CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

SECUKINUMAB
(Cosentyx — Novartis Pharmaceuticals Canada Inc.)
Indication: Moderate to Severe Plaque Psoriasis

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that secukinumab be listed for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy, if the following clinical criterion and condition are met:

Clinical criterion
- Treatment discontinued if a Psoriasis Area and Severity Index (PASI) 75 response has not been demonstrated after 12 weeks.

Condition
- The drug plan cost for secukinumab should not exceed the drug plan cost of the least costly biologic reimbursed for the treatment of moderate to severe plaque psoriasis.

Reasons for the Recommendation:
1. Four randomized controlled trials (RCTs) (ERASURE [N = 738], FEATURE [N = 177], JUNCTURE [N = 182], and FIXTURE [N = 1,306]), conducted in adult patients with moderate to severe chronic plaque psoriasis who were inadequately controlled by topical treatments, phototherapy, or previous systemic therapy, demonstrated that secukinumab 300 mg was superior to placebo for the proportion of patients achieving a PASI 75 response.
2. One RCT (FIXTURE) demonstrated that secukinumab 300 mg was superior to etanercept 50 mg twice weekly for the proportion of patients achieving a PASI 75 response.
3. Reanalyses of the manufacturer's pharmacoeconomic model conducted by the CDR suggested that the ICUR for secukinumab compared with standard of care (SoC) ranges from $82,534 to $122,365 per QALY. Based on current list prices for comparators, secukinumab 300 mg is more costly in the first year than adalimumab and ustekinumab ($20,730 and $22,966, respectively) and less costly than etanercept, and infliximab-Remicade and SEB-infliximab (range: $25,297 to $39,502). In subsequent years, secukinumab 300 mg is less costly than other biologics (range: $19,249 to $32,096).
4. The clinical trials included in the CDR submission for secukinumab evaluated PASI 75 response at 12 weeks.

Of Note:
CDEC noted that new evidence from an RCT (CLEAR; N = 676) comparing secukinumab with ustekinumab for the treatment of psoriasis became available after the CDR clinical and pharmacoeconomic review reports for secukinumab had been completed. This study was not submitted to CDR.

Background:
Secukinumab is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The product monograph recommends a weekly dose of 300 mg at weeks 0, 1, 2, and 3, followed by monthly 300 mg doses starting at week 4. Secukinumab is available as a 150 mg/1 mL solution for subcutaneous injection in pre-filled syringes or pens. Each dose is given as two injections of 150 mg.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a systematic review of RCTs of secukinumab, a critique of the manufacturer's pharmacoeconomic evaluation, and a summary of patient group–submitted information about outcomes and issues important to individuals living with plaque psoriasis.

Patient Input Information
The following is a summary of key information provided by three patient groups that responded to the CDR call for patient input:

- Persons with psoriasis experience bleeding, cracking and crusting skin, flaking lesions, and plaques on their body. Many experience severe itch, and some experience joint pain related to their psoriasis.
- Psychosocially, persons with psoriasis may experience stigma, depression, suicidal ideations, shame, and feelings of helplessness and frustration. The depression and impact on self-esteem of persons with psoriasis negatively affect personal relationships. Psoriasis occurring in sensitive areas may affect a person's perceptions of their own attractiveness and sexuality.
- Those living with psoriasis report that the condition can limit mobility, ability to perform day-to-day tasks, and participation in sports or hobbies, and can result in an avoidance of activities that may subject them to stares and comments. Increased absenteeism and lost productivity while at work are common and can lead to job loss. Patients may also suffer from concentration issues related to sleep loss. Constant cleaning associated with flaking and bleeding skin is a burden.

Clinical Trials
The CDR systematic review included four multi-centre, double-blind, parallel-group, placebo-controlled, phase 3 RCTs. ERASURE (N = 738), FEATURE (N = 177), JUNCTURE (N = 182), and FIXTURE (N = 1,306) enrolled adults with moderate to severe chronic plaque psoriasis who were inadequately controlled by topical treatments, phototherapy, or previous systemic therapy. Patients with a form of psoriasis other than the chronic plaque type were excluded.

The trials consisted of four periods: screening (one to four weeks), induction (12 weeks), maintenance (40 weeks), and follow-up (8 weeks). Blinding was maintained to the end of the follow-up period. At the beginning of the induction period, patients were randomized to subcutaneous secukinumab 150 mg, secukinumab 300 mg, or placebo administered at weeks 0, 1, 2, 3, 4 and 8. FIXTURE included an active control group that received subcutaneous etanercept 50 mg twice weekly. At the start of the maintenance period, patients receiving secukinumab 150 mg or secukinumab 300 mg in the induction period continued treatment as per initial randomization until week 48. Non-responders (i.e., those with less than a PASI 75 response) from the placebo groups were re-randomized to secukinumab 150 mg or secukinumab 300 mg. For patients on etanercept in FIXTURE, the dose decreased to 50 mg once weekly at the start of the maintenance period.

Based on the recommended dosages for secukinumab, CDEC focused its discussion on the results reported for the 300 mg dosage regimen.

Outcomes

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

- PASI score — a measure of psoriatic disease severity taking into account qualitative lesion characteristics (erythema, thickness, and scaling) and the degree of skin surface area involvement. A PASI 50/75/90 response indicates ≥ 50%, ≥ 75%, or ≥ 90% improvement in PASI score compared with baseline, respectively. A PASI 100 response indicates remission or complete clearing of psoriasis compared with baseline.
- Investigator's Global Assessment (IGA) modified (mod) 2011 — an investigator's impression of psoriasis severity. An IGA response of 0 indicates clear skin (e.g., no signs of psoriasis; some post-inflammatory hyperpigmentation may be present) and a response of 1 indicates almost clear skin (e.g., no thickening, normal coloration).
- Dermatology Life Quality Index (DLQI) — a dermatology-specific quality-of-life instrument that assesses six different aspects that may affect quality of life related to symptoms and feelings, daily activities, leisure, work and school performance, personal relationships, and treatment.
- EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire (EQ-5D) — a generic, non-disease-specific, preference-based utility instrument that includes a descriptive system used to rate five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

The co-primary outcomes in all four trials were PASI 75 response and IGA mod 2011 0 or 1 response at week 12.

Efficacy

- The proportion of patients obtaining a PASI 75 response at week 12 was statistically significantly greater with secukinumab (range: 75.9% to 86.7%) compared with placebo (0% to 4.9%) ($P < 0.0001$ for all comparisons):
  - FEATURE: risk difference 75.9% (95% confidence interval [CI], 61.5% to 86.1%)
  - JUNCTURE: risk difference 83.4% (95% CI, 70.7% to 91.7%)
  - ERASURE: odds ratio 82.7 (95% CI, 38.7 to 176.7)
  - FIXTURE: odds ratio 66.0 (95% CI, 36.1 to 120.6).

- Secukinumab was shown to be non-inferior and superior compared with etanercept for PASI 75 at week 12. The risk differences in the non-inferiority analysis were [redacted] (lower limit of [redacted] CI, [redacted]) and [redacted] (lower limit of [redacted] CI, [redacted]) in the per-protocol and full analysis data sets, respectively.
- The proportion of treatment-experienced patients who obtained a PASI 75 response was greater with secukinumab than with placebo; however, no statistical comparisons were performed for these subgroups. The proportions of PASI 75 responders were:
  - Previous failure of systemic therapy: [redacted] to [redacted] with secukinumab and [redacted] to [redacted] with placebo
  - Previous failure with a biologic: [redacted] to [redacted] with secukinumab and [redacted] to [redacted] with placebo.
- The proportion of patients obtaining an IGA of 0 or 1 response at week 12 was statistically significantly greater with secukinumab (range: 62.5% to 73.3%) compared with placebo (range: 0% to 2.8%) in all studies ($P < 0.0001$ for all comparisons):
  - FEATURE: risk difference [redacted] (95% CI, [redacted] to [redacted])
  - JUNCTURE: risk difference [redacted] (95% CI, [redacted] to [redacted])
  - ERASURE: odds ratio [redacted] (95% CI, [redacted] to [redacted])
  - FIXTURE: odds ratio [redacted] (95% CI, [redacted] to [redacted]).
- The proportion of patients obtaining an IGA of 0 or 1 response at week 12 was statistically significantly greater with secukinumab (62.5%) than with etanercept (27.8%) in FIXTURE (odds ratio [redacted]; 95% CI, [redacted] to [redacted]).
- The median differences in DLQI total score between secukinumab and placebo were:
  - ERASURE: [redacted] (95% CI, [redacted] to [redacted])
  - FEATURE: [redacted] (95% CI, [redacted] to [redacted])
  - JUNCTURE: [redacted] (95% CI, [redacted] to [redacted])
  - FIXTURE: [redacted] (95% CI, [redacted] to [redacted]).
- At week 12, the median change from baseline EQ-5D visual analogue scale ranged from [redacted] to [redacted] with secukinumab and from [redacted] to [redacted] with placebo, and was [redacted] with etanercept.

Harms (Safety and Tolerability)

- The proportions of patients who experienced at least one serious adverse event were:
  - 12 weeks: 1.2% to 5.1% with secukinumab, 1.6% to 1.8% with placebo, and 0.9% with etanercept
  - Entire treatment period: [redacted] to [redacted] with secukinumab, [redacted] to [redacted] with placebo, and [redacted] with etanercept.
- Adverse events that occurred more frequently with secukinumab included nasopharyngitis, headache, diarrhea, pruritus, and hypertension. The proportions of patients who experienced at least one adverse event were:
  - 12 weeks: 51% to 70% with secukinumab, 47% to 54% with placebo, and 58% with etanercept
  - Entire treatment period: [redacted] to [redacted] with secukinumab, [redacted] to [redacted] with placebo, and [redacted] with etanercept.
- The proportions of patients who withdrew as a result of adverse events were:
  - 12 weeks: [redacted] to [redacted] with secukinumab, [redacted] to [redacted] with placebo, and [redacted] with etanercept

- Entire treatment period: [redacted] to [redacted] with secukinumab, [redacted] to [redacted] with placebo, and [redacted] with etanercept.

Cost and Cost-Effectiveness

The manufacturer submitted a reduced price during the embargo period of $[redacted] for two 150 mg/1.0 mL pre-filled syringes or pens, a [redacted] price reduction from the original submitted price of $1,645.

The manufacturer submitted a cost-utility analysis comparing secukinumab 300 mg to other biologics (adalimumab 40 mg, etanercept 50 mg, ustekinumab 45 mg and 90 mg, and infliximab 5 mg/kg), secukinumab 150 mg, and SoC (defined as oral systemic therapy, phototherapy, and topical treatment) in patients with moderate to severe plaque psoriasis (PASI ≥ 12, IGA mod 2011 ≥ 3 and total body surface area ≥ 10%) who are candidates for phototherapy or systemic therapy. The analysis was undertaken from a publicly funded health care system perspective over a 10-year time horizon. The analysis was based on a Markov model. In the first year, the model used four-week cycles and consisted of four health states based on PASI response (PASI < 50, PASI 50 to 74, PASI 75 to 89, and PASI 90 to 100). Patients who responded to treatment at week 12 (defined as achieving PASI 75) continued with their initial therapy, while non-responders switched to SoC. Response was then assessed at week 52 and annually thereafter. In years 2 to 10, the model had annual cycles and three health states (response to treatment [PASI ≥ 75] with continuing active therapy, non-response [PASI < 75] with switching to SoC, and death). Data on comparative efficacy for all comparators, in terms of PASI response, were obtained from a manufacturer-sponsored mixed-treatment comparison (MTC). Treatment withdrawal rates were based on observed withdrawal in the secukinumab trials for year 1 and from the literature for years 2 to 10. ICURs for all comparators were calculated compared with SoC. Compared with SoC, secukinumab 300 mg was the most cost-effective option, with an ICUR of $78,007 per QALY, followed by infliximab-Remicade, with an ICUR of $133,190 per QALY (ICUR of $1.22 million per QALY for infliximab-Remicade versus secukinumab 300 mg). All other biologics were either dominated (more costly and less effective) or extendedly dominated (not preferred compared with the combination of SoC and secukinumab 300 mg).

CDR noted a number of limitations with the manufacturer's analysis:

- Efficacy of secukinumab 300 mg was based on 13 maintenance doses per year, while costs were based on 12 doses per year
- Uncertainty regarding comparative effectiveness of secukinumab 300 mg against other biologics due to limitations in the MTC
- Lack of consideration of subsequent entry biologic (SEB) price for infliximab in the base-case analysis
- Uncertainty regarding utility values based on indirect mappings
- Lack of subgroup analyses based on previous treatment experience.

Based on CDR analyses to account for the above limitations (e.g., annual cost of secukinumab 300 mg based on 13 doses and inclusion of SEB infliximab), secukinumab 300 mg was associated with an ICUR of $82,534 compared with SoC. When accounting for uncertainty in utility values, the ICUR for secukinumab 300 mg could vary could vary from $82,534 to $122,365 per QALY.

Based on the reduced price during the embargo period and recommended doses, the annual cost of secukinumab 300 mg is $[redacted] for the first year of treatment (assuming five doses are administered in the first month at weeks 0, 1, 2, 3, and 4 and one dose is administered in each of the following months, 16 doses in total) and $[redacted] to $[redacted] annually thereafter, depending on the interval between doses (28 days as per clinical trials, or up to 31 days). Based on this and current list prices for comparators, in year 1, secukinumab 300 mg is more expensive than adalimumab and ustekinumab ($20,730 and $22,966, respectively) but less expensive than etanercept, infliximab-Remicade, and SEB infliximab (range: $25,297 to $39,502). In subsequent years, secukinumab 300 mg is less costly than other biologics (range: $19,249 to $32,096).

Other Discussion Points:

CDEC noted the following:

- The manufacturer has suggested that the initial response to treatment should be evaluated after 16 weeks and that further doses should be provided only for responders. However, the studies were designed to assess PASI response at week 12 and the pharmacoeconomic evaluation assumed treatment would be discontinued in non-responders at 12 weeks.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- The long-term efficacy and safety of secukinumab
- Studies evaluating the efficacy of secukinumab in patients with less severe plaque psoriasis
- Additional direct comparisons to therapies that are commonly used in the treatment of plaque psoriasis.

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.

Regrets:

May 20-21, 2015: None
August 18-19, 2015: None
October 20, 2015: One CDEC member was unable to attend this portion of the meeting.

Conflicts of Interest:

May 20-21, 2015: None
August 18-19, 2015: None
October 20-21, 2015: None

About This Document:
CDEC provides formulary listing 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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