverse events (AEs) was comparable between the secukinumab 150 mg group (64.9%) and the placebo group (58.4%) by week 16.
- Upper respiratory tract infection and nasopharyngitis were the most frequently reported AEs in FUTURE 2 and FUTURE 1, respectively.
- Risks of sudden AEs were low in both studies: 5% in the secukinumab 300 mg treatment group, from 1% to 4.5% in the secukinumab 150 mg groups, and 2% to 5% in the placebo groups.
- In FUTURE 2, higher rates of discontinuations because of AEs were reported in the placebo group (3%) compared with the secukinumab 300 group (2%) and the secukinumab 150 mg group (0%). In FUTURE 1, up to week 16, the proportion of patients discontinuing because of an AE was low and comparable among the secukinumab group and placebo (1.5% for secukinumab 150 mg and 2.5% for placebo).
- The frequency of serious infections and injection-site reactions was low.
- There were no deaths in either study after 16 weeks of therapy.

Cost and Cost-Effectiveness

At the manufacturer-submitted confidential price of [redacted] per 150 mg/mL pre-filled syringe or pen, or [redacted] per 2 x 150 mg/mL pre-filled syringe or pen (300 mg dose), the cost of secukinumab 150 mg is [redacted] for the first year and [redacted] to [redacted] per year in subsequent years. The annual cost of secukinumab 300 mg is [redacted] in the first year and [redacted] to [redacted] in subsequent years. The manufacturer submitted a cost comparison of secukinumab with other biologic drugs (adalimumab, certolizumab, etanercept, golimumab, infliximab, ustekinumab) indicated for active PsA in Canada, and apremilast. Similar efficacy and harms for secukinumab and these comparators were assumed based on an NMA submitted by the manufacturer.

CDR noted the following limitations with the manufacturer's analysis:

- No head-to-head trial evidence was provided to show similar efficacy between secukinumab, other biologic drugs, and apremilast; and the conclusions of similar efficacy in the submitted NMA were limited by heterogeneity across patient populations in the included trials.
- The manufacturer assumed 15 administrations of secukinumab in the first year, leading to a conservative estimate of the treatment cost of secukinumab, as 16 administrations would be required in the first year according to the approved dosing regimen.
- The same discontinuation rates over the three-year time horizon were assumed for secukinumab and other biologics; however, there are no data to support this assumption. Separate analyses of costs for the first and subsequent years were therefore considered more appropriate than total three-year costs.

At the submitted price and based on CDR reanalysis to account for 16 administrations of secukinumab in the first year, costs for secukinumab 150 mg in both the first and subsequent years are lower than for the other biologics and apremilast (first-year savings ranged from [redacted] compared with apremilast to [redacted] compared with infliximab [Remicade]; and subsequent-year savings ranged from at least [redacted] compared with apremilast to as much as [redacted] compared with infliximab [Remicade]).

First- and subsequent-year costs are also lower for secukinumab 300 mg than for infliximab (Remicade) — by [redacted] in the first year, up to [redacted] in subsequent years. However, secukinumab 300 mg is more expensive than the subsequent entry biologics infliximab, certolizumab pegol, and apremilast (by at least [redacted] to as much as [redacted] in the first year, and [redacted] to as much as [redacted] in subsequent years). It is also more costly in the first year than adalimumab, etanercept, and ustekinumab (by [redacted] to [redacted]) but less costly in subsequent years (by at least [redacted] to as much as [redacted]). Secukinumab 300 mg is more expensive than golimumab in the first year (by [redacted]) and may be more or less expensive in subsequent years depending on the number of annual administrations of secukinumab ([redacted] savings with 12 secukinumab administrations annually; [redacted] more expensive with 13 administrations annually).

Other Discussion Points:
CDEC noted the following:

- While the manufacturer has [redacted], there is no evidence to demonstrate that secukinumab has greater efficacy or safety compared with other available biologics.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

July 20, 2016 Meeting

Regrets:

None

Conflicts of Interest:

None

About This Document:
CDEC provides formulary reimbursement recommendations or advice to CDR-participating drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a

recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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