



## CDEC FINAL RECOMMENDATION

### TOCILIZUMAB

(Actemra — Hoffmann-La Roche Limited)

**New Indication: Polyarticular Juvenile Idiopathic Arthritis**

#### **Recommendation:**

The Canadian Drug Expert Committee (CDEC) recommends that tocilizumab be listed for the treatment of polyarticular juvenile idiopathic arthritis (pJIA) if the following clinical criterion and condition are met:

#### **Clinical Criterion:**

- Inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs).

#### **Condition:**

- Treatment should be initiated by a rheumatologist who is familiar with the use of DMARDs and/or biologic DMARDs in children.

#### **Reasons for the Recommendation:**

1. One double-blind randomized controlled trial (RCT) (CHERISH; N = 166) demonstrated that tocilizumab was superior to placebo for reducing the occurrence of disease flare in children with pJIA.
2. At the submitted price, tocilizumab is less costly than alternative biologic drugs currently available for patients weighing 34 kg to 75 kg.

#### **Of Note:**

CDEC noted that the CHERISH trial had a short duration and a relatively small sample size compared with tocilizumab trials that were conducted in adult populations, and expressed concern about the limited long-term safety data for the use of tocilizumab in children with pJIA.

#### **Background:**

Tocilizumab is a recombinant anti-human interleukin-6 (IL-6) receptor immunoglobulin monoclonal antibody indicated for use in the treatment of patients with rheumatoid arthritis, systemic juvenile idiopathic arthritis, and pJIA. This submission for tocilizumab is for the

treatment of active pJIA in patients two years of age and older, who have responded inadequately to previous therapy with one or more DMARDs and systemic corticosteroids.

Tocilizumab is available as a 20 mg/mL concentrate solution for intravenous (IV) infusion in single-dose vials of 4 mL (80 mg), 10 mL (200 mg), and 20 mL (400 mg). The dose recommended in the product monograph for pJIA is 8 mg/kg (for patients  $\geq$  30 kg) or 10 mg/kg (for patients < 30 kg) every four weeks by IV infusion. Tocilizumab should be given in combination with methotrexate (MTX), but may be given as monotherapy in cases of intolerance to MTX or where treatment with MTX is not appropriate.

### Submission History

Tocilizumab was previously reviewed by the Canadian Expert Drug Advisory Committee (CEDAC) for the treatment of patients with moderately to severely active rheumatoid arthritis and received a recommendation to “list with criteria/condition” (see Notice of CEDAC Final Recommendation, November 17, 2010). Tocilizumab was subsequently reviewed in 2012 for active systemic juvenile idiopathic arthritis and received a recommendation to list in patients two years of age and older who have responded inadequately to non-steroidal anti-inflammatory drugs and systemic corticosteroids (with or without MTX), due to intolerance or lack of efficacy (see *Notice of CDEC Final Recommendation*, July 19, 2012).

### Summary of CDEC Considerations

CDEC considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs for tocilizumab in pJIA, a critique of the manufacturer’s pharmaco-economic evaluation, and patient group-submitted information about outcomes and issues important to patients.

### Patient Input Information

The following is a summary of key information provided by three patient groups that responded to the CDR call for patient input:

- Individuals with pJIA commonly endure inflammation, chronic pain, limited range of motion in joints, and fatigue, which affect their day-to-day functioning. If left untreated, pJIA may result in permanent joint damage and a lifetime of disability.
- Children and youth with pJIA are often unable to participate fully, if at all, in social and recreational activities with their peers and have difficulty with common tasks at home and in school. Isolation and anxiety commonly result.
- Some individuals do well with currently available treatments such as MTX and other biologics. On the other hand, some patients experience nausea while taking MTX and that the treatment effect weans over time. Still, the patient groups regard biologics as the most effective of currently available therapies.
- Tocilizumab would add another treatment option for those with pJIA who do not adequately respond to currently available therapies, including other biologics.

### Clinical Trials

The CDR systematic review included one double-blind, manufacturer-sponsored, placebo-controlled RCT. The CHERISH study (N = 166) evaluated the efficacy and safety of tocilizumab, as monotherapy or in combination with MTX, compared with placebo in patients with active pJIA who had previously experienced an inadequate response or intolerance to MTX. Tocilizumab

was administered intravenously at dosages of 8 mg/kg or 10 mg/kg for patients who were < 30 kg and 8 mg/kg for patients who were ≥ 30 kg. After an initial 16-week open-label lead-in phase where all patients received tocilizumab treatment, patients that demonstrated a JIA American College of Rheumatology (ACR) 30 response entered the 24-week double-blind phase where they were randomized (1:1) to tocilizumab or placebo with stratification by concomitant MTX and oral glucocorticoid use. Patients who completed the double-blind phase, or who escaped due to a disease flare during the double-blind phase were eligible to enter a 64-week open-label extension phase. During the double-blind phase, patients were treated for a mean of 20.4 weeks with tocilizumab and 17.7 weeks with placebo.

### Outcomes

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

- Disease flare — defined as a worsening of ≥ 30% in at least three of the six JIA ACR core criteria, in addition to a ≥ 30% improvement in no more than one JIA ACR criterion. The JIA ACR core components are as follows:
  - Physician’s global assessment of disease activity — measured on a 0 to 100 visual analogue scale.
  - Patient’s or parent’s global assessment of overall well-being — measured using a 0 to 100 visual analogue scale.
  - Number of joints with active arthritis — defined as a swelling or, in the absence of swelling, limitation of movement accompanied by pain.
  - Number of joints with limitation of movement.
  - Physical function — measured using the Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI).
  - Laboratory assessment of inflammation (erythrocyte sedimentation rate).
- JIA ACR 30, 50, 70, or 90 responses — defined as an improvement of at least 30%, 50%, 70%, or 90% in at least three of the six JIA ACR core criteria, and a worsening of ≥ 30% in no more than one of the criterion.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The primary efficacy outcome was the proportion of patients who developed a JIA ACR 30 flare relative to week 16 in the double-blind phase (week 16 to week 40).

### Efficacy

- The proportion of patients who experienced a JIA ACR 30 flare during the double-blind phase was statistically significantly less in the tocilizumab group compared with the placebo group (25.6% versus 48.1%; adjusted risk difference [RD] -0.21, 95% confidence interval [CI]: -0.35 to -0.08).
- The proportion of patients who demonstrated ACR responses was statistically significantly greater in the tocilizumab group compared with the placebo group:
  - JIA ACR 30 response: 74.4% versus 54.3% ( [REDACTED] )
  - JIA ACR 50 response: 73.2% versus 51.9% ( [REDACTED] )
  - JIA ACR 70 response: 64.6% versus 42.0% ( [REDACTED] )
  - JIA ACR 90 response: 45.1% versus 23.5% ( [REDACTED] ).

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## Common Drug Review

**Harms (Safety and Tolerability)**

- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

**Cost and Cost-Effectiveness**

The manufacturer submitted a cost-minimization analysis (CMA) comparing tocilizumab with etanercept pre-filled syringes (50 mg per week; \$20,207 annual cost for an average weight patient of 40 kg), adalimumab (40 mg every two weeks; \$18,965 annual cost for an average weight patient of 40 kg), abatacept (10 mg/kg to 1,000 mg every four weeks; \$12,491 annual cost for an average weight patient of 40 kg after year 1), and two different regimens of infliximab (3 mg/kg and 6 mg/kg every eight weeks; \$12,587 and \$18,880 annual cost, respectively, for an average weight patient of 40 kg after year 1) in pJIA patients. Infliximab is not indicated for use in pJIA in Canada, although it is reimbursed for pJIA under exceptional access programs in British Columbia and Ontario. CDR considered etanercept multi-use vials (50 mg per week; \$12,786 annual cost for an average weight patient of 40 kg) to also be a valid comparator.

The perspective of the manufacturer’s CMA was that of a public drug plan and considered annual costs per patient for the first and subsequent years of treatment, and the average annual cost of treatment for the first three years. Only drug and administration costs were considered.

Based on the manufacturer’s analysis, the average annual cost of the first three years for treating an average weight child with pJIA with tocilizumab was less than each of the selected comparators. However, the following limitations with the manufacturer’s analysis were noted:

- overestimation of the cost for the initial year for a patient with pJIA receiving abatacept
- lack of cost discounting beyond one year
- failure to calculate relative costs for a range of body weights rather than an average weight-based dose.

CDR recalculated the relative treatment costs after correcting for the above limitations. The results of the CDR calculations indicated that, at the current marketed prices of \$179.20 (80 mg vial), \$448 (200 mg vial), and \$896 (400 mg vial), tocilizumab is the least expensive treatment for patients with pJIA who weigh between 34 kg and 75 kg, but tocilizumab is more expensive than abatacept, adalimumab, and etanercept in patients with pJIA who weigh more than 75 kg (CDR analyses). Tocilizumab may be more expensive than abatacept, etanercept multi-use vials, and 3 mg/kg infliximab in patients with pJIA who weigh less than 34 kg. Given the distribution of body weights in pJIA patients, it is likely that reimbursement of tocilizumab for pJIA would result in cost savings to public drug plans.

### Other Discussion Points:

CDEC noted the following:

- Tocilizumab is indicated for the treatment of pJIA in patients who responded inadequately to previous therapy with one or more DMARDs and systemic corticosteroids. When establishing the clinical criteria for this recommendation, CDEC discussed the issue of patients requiring an inadequate response to previous steroid therapy and noted the following: an inadequate response to previous steroid therapy is difficult to define in the context of pJIA; and, reducing the need for corticosteroids is an important goal of treating children with juvenile idiopathic arthritis. Based on these considerations, CDEC concluded that an inadequate response to systemic corticosteroids should not be included in the clinical criteria for this recommendation.
- Patients who did not achieve a JIA ACR 30 response in the open-label lead-in phase of the CHERISH trial did not continue into the double-blind phase. Therefore, the response rates reported may be higher than would be expected in a non-enriched or tocilizumab-naive population.
- The double-blind treatment phase of the CHERISH trial was limited to 24 weeks; therefore, the long-term efficacy of tocilizumab in the treatment of pJIA is uncertain.

### Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- There are no direct comparisons of tocilizumab with other biologic drugs approved for the treatment of pJIA.
- The long-term safety of tocilizumab has not been established in children with pJIA.

### CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

### February 19, 2014 Meeting

#### Regrets:

One CDEC member could not attend the meeting.

#### 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 in conformity with the *CDR Confidentiality Guidelines*.

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## Common Drug Review

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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