

CEDAC FINAL RECOMMENDATION

CANAKINUMAB

(Ilaris – Novartis Pharmaceuticals Canada Inc.)

Indication: Cryopyrin-Associated Periodic Syndromes

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that canakinumab not be listed.

Reasons for the Recommendation:

1. One 24-week double-blind randomized controlled trial (RCT) in 31 patients with Muckle-Wells Syndrome (MWS) reported statistically significantly less episodes of disease flare in patients treated with canakinumab compared with placebo; however, there were no statistically significant between-treatment differences in patient global assessment of symptoms or quality of life.
2. None of the RCT or open-label studies reviewed by CEDAC provided evidence that canakinumab treatment reduces or reverses severe disease complications. Given the limited evidence available it is unclear if potential benefits exceed potential harms from this lifelong treatment.

Of Note:

1. There are differing clinical opinions regarding the use of canakinumab in the treatment of flare versus continuous treatment; however, there are no RCTs comparing these different treatment approaches.
2. The definition of complete response in the clinical trials was not validated, and the Committee expressed concern regarding the absence of measures to evaluate partial as well as complete response.
3. As the majority of trial participants were diagnosed with MWS, there are limited data regarding effects of canakinumab in familial cold autoinflammatory syndrome (FCAS) or neonatal-onset multisystem inflammatory disease (NOMID).
4. Cryopyrin-associated periodic syndromes (CAPS) is a rare disease condition. Using conventional criteria, canakinumab has not been shown to be cost-effective, though cost-effectiveness is only one factor that is used by drug plans in making funding decisions. It has

Common Drug Review

been argued that the costs of drugs to treat rare diseases are often high because of the relatively small number of patients for whom the drug is indicated.

Background:

CAPS is a heterogeneous group of extremely rare autosomal-dominant, autoinflammatory diseases. Canakinumab is a human interleukin (IL)-1 beta monoclonal antibody that Health Canada approved for the ongoing management of CAPS in adults and children aged four years and older, including: FCAS or familial cold urticaria (FCU), and MWS. Canakinumab may also be used in NOMID or chronic infantile neurological, cutaneous, articular (CINCA) syndrome. Clinical data to support the use of canakinumab in patients with the NOMID phenotype are very limited.

The recommended dose of canakinumab is 150 mg for patients with body weight greater than 40 kg and 2 mg/kg for patients with body weight between 15 kg and 40 kg. For children 15 kg to 40 kg, with an inadequate response, the dose may be increased to 3 mg/kg. Canakinumab is administered every eight weeks as a subcutaneous injection. If a satisfactory clinical response (resolution of rash and other generalized inflammatory symptoms) has not been achieved seven days after treatment, a second dose of 150 mg or 2 mg/kg may be considered. The drug is available as single-use vials containing 150 mg of canakinumab.

Summary of CEDAC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs and observational studies of canakinumab, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials

The systematic review included two open-label, single-arm, observational studies (A2102 and D2306) and one study with a double-blind randomized withdrawal design (D2304) in patients with CAPS.

- A2102 (N = 34) was a dose-titration study in patients with CAPS who were four to 75 years old; phenotypes enrolled included, MWS (n = 27), FCAS (n = 2), MWS/NOMID overlap (n = 4), and NOMID (n = 1). Approximately 70% of patients reported previous anakinra use. In part one of the trial, four patients received 10 mg/kg of canakinumab intravenously; upon relapse, patients subsequently received the following doses: 1 mg/kg intravenously, followed by 150 mg subcutaneously upon subsequent relapse. In part two, all 34 patients received canakinumab subcutaneously (150 mg if older than 16 years, and 2 mg/kg if four to 16 years old); rescue doses of 5 mg/kg to 10 mg/kg could be given if no response occurs after seven days. Repeat dosing occurred with each relapse until study discontinuation or until rollover to study D2304 or D2306. Median patients exposure to canakinumab was 324 days (range 121 to 860 days).
- D2304 (N = 35) enrolled patients aged four to 75 years old with MWS. Approximately 50% of patients reported previous anakinra use. In part one of the trial (weeks zero to eight), all patients received a single dose of subcutaneous canakinumab. In part two (weeks nine to 32), patients were randomized to canakinumab or placebo every eight weeks. In part three (weeks 32 to 48) all patients received canakinumab every eight weeks. In all parts of the trial

Common Drug Review

Common Drug Review

canakinumab was administered subcutaneously in doses of 150 mg, or 2 mg/kg for patients weighing less than 40 kg.

- D2306 (N = 166) enrolled patients older than four years and the phenotypes enrolled included, MWS (n = 103), FCAS (n = 30), and MWS/NOMID overlap (n = 32). The proportion of patients with previous anakinra use was not reported. All patients received subcutaneous canakinumab every eight weeks; the usual starting dose was 150 mg (or 2 mg/kg for patients weighing 15 kg to 40 kg); however, patients with a history of requiring additional medication could be started at 300 mg (or 4 mg/kg for patients weighing 15 kg to 40 kg). Doses up to 600 mg of canakinumab every eight weeks were allowed. Minimum and maximum treatment durations were six months and two years respectively.

The lack of comparator groups in A2102 and D2306 meant these studies provided low-quality evidence; thus, the Committee focused mostly on study D2304. Although study D2304 included a double-blind treatment phase, there are likely carry-over effects from the earlier phase of the study, which makes it difficult to assess comparative treatment efficacy and harms. In addition there were between-treatment imbalances in patient characteristics between the canakinumab and placebo groups in study D2304, which may have biased the results in favour of canakinumab. The majority of patients in all three trials had MWS.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of those defined, the Committee discussed the following: quality of life, relapse, flare, global symptom severity, skin symptoms, C-reactive protein (CRP), serum amyloid A (SAA), amyloidosis, and serious adverse events.

- The primary outcome in study A2102 was time from each dose to relapse, after response was achieved.
- The primary outcome in study D2304 was the proportion of patients with disease flare in the double-blind portion of the study. Disease flare was defined as those who experienced a relapse or discontinued from part two of the trial for any reason.
- The primary outcome in D2306 was the proportion of patients who did not experience relapse.

In all three studies relapse was defined as having both of (i) CRP or SAA greater than 30 mg/L and (ii) physician global assessment of disease activity score of worse than minimal, or physician global assessment of disease activity of minimal and skin disease activity score of worse than minimal.

Patient groups identified specific problematic symptoms of CAPS, including rashes, joint pain and stiffness, and conjunctivitis. Also of concern were long-term complications of the disease, such as kidney failure, deafness, blindness, crippling arthritis, and learning disabilities. Other than rash, trials did not specifically examine individual problematic symptoms mentioned by patients. Complications of the disease were assessed through audiological, ophthalmological, neurological, and biochemistry assessments.

Common Drug Review

Results

Efficacy or Effectiveness

In all three studies, complete response (defined as physician global assessment of disease activity and skin disease assessment score of absent or minimal, and CRP and/or SAA level less than 10 mg/L) was achieved by approximately 90% of patients within approximately one week of initiation of canakinumab at Health Canada recommended doses. In the D2304 study, half of the placebo patients experienced a flare within 100 days, which was similar to the median time to relapse reported in study A2102 for the 150 mg subcutaneous dose (115 days). No evidence regarding time to relapse was available from study D2306.

The remaining efficacy data reported below are from the 24-week results of the double-blind phase of study D2304.

- Quality of life was measured using several scales; however, small differences between canakinumab and placebo that were not determined to be statistically significant were of uncertain clinical significance.
- Disease flare was statistically significantly more frequent for placebo-treated patients compared with canakinumab; 13 of 16 compared with zero of 15 patients respectively. However, the definition of flare, for predicting long-term risk of morbidity in CAPS patients, is of uncertain validity.
- Canakinumab statistically significantly improved physician global assessment of disease activity and physician assessment of skin rash compared with placebo.
- There was no statistically significant difference in patient global assessment of symptoms between canakinumab and placebo.
- There were no clear improvements with canakinumab relative to placebo for audiological, ophthalmological, or neurological outcomes.

Harms (Safety and Tolerability)

- The lack of a comparator group in A2102 and D2306, the small number of patients, and the limited duration of the double-blind phase of D2304 results in limited harms data. This is of concern for a product that may be used for many years in adults and young children.
- Serious adverse events observed in patients receiving canakinumab included, upper respiratory tract infections, vertigo, pyrexia/sepsis, abdominal abscess, appendicitis, nerve root compression, and depression.
- During the double-blind phase of D2304, there were more patients in the canakinumab group reporting adverse events related to immune system disorders; infections and infestations; injury; poisoning and procedural complications; nervous system disorders; psychiatric disorders; and respiratory, thoracic and, mediastinal disorders. There were no clear differences in the incidence of specific adverse events between canakinumab and placebo.

Cost and Cost-Effectiveness

Based on the cost containment cap proposed by the manufacturer, the annual cost of canakinumab would not exceed \$96,000 per patient (i.e., the manufacturer would cover the cost of canakinumab for patients who require more than six vials annually).

Common Drug Review

Common Drug Review

The manufacturer submitted a cost-effectiveness analysis comparing canakinumab with placebo for individuals with CAPS (FCAS, MWS, and NOMID). Clinical effectiveness was based on response rates from study D2304 part one, where response (i.e., complete response as referred to in the trial) was defined as ratings of minimal or better on both the physician global assessment of disease scale and the assessment of skin disease, and CRP and/or SAA < 10 mg/L at week eight. A government-payer perspective was used for the analysis, where only the cost of canakinumab treatment was considered.

A number of limitations with the analysis were noted, which creates uncertainty around the likely cost-effectiveness of canakinumab. The limitations include, response rate based on data from an eight-week run-in period; pooling all patients with CAPS (FCAS, MWS, and NOMID), despite differences in disease severity by phenotype; lack of clinical information for patients with NOMID; and lack of quality of life data.

Patient Input Information:

- One patient group submitted input for this review.
- It was noted that until recently the only treatment for CAPS consisted of multiple medications for the management of symptoms. Canakinumab is the first drug specifically indicated for the management of CAPS. Some Canadian patients have participated in clinical trials and been subsequently treated with anakinra (off-label) or riloncept (through compassionate access). However, the simplified administration of canakinumab (one subcutaneous injection every eight weeks) is considered an advantage compared with anakinra and riloncept, neither of which has been approved for treatment of CAPS in Canada.

Other Discussion Points:

- The lack of a diagnostic test for CAPS to guide appropriate use of the drug was noted.
- The withdrawal design of study D2304 may bias estimates of efficacy and safety.
- There was low congruence between physician global assessment of disease activity and patient global assessment of symptoms in the RCT; physician assessment was more favourable compared with patient assessment and the disparity was greatest in the canakinumab treatment group. The agreement between physician and patient global assessments during the randomized withdrawal phase of the RCT was 33% for the canakinumab group and 60% for the placebo group.
- The effect of canakinumab on skin rash was considered beneficial in comparison with placebo. The Committee questioned the validity of the global assessments, given the lack of congruence between patient and physician assessments.
- It is unknown whether canakinumab is effective at reversing organ damage due to amyloidosis in patients with advanced disease.
- The three studies are too short in duration to provide an adequate assessment of the harms of canakinumab, which is for lifelong therapy. Potential risks include those associated with other interleukin 1-beta inhibitors (e.g., neutropenia) and anti-tumour necrosis factor drugs (e.g., tuberculosis reactivation).
- The absence of therapeutic alternatives was discussed. Although treatment with anakinra is off-label, a large proportion of patients in two of the reviewed trials reported previous anakinra use.

Common Drug Review

Common Drug Review

- Individual drug plans will need to assess the logistics of how to implement the manufacturer's proposed cost containment cap.

CEDAC Members Participating:

Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, and Dr. Yvonne Shevchuk.

Regrets:

None

Conflicts of Interest:

None.

About this Document:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CEDAC Recommendation 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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Common Drug Review