



CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

SARILUMAB

(Kevzara — Sanofi Genzyme)

Indication: Rheumatoid Arthritis

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that sarilumab be reimbursed for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more biologic or non-biologic disease-modifying antirheumatic drug (DMARD), as monotherapy or in combination with methotrexate (MTX) or another non-biologic DMARD, if the following conditions are met:

Conditions:

- Reimburse in a similar manner to other biologics for the treatment of moderately to severely active RA.
- The drug plan cost of treatment with sarilumab should not exceed the drug plan cost of treatment with the least costly alternative biologic.

Reasons for the Recommendation:

1. Three double-blind randomized controlled trials (RCTs) conducted in patients with moderately to severely active RA who had an inadequate response or intolerance to one or more biologic(s) or DMARD(s) demonstrated that treatment with sarilumab, with or without background DMARD therapy, was superior to placebo and adalimumab for achieving clinical response (American College of Rheumatology [ACR] 20, ACR 50, and ACR 70 criteria), clinical remission (Disease Activity Score [DAS] 28 < 2.6), and improvement in physical functioning (Health Assessment Questionnaire Disability Index [HAQ-DI]).
2. A manufacturer-provided network meta-analysis (NMA) suggested that sarilumab [REDACTED]
3. At the submitted price of \$700 per pre-filled syringe (for both 150 mg and 200 mg doses), the estimated annual cost of sarilumab therapy is \$18,200 per patient when administered as recommended every two weeks. Therefore, sarilumab is more expensive than intravenous (IV) tocilizumab (annual cost range of \$9,402 to \$17,629 per patient). Sarilumab is also more expensive than biweekly subcutaneous (SC) tocilizumab (\$9,230 per patient annually),

Common Drug Review

but similar to weekly SC tocilizumab (\$18,460 per patient per year). The annual cost of sarilumab is \$2,908 less than branded etanercept, but \$2,340 more per patient per year than the biosimilar etanercept.

Discussion Points:

CDEC discussed the following:

- Tocilizumab was the first interleukin-6 (IL-6) receptor antagonist indicated for the treatment of adults with moderately to severely active RA; sarilumab is the second drug in this class.
- Sarilumab was studied with IV tocilizumab in the manufacturer-submitted ASCERTAIN study.

[REDACTED]

- The manufacturer conducted an NMA to evaluate the comparative efficacy and safety of sarilumab against other biologics that have been approved for use in the treatment of RA.

[REDACTED]

Based on the results of the NMA, the manufacturer reported that sarilumab compared with other biologics when used in combination with DMARDs.

[REDACTED]

[REDACTED]

- Dose escalation of sarilumab was not evaluated in any of the included clinical trials or in the EXTEND extension study and the current Canadian product monograph does not provide guidance regarding potential dose escalation scenarios.

Background:

Sarilumab is an IL-6 receptor antagonist indicated for the treatment of adults with moderately to severely active RA who have had an inadequate response or intolerance to one or more biologic or non-biologic DMARD. Sarilumab may be used as monotherapy or in combination with methotrexate (MTX) or another non-biologic DMARD. The recommended dose of sarilumab is 200 mg once every two weeks given as a subcutaneous injection. A reduced dose of 150 mg once every two weeks is recommended for patients with neutropenia, thrombocytopenia, or with elevated liver enzymes. Sarilumab is available as a solution for subcutaneous injection in 150 mg/1.14 mL or 200 mg/1.14 mL single-dose pre-filled syringes.

Summary of CDEC Considerations:

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs, a NMA submitted by the manufacturer, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to individuals living with RA.

Patient Input Information:

Three patient groups provided input for the CDR submission for sarilumab: the Arthritis Consumer Experts, the Canadian Arthritis Patient Alliance, and the Arthritis Society. The latter two prepared a joint submission. The submissions from the patient groups included: information obtained from authors' and organizational leaders' personal experiences, the authors' day-to-day interactions with patients who are living with RA, researchers' experience in Canada, surveys of patients, and from social media. The following is a summary of key information provided by the patient groups:

- Patients reported that RA affects every aspect of their day-to-day living. Those living with RA commonly experience joint pain and stiffness that can limit their ability to carry-out the daily activities of living, pursue education, obtain and retain employment, and participate in social and family activities. Patients may experience irreversible joint damage that can result in the need for surgery or for the use of mobility aids (e.g., cane or wheelchair).
- Current treatments for RA include DMARDs (biologic and non-biologic), nonsteroidal anti-inflammatory drugs, corticosteroids, and analgesics. These treatments have notable adverse effects, including fever, night sweats, nausea, vomiting, fatigue, easy bruising or bleeding, dizziness, itching, weight loss, stomach pain, pale skin, shortness of breath, rapid heart rate, loss of appetite, jaundice, dry skin, hair loss, and suppression of the immune system. The groups noted that many patients find methotrexate particularly hard to take because of the adverse events associated with it.
- Patient groups emphasized that not all individuals living with RA will respond to each available treatment in the same manner. In addition, patient groups indicated that treatments can cease to be effective after a period of time, requiring them to switch to a different therapy. Overall, as a result of differential responses and the gradual loss of effectiveness of once-effective treatments, patients strongly believe that multiple treatment options should be available.
- Some patients have a particular expectation that sarilumab will work well in many patients who have already failed another biologic therapy.

Clinical Trials

The CDR systematic review included four double-blind RCTs that investigated the safety and efficacy of sarilumab for the treatment of patients with moderately to severely active RA. These included one 24-week placebo-controlled trial (TARGET; N = 546), one 52-week placebo-controlled trial (MOBILITY; N = 1,197), and two 24-week active-controlled trials that compared sarilumab against adalimumab (MONARCH; N = 369) or tocilizumab (ASCERTAIN; N = 202). The MOBILITY and MONARCH studies required patients to have been previously treated with MTX; whereas, the TARGET and ASCERTAIN trials were conducted in patients who were treatment-experienced with one or more tumour necrosis factor (TNF)-alpha antagonists. The studies investigated the use of sarilumab as monotherapy (MONARCH), in combination with MTX (MOBILITY), and in combination with various non-biologic DMARDs (ASCERTAIN and TARGET).

Three of the included studies (MOBILITY, TARGET, and ASCERTAIN) randomized patients to two different doses of sarilumab (i.e., 150 mg or 200 mg once every two weeks). The recommended dose of sarilumab is 200 mg once every two weeks, with a 150 mg dosage recommended for patients with neutropenia, thrombocytopenia, or with elevated liver enzymes. The CDR review focused primarily on the Health Canada–approved dosage regimen and, since the 150 mg dosage regimens were not restricted to those with the adverse events noted above, the emphasis is placed on the efficacy and safety data for the 200 mg once every two weeks regimen.

The protocols for the two placebo-controlled trials included early escape criteria for patients who demonstrated a lack of efficacy beginning at week 16 in MOBILITY and week 12 in TARGET if they failed to demonstrate at least a 20% improvement from baseline in either swollen joint count or tender joint count for two consecutive study visits, or demonstrated any other clear lack of efficacy, based on the judgment of the investigator. These patients were eligible to receive rescue therapy with open-label sarilumab. Rescue therapy was more commonly initiated in the placebo groups (39.3% to 34.8%) compared with the sarilumab groups (12.9% to 14.1%).

Outcomes

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

- ACR 20 response rate — defined as the proportion of patients who demonstrated a $\geq 20\%$ improvement in tender and swollen joint counts and $\geq 20\%$ improvement from baseline in three of the five remaining ACR core set measures: patient global assessment of arthritis, physician global assessment of arthritis, patient assessment of arthritis pain, HAQ-DI, and C-reactive protein (CRP).
- ACR 50 and ACR 70 response rates — similar to the ACR 20, but with improvements of $\geq 50\%$ and $\geq 70\%$.
- HAQ-DI — assesses the degree of difficulty a patient had experienced during the past week in eight domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities. The minimal clinically importance difference (MCID) is estimated to be 0.22.
- DAS Assessments — evaluates disease activity using the following measures: tender/painful joint count (28 joints); swollen joint count (28 joints); CRP or erythrocyte sedimentation rate (ESR); and patient global assessment of arthritis. Remission rates were calculated for the proportion of patients achieving a DAS 28-CRP score of less than 2.6.

- Modified Total Sharp Scores (mTSS) — measures the presence of erosions in the hands and feet and the presence of joint space narrowing in the hands, wrists, and feet. The scores for each feature for the individual joints are summed. For erosion scores, 16 locations in each hand and wrist and 12 locations in each foot were scored using a six-point scale from 0 to 5. For joint space narrowing, 15 locations in each hand and wrist, and six locations in each foot were scored using a five-point scale from 0 to 4. The MCID is estimated to be 4.6.
- Short-Form 36 (SF-36) — a 36-item generic health status instrument that measures eight general health domains: physical functioning, role physical (PCS), bodily pain, general health, vitality, social functioning, role emotional, and mental health (MCS). Higher scores indicate better health-related quality of life. The eight sub-domains are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. The MCID is estimated to be 2.5 to 5.0 points.
- Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale — a patient-completed questionnaire, consisting of 13 items, that evaluates fatigue. Instrument scoring yields a range from 0 to 52, with higher scores representing better patient status (i.e., less fatigue). A suggested MCID for the FACIT-Fatigue scale in RA patients is between 3 and 4 points.

Multiple primary efficacy end points were used within and across the studies, including ACR 20 response, HAQ-DI, DAS 28-ESR, and mTSS. Safety and tolerability were the primary end points of the ASCERTAIN trial.

Efficacy

Inadequate Response to DMARD/MTX

Sarilumab plus MTX versus Placebo plus MTX (MOBILITY Part B)

- Sarilumab was associated with statistically significant improvements in the proportion of patients with ACR 20 (odds ratio [OR] 3.975 [95% confidence interval [CI], 2.957 to 5.344]), ACR 50 (OR 4.269 [95% CI, 3.064 to 5.948]), and ACR 70 (OR 4.280 [95% CI, 2.743 to 6.678]) responses compared with placebo at 24 weeks (all $P < 0.0001$).
- Sarilumab was associated with a statistically significant difference in mTSS compared with placebo (0.25 versus 2.78; $P < 0.0001$) and a statistically significantly greater proportion of sarilumab-treated patients had no evidence of radiographic disease progression compared with placebo (55.6% versus 38.7%; OR 2.001 [95% CI, 1.506 to 2.660]).
- Treatment with sarilumab was associated with statistically significant improvements in DAS 28-CRP compared with placebo at 24 weeks ([REDACTED]). Sarilumab-treated patients were also statistically significantly more likely to achieve DAS 28-CRP remission than those treated with placebo (OR 4.690 [95% CI, 3.176 to 6.926]).
- Treatment with sarilumab was associated with a statistically significant improvement in HAQ-DI compared with placebo (LSMD -0.258 [95% CI, -0.336 to -0.181]).

[REDACTED]

- Compared with placebo, sarilumab resulted in greater improvements in SF-36 PCS (LSMD 3.530 [95% CI, 2.164 to 4.897]) and SF-36 MCS (LSMD 2.896 [95% CI, 1.199 to 4.593]) at 52 weeks.
- Treatment with sarilumab was associated with greater improvements FACIT-Fatigue compared with placebo at 24 and 52 weeks (LSMD 3.351 [95% CI, 2.092 to 4.611] and 3.148 [95% CI, 1.746 to 4.551], respectively).

Sarilumab versus Adalimumab (MONARCH)

- Sarilumab was associated with statistically significant improvements in the proportion of patients with ACR20, ACR50, and ACR70 responses compared with adalimumab at 24 weeks (all $P < 0.0001$). The odds ratios for achieving ACR responses were: ACR20 (1.80 [95% CI, 1.168 to 2.773]); ACR50 (1.976 [95% CI, 1.289 to 3.028]); ACR70 (2.286 [95% CI, 1.30 to 4.020]).
- In MONARCH, sarilumab was associated with a statistically significantly greater improvement in DAS28-ESR (LSMD -1.077 [95% CI, -1.361 to -0.793]) and DAS28-CRP -0.884 [95% CI, -1.138 to -0.629]) compared with adalimumab. Sarilumab-treated patients were also statistically significantly more likely to achieve DAS28-CRP remission than those treated with adalimumab (OR: 3.314 [95% CI, 1.973 to 5.566]).
- Sarilumab was associated with a statistically significant improvement in the CDAI compared with adalimumab at 24 weeks (LSMD -3.741 [95% CI, -6.016 to -1.466]). There was no statistically significant difference between sarilumab and adalimumab for the proportion of patients with a CDAI response at week 12 (OR 1.935 [95% CI, 0.695 to 5.382]); however, there was a statistically significant difference at week 24 (OR 2.869 [95% CI, 0.981 to 8.389]).
- Treatment with sarilumab was associated with a statistically significant improvement in HAQ-DI compared with adalimumab (LSMD -0.182 [95% CI, -0.305 to -0.059]).
- Treatment with sarilumab was associated with a statically significant difference in SF-36 PCS compared with adalimumab at 24 weeks (LSMD 2.650 [95% CI, 1.147 to 4.153]); however, there was no difference between sarilumab and adalimumab in SF-36 MCS at 24 weeks (LSMD 1.036 [95% CI, -1.061 to 3.132]).
- There was no statistically significant difference between sarilumab and adalimumab for change from baseline in FACIT-Fatigue at 24 weeks.

Inadequate Response to TNF-alpha Antagonist

Sarilumab plus DMARD versus Placebo plus DMARD (TARGET)

- Sarilumab was associated with statistically significant improvements in the proportion of patients with ACR 20 (3.284 [95% CI, 2.108 to 5.115]), ACR 50 (3.374 [95% CI, 2.045 to 5.566]), and ACR 70 (2.653 [95% CI, 1.308 to 5.383]) responses compared with placebo at 24 weeks (all $P < 0.0001$).
- Sarilumab was associated with a statistically significant improvement in HAQ-DI compared with placebo (LSMD -0.210 [95% CI, -0.325 to -0.095]).

- Sarilumab was associated with greater improvements in FACIT-Fatigue at 24 weeks compared with placebo (LSMD 3.246 [95% CI, 1.037 to 5.456]).
- Treatment with sarilumab was associated with statistically significant improvements in DAS 28-CRP compared with placebo at 24 weeks (LSMD -1.444 [95% CI, -1.752 to -1.135]). Sarilumab-treated patients were also statistically significantly more likely to achieve DAS 28-CRP remission than those treated with placebo (OR 5.801 [95% CI, 2.948 to 11.413]).
- Sarilumab was associated with a statistically significant improvement in the CDAI [REDACTED]).
- Compared with placebo, treatment with sarilumab was associated with a statistically significant improvement in the SF-36 PCS at 24 weeks (LSMD 4.075 [95% CI, 2.305 to 5.846]). There was no statistically significant difference for change from baseline in SF-36 MCS (LSMD 2.013 [95% CI, -0.282 to 4.309]).

Sarilumab plus DMARD versus Tocilizumab plus DMARD (ASCERTAIN)

- The proportion of patients with DAS 28-CRP remission was similar between the sarilumab (31.4%) and tocilizumab groups (29.4%).

Harms (Safety and Tolerability)

- The proportions of patients who experienced at least one adverse event were:
 - MOBILITY: 78.1% with sarilumab plus MTX versus 61.6% with placebo plus MTX
 - TARGET: 65.2% with sarilumab plus DMARD versus 49.7% with placebo plus DMARD
 - MONARCH: 64.1% with sarilumab versus 63.6% with adalimumab
 - ASCERTAIN: 70.6% with sarilumab plus DMARD versus 66.7% with tocilizumab plus DMARD.
- The proportions of patients who experienced at least one serious adverse event were:
 - MOBILITY: 11.3% with sarilumab plus MTX versus 5.4% with placebo plus MTX
 - TARGET: 5.4% with sarilumab plus DMARD versus 3.3% with placebo plus DMARD
 - MONARCH: 4.9% with sarilumab versus 6.5% with adalimumab
 - ASCERTAIN: 5.9% with sarilumab plus DMARD versus 6.9% with tocilizumab plus DMARD.
- The proportions of patients who withdrew as a result of adverse events were:
 - MOBILITY: 13.9% with sarilumab plus MTX versus 4.7% with placebo plus MTX
 - TARGET: 9.2% with sarilumab plus DMARD versus 4.4% with placebo plus DMARD
 - MONARCH: 6.0% with sarilumab versus 7.1% with adalimumab
 - ASCERTAIN: 15.7% with sarilumab plus DMARD versus 3.9% with tocilizumab plus DMARD.

- Serious infections and infestations were more commonly reported with sarilumab plus MTX compared with placebo plus MTX in MOBILITY (4.0% versus 2.3%); however, the proportions were the same with sarilumab plus DMARD and placebo plus DMARD groups of TARGET (1.1% in both). There were no differences between the treatment groups for the proportion of patients who experienced at least one serious infection in MONARCH (1.1% in each group) and ASCERTAIN (2.0% in each group).
- Compared with placebo, a greater proportion of sarilumab-treated patients experienced at least one adverse event that was classified as an infection or infestation (39.6% versus 31.1% in MOBILITY and 30.4% versus 26.5% in TARGET). Infections and infestations were reported for a similar proportion of patients in both the sarilumab and adalimumab groups in MONARCH (28.8% versus 27.7%) [REDACTED].
- Neutropenia was more commonly reported with sarilumab than with placebo (14.4% versus 0.2% in MOBILITY and 12.5% versus 1.1% in TARGET), adalimumab (13.6% versus 0.5%), and tocilizumab (15.7% versus 3.9%). The manufacturer reported that patients who had neutropenia in the included studies did not have an increased rate of serious infections.
- Gastrointestinal adverse events were more common with sarilumab compared with placebo (15.1% versus 10.8% in MOBILITY and [REDACTED]) and [REDACTED].

Cost and Cost-Effectiveness

The manufacturer submitted a price of \$700 per pre-filled syringe (for both 150 mg and 200 mg doses) which, when administered as recommended every two weeks, results in an annual cost of \$18,200 per patient.

The manufacturer submitted a cost comparison of sarilumab 200 mg every two weeks to the monograph-recommended doses of other biologics used for the treatment of RA. Clinical similarity among biologics was assumed on the basis of head-to-head trials comparing sarilumab with adalimumab (MONARCH) and tocilizumab (ASCERTAIN) [REDACTED]. The perspective was that of a public drug plan, with all other costs assumed to be equal. Drug costs were considered over a three-year time horizon in order to account for dose titration in the first year and two years of maintenance therapy. A patient weight of 75 kg was assumed for weight-based comparator dosing.

Key limitations in the manufacturer's analysis included uncertainty in the assumption of clinical similarity for sarilumab versus comparators, the recent availability of the biosimilar etanercept, and the presentation of results (i.e., reporting of a three-year average as opposed to separate reporting of first year costs to highlight the costs of dose titration where applicable and the annual cost of maintenance treatment thereafter).

When compared with the most widely used biologics for the treatment of RA, sarilumab (\$18,200 per patient per year) is less expensive than adalimumab (\$20,019 per patient per year) and branded etanercept (\$21,108 per patient per year), but more expensive than the biosimilar etanercept (\$15,860 per patient per year). A price reduction of 13% would be required for sarilumab to be considered cost-neutral to biosimilar etanercept.

When compared with other biologics, such as tocilizumab, the other IL-6 inhibitor, sarilumab is more expensive than the IV formulation (\$9,402 to \$17,629 per patient per year) and biweekly

Common Drug Review

SC use (\$9,230 per patient per year), but similar to weekly SC use (\$18,460 per patient per year). In order for sarilumab to be considered cost-neutral to a weighted average cost of tocilizumab SC, 97% of patients would need to be using weekly versus biweekly doses of tocilizumab. Where more than 3% of patients are receiving tocilizumab biweekly, price reductions for sarilumab would be required for cost neutrality.

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 Wijeyesundera.

March 15, 2017 Meeting:**Regrets:**

None

Conflicts of Interest:

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*.

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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