



CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

CANAKINUMAB

(Ilaris — Novartis Pharmaceuticals Canada Inc.)

Indication: Systemic Juvenile Idiopathic Arthritis

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that canakinumab be reimbursed for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients two years and older with the following clinical criteria and conditions.

Criteria:

1. Patients who have had an inadequate response or intolerance to oral steroids or methotrexate.
2. Treatment to be discontinued if there is no improvement after day 15.

Conditions:

1. Cost should not exceed the drug plan cost of tocilizumab.
2. Patients should be under the care of a physician with experience in treating sJIA.

Reasons for the Recommendation:

1. Two randomized controlled trials (RCTs) — Study 2301 and Study 2305 — demonstrated that canakinumab is an effective therapy compared with placebo for the treatment of sJIA by improving patient well-being, decreasing pain, improving function, and enhancing overall quality of life. There are no direct comparisons for canakinumab versus other treatments for sJIA. However, indirect comparisons suggest that the efficacy of canakinumab is similar to other biologic therapies used for sJIA.
2. There is insufficient evidence to determine whether canakinumab would still be an effective treatment for patients who have previously discontinued treatment with other biologic drugs, including tocilizumab, due to a lack of efficacy or intolerance.
3. Canakinumab is 10 to 15 times higher in price than other treatments for sJIA. Canakinumab is unlikely to be cost-effective at current prices for patients who are either treatment-experienced or treatment-naive with sJIA. A reduction in the price of canakinumab of approximately 90% would be required to make it a cost-effective treatment option compared with tocilizumab.

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Of Note:

Drug plans that do not reimburse tocilizumab for sJIA may also opt not to reimburse canakinumab.

Background:

Canakinumab is a human monoclonal antibody that inhibits interleukin-1 beta. In 2011, CEDAC recommended that canakinumab not be reimbursed for the treatment of cryopyrin-associated periodic syndromes (CAPS). The Health Canada indication that was reviewed for the current submission was the treatment of active sJIA in patients two years and older. The recommended dose of canakinumab for treating sJIA is 4 mg/kg (up to a maximal dose of 300 mg) administered every four weeks through subcutaneous injection.

Summary of CDEC Considerations

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of randomized controlled trials (RCTs) and pivotal studies of canakinumab, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to children with sJIA.

Patient Input

The following is a summary of key information provided by The Arthritis Society and the Canadian Arthritis Patient Alliance, which responded to the CDR call for patient input. Information was gathered from personal experiences, conversations with multiple parents, and from a 2013 survey on childhood arthritis.

sJIA affects every aspect of the patients' lives, including day-to-day activities such as sleeping; caring for oneself; walking; participating in school; social; and recreational activities; and in their ability to pursue hobbies and interests. The limitations associated with the inability to perform daily routine activities can cause a severe psychological burden on the children as well as on their families and caregivers. Responses to the various treatment options available can vary significantly. Some patients may respond well to treatment; others may not respond at all; still others will have their disease managed for only a short period of time before becoming non-responsive. The pain associated with daily injections of anakinra is reported to have a significant impact on the quality of life for the child and their family.

Clinical Trials

The CDR systematic review included two RCTs. Study 2305 (n = 84) evaluated the superiority of canakinumab compared with placebo based on the proportion of patients who achieved at least an adapted American College of Rheumatology Pediatric (ACR Pedi) 30 response at day 15 and were followed-up for a total of four weeks. Study 2301 (n = 100) evaluated the superiority of canakinumab compared with placebo based on the primary outcome of time to flare events, using a flare prevention design. Study 2301 included an open-label, run-in trial where all patients received canakinumab to induce and maintain, at a minimum, an adapted ACR Pedi 30 response. All patients with active sJIA were allowed to participate in Study 2305 and Study 2301; however, baseline characteristics indicated that both trial populations involved patients with a high level of disease activity. In addition, the majority of patients received prior

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treatment with various initial therapeutic options including oral steroids, methotrexate, anakinra and etanercept, which were discontinued mostly due to lack of efficacy or tolerability.

Outcomes

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

- ACR Pedi response
- disease activity including absence of disease flares
- health-related quality of life based on the Child Health Questionnaire (CHQ)
- functional and disability outcomes based on the Child Health Assessment Questionnaire (CHAQ)
- serious adverse events (SAEs), total adverse events (AEs), and withdrawals due to adverse events (WDAEs).

Efficacy

Results from Study 2305 demonstrated the superiority of canakinumab over placebo in achieving an adapted ACR Pedi 30 response after 15 days of treatment in patients with sJIA: odds ratio (OR) = 62 (95% confidence interval [CI], 12 to 306; $P < 0.0001$). Patients receiving canakinumab were also statistically significantly more likely to achieve an adapted ACR Pedi 70 response (OR = 105; 95% CI, 12 to 923; $P < 0.0001$) or an adapted ACR Pedi 100 response (OR = 23; 95% CI, 3 to 183; $P < 0.0001$) after 30 days of treatment. These results were considered particularly relevant and clinically meaningful according to the pediatric expert consulted, as they may be consistent with the treatment goal of remission.

With the use of a withdrawal design, Study 2301 demonstrated the sustained efficacy of canakinumab, which was associated with a statistically significant reduction in the risk of a disease flare compared to placebo in patients who previously achieved a minimum response with the drug: hazard ratio (HR) = 0.36 (95% CI, 0.17 to 0.75; $P = 0.0032$). In Study 2301, canakinumab was superior to placebo in reducing the risk of a worsening in adapted ACR Pedi response level throughout the study duration (HR = 0.49; 95% CI, 0.27 to 0.90; $P = 0.0131$), and canakinumab was also associated with a statistically significantly higher likelihood of inactive disease compared with placebo (OR = 3.4; 95% CI, 1.5 to 8.0; $P = 0.0020$).

Canakinumab compared with placebo in Study 2305 was associated with a statistically significant and clinically meaningful benefit in relation to health-related quality of life, pain, and functionality after 29 days of treatment. All three were identified as important outcomes for patients according to the patient input received by CADTH. Results of Study 2301 showed a non-significant trend favouring canakinumab compared with placebo in regard to these outcomes; however, the withdrawal design may have undermined the potential for canakinumab to show a statistically significant between-group difference in these circumstances.

Harms

No deaths were reported in Study 2305. Deaths during Study 2301 were reported for one patient each in the canakinumab and placebo groups. Both deaths were due to macrophage activation syndrome (MAS). At least one SAE was reported for 5% of patients in both groups in Study 2305. In Study 2301, during the double-blind phase, SAEs were reported for 12% of patients in both groups. The most commonly reported SAEs were MAS and juvenile arthritis. In

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Study 2305, at least one AE was reported for 56% of patients in the canakinumab group and 39% of patients in the placebo group. In Study 2301, 80% of patients in the canakinumab group experienced AEs compared with 70% in the placebo group. The most commonly reported AEs were arthralgia, cough, nasopharyngitis, pyrexia, upper respiratory tract infection, abdominal pain, and pain in an extremity. SAEs related to infection were infrequent (< 5%). MAS was less common among canakinumab-treated patients compared with placebo-treated patients (no patients in the canakinumab group versus 2% in the placebo group in Study 2301; and 5% of patients in the canakinumab group versus 10% of patients in the placebo group in Study 2305). No WDAEs were reported in Study 2305. In Study 2301, no WDAEs were reported in the canakinumab group, while WDAEs were reported in 12% of patients in the placebo group.

Cost and Cost-Effectiveness

At the submitted price of \$16,000 per 150 mg vial, the annual cost of canakinumab (\$208,000 to \$416,000 per patient) is substantially higher than that of tocilizumab (\$9,402 to \$28,207 per patient; based on the Ontario Drug Benefit list price, March 2016).

The manufacturer submitted a cost-utility analysis (CUA) that primarily compared canakinumab and tocilizumab as first-line biologic treatments for patients two years and older with active sJIA who have responded inadequately due to intolerance or lack of efficacy to nonsteroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Additionally, the manufacturer undertook a secondary CUA, in line with the requested reimbursement criteria, comparing canakinumab and best supportive care (BSC) as second-line biologic treatment for patients two years and older with active sJIA who are contraindicated to or have discontinued any biologic therapy for lack of efficacy or due to intolerance. The manufacturer's analyses were undertaken from the perspective of a third-party payer in Canada, using an individual-level, time-to-event simulation modelling approach for predicting patients' disease course and evolution, considering treatment effects and outcomes, until patients reached 20 years of age (average time horizon of ~10 years). Efficacy data were derived from an indirect treatment comparison (ITC) comparing canakinumab with tocilizumab, and a pooled analysis from two of the manufacturer's studies comparing canakinumab with placebo (assumed to represent BSC). Utility values were derived using a mapping algorithm that correlates quality of life and ACR scores. The manufacturer reported an incremental cost-utility ratio (ICUR) for canakinumab compared with tocilizumab of more than \$3,000,000 per quality-adjusted life-year (QALY) gained, while the ICUR for canakinumab compared with BSC was approximately \$824,000 per QALY gained. The manufacturer also presented scenarios considering a confidential risk-sharing arrangement, where the annual cost per patient ██████████ of the drug, which improved the ICURs, but not to a point that canakinumab could be considered cost-effective at a conventionally accepted threshold.

The main limitation of the analyses was that the data used to model the primary analyses (first-line biologic treatment) were not based on stratified analyses but on a mixed population (comprised of biologic-naive and biologic-experienced patients), and the data used for the secondary analysis (second-line biologic treatment) were not from the population under assessment for the canakinumab group, but from a mixed population for the BSC group. CDR was unable to test this limitation as stratified analyses for the clinical studies were not available. Other important limitations that were identified and tested by CDR included:

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- The applicability of predictive equations derived from patients' characteristics from Study 2301 may not apply to both the primary and secondary analysis populations.
- A mapping algorithm that weighted quality of life values and CHAQ scores from the canakinumab trials was used to derive utility scores. This approach is associated with a high level of uncertainty.
- An ACR 30 was used as the threshold for treatment response in the model. The CDR clinical expert suggested that the ACR 50 is used in clinical practice.
- The ITCs assessed by CDR [REDACTED]. Hence, CDR tested the assumption of equal efficacy of the drugs for the primary analysis.

When patients' baseline characteristics and utility scores were varied and a response threshold of ACR 50 was considered for first-line biologic treatment, the CDR best estimate ICUR ranged from \$1,846,000 to \$6,521,000 per QALY for canakinumab compared with tocilizumab (or \$576,000 to \$2,034,000 per QALY when considering the manufacturer's proposed risk-sharing agreement). For the second-line biologic treatment (as per the reimbursement request), the CDR best estimate ICUR ranged from \$459,000 to \$1,584,000 per QALY for canakinumab compared with BSC (or \$171,000 to \$591,000 per QALY when considering the manufacturer's proposed risk-sharing agreement). Based on CDR best estimates, without consideration of the risk-sharing arrangement, a price reduction of more than 79% would be required to reduce the ICUR for canakinumab below \$100,000 per QALY in all instances. However, it should be emphasized that given the main limitation of lack of data for the stratified populations based on experience with biologics, the ICURs remain highly uncertain.

For the primary analysis, if equivalent efficacy is assumed, total costs are substantially higher for canakinumab compared with tocilizumab (incremental cost of \$776,000 over the ~10 years' time horizon; reduces to [REDACTED] when considering the risk-sharing arrangement). The cost per vial of canakinumab would have to be reduced by more than 93% to have an annual cost equivalent to that of tocilizumab to treat a patient weighing 20 kg; or by more than 89% for a patient weighing 50 kg.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the long-term safety of canakinumab.

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.

May 18, 2016 Meeting

Regrets: None

Conflicts of Interest: None

About This Document:

CDEC provides formulary drug 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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