Canadian Expert Drug Advisory Committee
Final Recommendation — Plain Language Version

CANAKINUMAB
(Ilaris — Novartis Pharmaceuticals Canada Inc.)
Indication: Cryopyrin-Associated Periodic Syndromes

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that Ilaris, which is also called canakinumab, not be listed by Canada's publicly funded drug plans for the treatment of cryopyrin-associated periodic syndromes (CAPS).

Reasons for the Recommendation:
1. In a study of 31 patients with Muckle-Wells Syndrome (MWS), a type of CAPS, Ilaris-treated patients were less likely to have a disease flare compared with patients treated with placebo (an injection containing no active medication). However, in the same study, Ilaris-treated patients did not report greater improvements in their symptoms or quality of life compared to patients treated with placebo.
2. None of the studies reviewed by CEDAC showed that Ilaris reduces or reverses the severe complications of CAPS. The available studies do not provide enough evidence to know if the possible benefits would be greater than the possible harmful effects of Ilaris, which is a drug that could be used for lifelong treatment.

Of Note:
1. There are different opinions about whether Ilaris could be used just to treat disease flares, rather than using Ilaris on an ongoing basis in patients with CAPS. However, no medical studies have compared these two methods of treating patients with CAPS.
2. The appropriateness of the definition of complete response used in the clinical studies was not confirmed and the Committee was concerned that the studies also did not have a definition for partial response.
3. As most of the patients in the study were diagnosed with MWS, there is not much data available regarding the effects of Ilaris in other types of CAPS, such as familial cold autoinflammatory syndrome (FCAS) or neonatal-onset multisystem inflammatory disease (NOMID).
4. CAPS is a rare disease condition. Ilaris has not been shown to provide enough health benefit to justify its cost using CEDAC's usual assessment criteria; however, cost is only one

factor that drug plans use in deciding whether to provide coverage for medications. The costs of drugs to treat rare diseases are often high because of the small number of patients for whom the medication is to be used.

Background:
In patients with CAPS, the body produces excessive amounts of a chemical messenger called interleukin-1 beta (IL-1 beta). This may lead to symptoms such as fever, headache, fatigue, skin rash, and painful joints and muscles. Some patients have more severe outcomes, such as hearing problems and reduced kidney function.

Ilaris belongs to a class of drugs called IL-1 beta inhibitors. The active substance in Ilaris is canakinumab, a fully-human monoclonal antibody. It works by binding to IL-1 beta and blocking its activity. Ilaris is approved by Health Canada for the treatment of adults and children aged four years and older, with the following autoinflammatory diseases, which together are known as CAPS, including FCAS (which is also called familial cold urticaria [FCU]) and MWS. Ilaris may also be used in NOMID (which is also called chronic infantile neurological, cutaneous, articular [CINCA] syndrome), but there is only a small amount of supportive evidence from medical studies of patients with this type of CAPS.

Ilaris is supplied as a powder which is to be made into a solution for injection. It is provided in a single-use vial. One vial of powder contains 150 mg canakinumab. The recommended dose of Ilaris is 150 mg for patients with a body weight greater than 40 kg, and 2 mg/kg for patients with body weight between 15 kg and 40 kg. For children between 15 kg and 40 kg who do not show enough improvement on the 2 mg/kg dose, the dose may be increased to 3 mg/kg. Ilaris is administered every eight weeks as an injection under the skin. If there is not enough improvement seven days after treatment (that is, the rash has not gone and other symptoms of inflammation are still present), a second dose of 150 mg or 2 mg/kg may be given.

Summary of CEDAC Considerations:
To make their decision, the Committee considered the following information prepared by the Common Drug Review (CDR): a review of the medical studies of Ilaris and a review of the economic information prepared by the manufacturer of Ilaris. Also, CEDAC considered information that patient groups submitted about outcomes and issues important to patients who have the condition for which the drug is indicated or who might use the drug.

Clinical Trials
CEDAC reviewed three studies in which 235 patients with CAPS received at least one dose of Ilaris. The review included two studies (A2102, D2306) where all of the patients were on Ilaris, and were aware that they were on this treatment, and one study (D2304) that compared Ilaris with placebo.

- Study A2102, which included 34 patients, was a study looking at the effect of different doses of Ilaris in CAPS patients aged four to 75 years; 27 patients had MWS, two patients had FCAS, four patients had MWS/NOMID overlap, and one patient had NOMID. Approximately 70% of patients had previously used Kineret (anakinra). In part one, four patients were given 10 mg/kg of Ilaris intravenously; when the symptoms recurred, the patients then received the following doses: 1 mg/kg intravenously, followed by 150 mg injected under the skin if the

symptoms recurred again. In part two, all 34 patients received Ilaris under the skin (150 mg if the patient was older than 16 years, and 2 mg/kg if the patient was four to 16 years old); also additional doses of 5 mg/kg to 10 mg/kg could be given if there was no improvement after seven days. Doses could be repeated each time the patient's symptoms recurred until patients stopped participating in the study, or patients entered study D2304 or D2306. The average number of days that the patients used Ilaris was 324 days (with a range of 121 to 860 days).

- Study D2304 included 35 patients aged four to 75 years with MWS. Approximately 50% of patients had previously used Kineret. In part one (weeks zero to eight), all patients received a single dose of Ilaris injected under the skin. In part two (weeks nine to 32) patients received either Ilaris or placebo every eight weeks. In part three (weeks 32 to 48) all patients received Ilaris every eight weeks. In all parts of the study, Ilaris was injected under the skin, in doses of 150 mg, or 2 mg/kg for patients weighing less than 40 kg.
- Study D2306 included 166 patients older than four years; there were 103 patients with MWS, 30 patients with FCAS, and 32 patients with MWS/NOMID overlap. It is not known how many patients had previously used Kineret. All patients were given Ilaris injected under the skin, every eight weeks; the usual starting dose was 150 mg (or 2 mg/kg for patients weighing 15 kg to 40 kg); however, patients who had previously needed additional medication could be started at 300 mg (or 4 mg/kg for patients weighing 15 kg to 40 kg). Doses of up to 600 mg of Ilaris every eight weeks were allowed. The length of treatment for the patients ranged from six months to two years.

As all patients in studies A2102 and D2306 were on Ilaris, a comparison with other treatments could not be made. Therefore, the information provided by studies A2102 and D2306 was not of good quality. Thus, CEDAC focused on the information provided by study D2304. Although study D2304 included a part where patients were either on Ilaris or on placebo, patients had already been on Ilaris earlier in the study and the effects of Ilaris could still be present, making it difficult to assess how well Ilaris was working as compared with placebo. Also, the characteristics of the patients were different between the Ilaris and placebo groups in study D2304, which may have biased the results in favour of Ilaris. The majority of patients in all three studies had MWS.

Outcomes

Outcomes of interest were defined in advance in the CDR systematic review protocol. Of these, the Committee discussed the following: quality of life, relapse, flare, global symptom severity, skin symptoms, C-reactive protein (CRP), serum amyloid A (SAA), amyloidosis (deposits of protein material in body tissues), and serious side effects.

- The main purpose of study A2102 was to measure the time from each dose to relapse, after improvement was achieved.
- The main purpose of study D2304 was to measure the percentage of patients with disease flare in the part of the study where Ilaris was being compared with placebo.
- The main purpose of study D2306 was to measure the percentage of patients who did not have a relapse.

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

global assessment of disease activity of minimal and skin disease activity of worse than minimal. In study D2304 patients were considered to have a flare if they either had a relapse (as defined above) or stopped participation in the study for any reason.

Patient groups identified certain symptoms of CAPS that cause problems, including rashes, joint pain and stiffness, and conjunctivitis (inflammation of eyelid membranes). Also of concern were long-term complications of the disease, such as kidney failure, deafness, blindness, crippling arthritis, and learning disabilities. Other than rash, studies did not specifically look at the symptoms mentioned by patients. Complications of the disease were assessed through hearing tests, eye tests, nerve tests, and blood tests.

Results

Efficacy or Effectiveness

- In all three studies, complete response (defined as having both a score of absent [not present] or minimal, for both the physician global assessment of disease activity and the skin disease assessment, and having the CRP and/or SAA level less than 10 mg/L) was reached by around 90% of patients within one week or so of starting Ilaris at Health Canada-recommended doses. In the D2304 study, half of the placebo patients experienced a disease flare within 100 days, which was similar to the average time to relapse shown in study A2102 for the 150 mg dose injected under the skin (115 days). The length of time to relapse was not available from study D2306.

Results regarding how well Ilaris works compared with placebo, from study D2304 (24-week data), are listed below:

- Quality of life was measured using several scales; however, there were only small differences between Ilaris and placebo, which may not be of importance to patients.
- Placebo-treated patients had a disease flare more often than Ilaris-treated patients; 13 of 16 patients compared with 0 of 15 patients respectively. However, it is not known if the definition of flare used for these studies can be used to predict the severity of CAPS in the long-term future.
- Ilaris improved physician global assessment of disease activity and physician assessment of skin rash compared with placebo.
- There was no difference in patient global assessment of symptoms between Ilaris and placebo.
- There were no clear improvements with Ilaris compared with placebo for hearing, eye, or nerve test results.

Harms (Safety and Tolerability)

- There is only a small amount of information about the possible harms of Ilaris because Ilaris was not compared with any other treatment in studies A2102 and D2306, and there was only a small number of patients for a short period of time in study D2304 where Ilaris was compared with placebo. This is of particular concern as this is a product that may be used for many years in adults and young children.
- Serious side effects seen in patients receiving Ilaris included: upper respiratory tract infections (common cold), vertigo (dizziness), pyrexia/sepsis (fever/blood infection),

abdominal abscess, appendicitis, nerve root compression (squashing of the nerve as it comes out of the spine), and depression.
- During the part of study D2304 that compared Ilaris with placebo, more patients in the Ilaris group had side effects related to the immune system; infections and infestations; injuries, poisonings and complications from tests; nervous system disorders; psychiatric disorders; and respiratory (lung), thoracic (chest), and mediastinal (centre of chest) disorders. There were no clear differences between Ilaris and placebo in the amount of specific side effects.

Cost and Cost-Effectiveness

Based on the cost containment cap proposed by the manufacturer, the yearly cost of Ilaris would not be greater than $96,000 per patient. That is, for patients who required more than six vials per year, the manufacturer would cover the additional cost that would result.

The manufacturer submitted economic information to compare Ilaris with placebo to evaluate the health benefit for individuals with CAPS (FCAS, MWS, and NOMID). The data used to calculate how well Ilaris works were based on response rates from part one of study D2304, where response was defined as ratings of minimal or better on both the physician global assessment of disease activity and the assessment of skin disease scales, and CRP and/or SAA less than 10 mg/L at week eight. A government-payer point of view was used for the analysis, where only the cost of Ilaris treatment was taken into account.

There are a few problems with the analysis, which make it difficult to decide if Ilaris is cost effective: the data regarding how well Ilaris works are based on data collected after an eight-week period where all patients received Ilaris, data from patients with all types of CAPS were combined even though these diseases can vary in severity; also there is only a little information for patients with the NOMID type of CAPS and there is a 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 various medications to manage the symptoms. Ilaris is the first medicine specifically indicated for the treatment of CAPS. Some Canadian patients have taken part in medical studies and later have been treated with Kineret (even though Health Canada has not approved Kineret for the treatment of CAPS) or rilonacept, also called Arcalyst, (through compassionate access). However, it is much easier to take Ilaris (one subcutaneous injection every eight weeks) compared with Kineret or Arcalyst, neither of which has been approved for treatment of CAPS in Canada.

Other Discussion Points:

- There is no specific test to diagnose CAPS that would help to guide the proper use of Ilaris.
- In part two of study D2304, the measurement of the difference between Ilaris and placebo, in terms of benefits and harms, may not have been accurate because all patients had recently been treated with Ilaris.

- There was low agreement between physician global assessment of disease activity and patient global assessment of symptoms in the study comparing Ilaris with placebo; physician assessment was more favourable compared with patient assessment and this difference was the greatest in the Ilaris treatment group. The agreement between physician and patient global assessments during the part of the study that compared Ilaris with placebo was 33% for the Ilaris group and 60% for the placebo group.
- Ilaris was better than placebo in treating skin rash. The Committee questioned how accurate the global assessments were, as the results of the patient assessments were different from those of the physicians.
- It is unknown if Ilaris can reverse damage to organs that results from amyloidosis (deposits of protein material in body tissues) in patients who have had severe CAPS for a long time.
- The length of time of the three studies was too short to provide enough evidence of the possible side effects of Ilaris, which may be used for life. The Committee considered that side effects that have occurred with other IL-1 beta inhibitors (e.g., low white blood cells) or anti-tumour necrosis factor drugs (e.g., reactivation of tuberculosis) may occur with Ilaris.
- The lack of other treatments was discussed. Although Health Canada has not approved the use of Kineret for CAPS, a large percentage of patients in two of the studies that were reviewed had previously used Kineret.

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

The information contained within this plain language version of the Canadian Expert Drug Advisory Committee (CEDAC) Recommendation about this drug is based on the information found within the corresponding technical version of the CEDAC Recommendation.

In making its recommendation, CEDAC considered the best clinical and pharmacoeconomic evidence available, up to that time. Health care professionals and those requiring more detailed information are advised to refer to the technical version available in the CDR Drug Database on the CADTH website (www.cadth.ca).

Background on CEDAC
CEDAC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). The Committee is made up of drug evaluation experts and public members. CEDAC provides recommendations about whether or not drugs should be listed for coverage through the participating publicly funded drug plans; however, the individual drug plans make their own decision about whether or not to cover a drug.

In making its recommendations, CEDAC decides if the drug under review ought to be covered by the participating public drug plans based on an evidence-informed review of the medication's effectiveness and safety, and based on an assessment of its cost-effectiveness in comparison with other available treatments. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

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The manufacturer has reviewed this document and has not requested the deletion of any confidential information.