CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

SECUKINUMAB
(Cosentyx — Novartis Pharmaceuticals Canada Inc.)
Indication: Ankylosing Spondylitis

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that secukinumab be reimbursed for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy, if the following condition is met:

Condition:

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

Reasons for the Recommendation:

1. Two randomized controlled trials (RCTs) (MEASURE 1 [N = 371] and MEASURE 2 [N = 219]), carried out in adult patients with AS, demonstrated that secukinumab 150 mg was superior to placebo for the proportion of patients achieving an Assessment of SpondyloArthritis International Society (ASAS) 20 response at week 16.
2. In the absence of head-to-head comparisons, a manufacturer-submitted mixed treatment comparison (MTC) analysis [redacted]. 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 AS.
3. At the submitted unit price [redacted], the annual cost of secukinumab 150 mg (first year: [redacted], subsequent years: [redacted]) is less than that of all other tumour necrosis factor alpha inhibitors (TNFis), based on publicly available prices.

Of Note:

1. A subgroup analysis in MEASURE 1 and MEASURE 2 suggested that [redacted].

Background:
Secukinumab is a fully human IgG1k monoclonal antibody that selectively binds and neutralizes interleukin-17A (IL-17A), a naturally occurring cytokine involved in normal inflammatory and immune responses. Secukinumab injections are approved for the following indications: treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy; treatment of adult patients with active psoriatic arthritis when the response to previous disease-modifying antirheumatic drug therapy has been inadequate; and treatment of adult patients with active AS who have responded inadequately to conventional therapy. The indication under review for the current submission is for adult patients with active AS.

The recommended dose of secukinumab for adult patient with AS 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.

Secukinumab is available as 150 mg/mL solution for injection in pre-filled syringe or pre-filled SensoReady pen.

Summary of CDEC Considerations:
CDEC 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 AS, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues that are important to individuals with AS.

Patient Input Information:
The following is a summary of information provided by three patient groups (Arthritis Consumer Experts, Canadian Arthritis Patient Alliance, and The Canadian Spondylitis Association) that responded to the CDR call for patient input.

- Symptoms of AS include pain (back, neck, hips, legs, shoulders, eyes, and feet), morning stiffness, limited motion, fatigue, stress, depression, anxiety, and feelings of social isolation. Those affected with AS reported that their quality of life is reduced given the symptoms, disability, and difficulty participating in daily activities.
- Existing therapies include nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics, as well as TNFis when patients do not respond well to NSAIDs and analgesics. Patients noted the need for several treatment options as TNFis are not effective for all patients. Treatment response may be different for each individual and the efficacy of any individual TNFi can wear off after a period of time. Currently available biologics are costly.
- It is possible that when patients no longer respond to the current TNFis, they may benefit from secukinumab, which has a different mechanism of action from TNFis. Patients expressed that if their overall well-being improves for most of the time after they are on the drug, they will be willing to experience the side effects related to the drug.

Clinical Trials
The CDR systematic review included two phase 3, double-blind RCTs: MEASURE 1 (N = 371) and MEASURE 2 (N = 219). In these two studies, adult patients with moderate to severe AS were randomized to receive double-blind treatment of secukinumab 150 mg, secukinumab 75 mg, or placebo every four weeks over a period of 16 weeks. In MEASURE 1, patients in the

placebo group were re-randomized to secukinumab 150 mg or secukinumab 75 mg group at week 16 or week 24, according to their response to placebo; the treatment was given for up to two years. In MEASURE 2, patients in the placebo group were re-randomized to secukinumab 150 mg or secukinumab 75 mg group at week 16 and they were treated for up to five years. In accordance with the Health Canada–approved indication, only results for the secukinumab 150 mg were considered by CDEC.

Outcomes

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

- ASAS 20 — defined as an improvement of at least 20% and absolute improvement of at least one unit on a 0 to 10 numerical rating scale in at least 3 of the 4 domains.
- ASAS 40 — defined as an improvement of at least 40% and absolute improvement of at least two units on a 0 to 10 scale in at least 3 of the 4 main ASAS domains.
- Health-related quality of life — assessed using the Medical Outcomes Study Short Form-36 (SF-36), the Ankylosing Spondylitis Quality of Life assessment (ASQol), Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-Fatigue), and EuroQol Health Status Questionnaire (EQ-5D).
    - SF-36: a 36-item, generic instrument to assess patient's physical and mental well-being. The physical component summary (PCS) and the mental component summary (MCS) range from 0 to 100, with higher scores indicating better health status. In MEASURE 1 and MEASURE 2, a patient was considered a PCS or MCS responder if the patient had an increase of ≥ 2.5 points from baseline.
    - ASQoL: an 18-item, disease-specific questionnaire for measuring health-related quality of life in patients with AS. Lower score indicates better quality of life. A change of –1.8 on the ASQoL scale has been identified as the minimum clinically important difference (MCID).
    - FACIT-Fatigue: a 13-item questionnaire for assessing the impact of fatigue on daily activities and function in patients with cancer or other chronic diseases. Higher scores represent less fatigue. A difference of 3 to 4 units is considered the MCID of FACIT-Fatigue.
    - EQ-5D: a widely used questionnaire to assess health status in adults. In MEASURE 1 and MEASURE 2, a score from the EQ-5D visual analogue scale was reported. Higher scores represent better health states. This was an exploratory outcome in MEASURE 1 and MEASURE 2.
- Disease activity — assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). The BASDAI is a self-report instrument used to measure severity of fatigue, spinal and peripheral joint pain and swelling, enthesitis, and morning stiffness during the previous last week. The MCID used to interpret scores is considered to be –1.96 on the 10-point BASDAI scale.
- Work productivity — assessed using the Work Productivity and Activity Impairment — General Health (WPAI-GH), an instrument used to examine the extent of absenteeism, presenteeism, and impairment in daily activities attributable to general health during the preceding four weeks. This was an exploratory outcome in MEASURE 1 and MEASURE 2.
- Radiographic changes: in MEASURE 1, results of magnetic resonance imaging (MRI) examinations were available in a subset of patients at week 16. X-ray results at year 2 were reported.
- Serious adverse events, total adverse events, and withdrawal due to adverse events.

The primary outcome in MEASURE 1 and MEASURE 2 was the proportion of patients who met ASAS 20 response criteria at week 16.

Efficacy

- For ASAS 20 at week 16, the proportion of patients achieving ASAS 20 response criteria for secukinumab 150 mg versus placebo was:
  - MEASURE 1: 60.8% versus 28.7% (odds ratio [OR], 3.9; 95% confidence interval [CI], 2.3 to 6.7; *P* < 0.0001).
  - MEASURE 2: 61.1% versus 28.4% (OR, 4.4; 95% CI, 2.1 to 9.0; *P* < 0.0001).

  The between-group differences were statistically and clinically significant.
  Subgroup analysis based on [redacted].
- For ASAS 40 at week 16, the proportion of patients achieving ASAS 40 response criteria for secukinumab 150 mg versus placebo was:
  - MEASURE 1: 41.6% versus 13.1% (OR, 4.9; 95% CI, 2.6 to 9.3; *P* < 0.0001).
  - MEASURE 2: 36.1% versus 10.8% (OR, 5.1; 95% CI, 2.1 to 12.4; *P* = 0.0004).

  The between-group differences were statistically and clinically significant.
- For health-related quality of life, the secukinumab 150 mg group demonstrated statistically greater improvement in SF-36 PCS, ASQol and FACIT-Fatigue compared with placebo at week 16. The between-group differences for secukinumab 150 mg versus placebo were:
  - SF-36 PCS:
    - MEASURE 1: 4.6 (95% CI, 3.0 to 6.2), *P* < 0.0001.
    - MEASURE 2: [redacted].
  - ASQoL:
    - MEASURE 1: –2.5 (95% CI, –3.7 to –1.4), *P* < 0.0001.
    - MEASURE 2: [redacted].
  - FACIT-Fatigue:
    - MEASURE 1: 4.3 (95% CI, 2.0 to 6.6), *P* = 0.0003.
    - MEASURE 2: [redacted].

  The between-group differences were considered statistically and clinically significant.
- For disease activity, secukinumab 150 mg was statistically superior to placebo for improvement in BASDAI total scores at week 16. The mean between-group differences for secukinumab 150 mg versus placebo were:
  - MEASURE 1: −1.7 (95% CI, −2.2 to −1.3), *P* < 0.0001.
  - MEASURE 2: −1.3 (95% CI, −2.0 to −0.7), *P* = 0.0002.

  The differences were statistically but not clinically significant.
- Data up to week 104 suggested that the efficacy and safety results at week 16 for secukinumab 150 mg were maintained; however, there was no comparison with placebo in MEASURE 1 and MEASURE 2 after week 16.

Harms (Safety and Tolerability)

- By week 16 in MEASURE 1, at least one serious adverse event was reported for 2.4% and 4.1% of patients in the secukinumab 150 mg group and the placebo group, respectively. In MEASURE 2, at least one serious adverse event was reported for 5.6% and 4.1% of patients in the secukinumab 150 mg group and the placebo group, respectively. There was one death reported in the placebo group in MEASURE 1.

- By week 16 in MEASURE 1, the proportion of patients who withdrew as a result of adverse events was 0.8% and 4.9% in the secukinumab 150 mg group and the placebo group, respectively. In MEASURE 2, the proportion of patients who withdrew as a result of adverse events was 6.9% and 5.4% in the secukinumab 150 mg group and the placebo group, respectively.
- By week 16 in MEASURE 1, at least one treatment-emergent adverse event was reported for 69.6% and 55.7% of patients in the secukinumab 150 mg group and the placebo group, respectively. In MEASURE 2, at least one treatment-emergent adverse event was reported for 65.3% and 63.5% of patients in the secukinumab 150 mg group and the placebo group, respectively. Nasopharyngitis was the most commonly reported adverse event in both studies.

Cost and Cost-Effectiveness

At the manufacturer-submitted confidential price of [redacted] per 150 mg/mL pre-filled syringe or pen, the cost of treatment with secukinumab 150 mg is [redacted] per year in the first year and [redacted] per year in subsequent years. The manufacturer submitted a cost comparison of secukinumab 150 mg to TNFis currently indicated for active AS in Canada (adalimumab, etanercept, golimumab, and infliximab) over a three-year time horizon. [redacted] for secukinumab and these comparators were assumed based on a network meta-analysis (NMA) submitted by the manufacturer.

CDR noted the following limitations with the manufacturer's pharmacoeconomic evaluation:

- No head-to-head trial evidence was provided to show similar efficacy between secukinumab and TNFis, and the conclusions of [redacted] 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 assumption of clinical equivalence between secukinumab and TNFis is uncertain for treatment-experienced patients based on the results from the MEASURE 1 and MEASURE 2 trials, which suggest that efficacy may be [redacted] in such patients.
- 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 first and subsequent year costs were therefore considered more appropriate than total three-year costs.

At the submitted price and based on CDR re-analysis 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 TNFis (first year savings ranged from [redacted] compared with subsequent entry biologic [SEB] infliximab to [redacted] compared with infliximab [Remicade], and subsequent year savings ranged from a minimum of [redacted] compared with SEB infliximab to as much as [redacted] compared with infliximab [Remicade]).

Other Discussion Points:

CDEC noted the following:

- While the manufacturer [redacted], there was no evidence to demonstrate that secukinumab has better 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*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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