CDEC FINAL RECOMMENDATION

TOCILIZUMAB
(Actemra — Hoffmann-La Roche)
New Indication: Arthritis, Systemic Juvenile Idiopathic

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that tocilizumab be listed for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients two years of age and older who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids (with or without methotrexate), due to intolerance or lack of efficacy.

Reason for the Recommendation:
Clinically and statistically significant improvements in sJIA symptoms favouring tocilizumab compared with placebo were reported in one multinational, double-blind randomized controlled trial (RCT) of patients with sJIA who had an inadequate response to NSAID and corticosteroid treatment. In another double-blind RCT of sJIA patients, the percentage of patients that maintained a therapeutic response was statistically significantly higher for patients continued on tocilizumab compared with those switched to placebo.

Of Note:
1. The Committee considered that tocilizumab should be used in patients who are under the care of a clinical team experienced in the treatment of patients with sJIA.
2. The Committee noted that the two reviewed trials were of short duration and had small sample sizes compared with tocilizumab trials in adults. The Committee expressed concern about the limited harms data, given that tocilizumab may be used for extended periods.

Background:
This submission for tocilizumab is for the new Health Canada indication for the treatment of active sJIA in patients two years of age and older, who have responded inadequately to previous therapy with one or more NSAIDs and systemic corticosteroids.

Tocilizumab is a recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass. It is available as a 20 mg/mL 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 by Health Canada for this indication is 8 mg/kg (for patients ≥ 30 kg) or 12 mg/kg (for patients < 30 kg) every two weeks by IV infusion.

Submission History:
Tocilizumab was previously reviewed for reducing signs and symptoms in adult patients with moderate-to-severely active rheumatoid arthritis and received a recommendation to list for adults with moderate-to-severely active rheumatoid arthritis who have failed to respond to an adequate trial of both disease-modifying antirheumatic drugs (DMARDs) and a tumour necrosis factor (TNF)-alpha inhibitor (see Notice of CEDAC Final Recommendation, November 17, 2010).

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of tocilizumab, 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 phase 3, double-blind RCTs of patients with sJIA.

- TENDER (N = 112) was conducted at 43 centres in 17 countries. Patients were randomized (2:1) to receive tocilizumab IV (8 mg/kg for patients ≥ 30 kg or 12 mg/kg for patients < 30 kg) or placebo every two weeks for 12 weeks.
- Study 316 (N = 56) was conducted at eight sites in Japan. It consisted of a six-week open-label phase in which all patients received tocilizumab IV, 8 mg/kg every two weeks for six weeks, after which patients who demonstrated response were randomized to either continued treatment with tocilizumab at the same dose, or placebo for an additional 12 weeks.

Trials were comprised mainly of patients who had responded inadequately to NSAIDs, corticosteroids, and methotrexate. Both studies 316 and TENDER specified early escape criteria wherein patients could be switched from their randomized treatment to open-label treatment with tocilizumab if their symptoms deteriorated from baseline or they failed to demonstrate an adequate response to treatment. The percentage of patients who received early escape treatment was higher for the placebo groups compared with the tocilizumab groups, in both studies 316 and TENDER; 78% versus 14%, and 54% versus 1% respectively.

Limitations include the uncertain generalizability of study 316 to the Canadian setting given that the trial was conducted solely in Japan and did not include a dose of 12 mg/kg for patients less than 30 kg. Finally, included trials did not report quality of life measures, and there were no head-to-head trials comparing tocilizumab with other biological or non-biological DMARD therapies.

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: JIA American College of Rheumatology (ACR) criteria, systemic features of JIA (i.e., fever and rash), pain, and adverse events.

JIA ACR response criteria include the following six components: parent/patient global assessment of overall well-being, physician global assessment of disease, number of joints with active arthritis, number of joints with limitation of movement, erythrocyte sedimentation rate, and the Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI). Patients were deemed to have achieved a JIA ACR 30, 50, 70, or 90 response if three of the six core components had improved by 30%, 50%, 70%, or 90% respectively, with no more than one of the remaining variables worsening by more than 30%.

The primary end point of the TENDER study was the proportion of patients with a JIA ACR 30 response with an absence of fever at end point. The primary end point in study 316 was the proportion of patients who completed the 12-week, double-blind treatment period and maintained a JIA ACR 30 response and C-reactive protein (CRP) concentrations of < 15 mg/L.

Results

Due to the uncertain generalizability of study 316, the Committee focused its discussion on the TENDER study. Thus, the following results reported are specific to the TENDER study, unless otherwise indicated.

Efficacy

Compared with placebo, patients treated with tocilizumab demonstrated statistically significant improvements in the following:

- proportion of patients with a JIA ACR 30 response with absence of fever at end point (85% versus 24%)
- proportion of patients achieving JIA ACR 50, ACR 70, and ACR 90 response criteria; 85% versus 11%, 71% versus 8%, and 37% versus 5% respectively
- proportion of patients with a reduction in corticosteroid dosage of ≥ 20% without subsequent JIA ACR 30 flare or occurrence of systemic symptoms (24% versus 3%)
- proportion of patients with fever or rash at baseline who were free of fever (85% versus 21%) or rash (64% versus 11%) in the 14 days before the end point.

Examination of the components of the JIA ACR criteria revealed that, compared with placebo, patients treated with tocilizumab demonstrated statistically significant improvements in the following: joints with active arthritis, joints with limitation of movement, global assessment of disease activity; global assessment of overall well-being, physical function as assessed by the CHAQ-DI, and erythrocyte sedimentation rate.

Mean change from baseline in visual analogue scale pain scores (improvements) were statistically significantly greater for tocilizumab compared with placebo.

In study 316, compared with placebo, a statistically significantly greater proportion of tocilizumab-treated patients completed the 12-week, double-blind phase and maintained a JIA ACR 30 response with a CRP concentration of < 15 mg/L; 80% versus 17%.

Harms (Safety and Tolerability)

- The percentage of patients experiencing adverse events was 88% in the tocilizumab group compared with 62% for placebo. The most frequently reported adverse events in tocilizumab-treated patients were upper respiratory tract infection, headache, nasopharyngitis, and diarrhea.
- Three patients treated with tocilizumab experienced a total of four serious adverse events including bacterial arthritis, urticaria and angioedema, and varicella. No serious adverse events were reported in the placebo group.
- Two patients were withdrawn as a result of adverse events during the 12-week treatment phase. One patient randomized to tocilizumab 12 mg/kg was withdrawn after experiencing angioedema during infusion. One patient who was randomized to the placebo group and escaped to open-label tocilizumab 12 mg/kg was withdrawn after experiencing macrophage activation syndrome.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing tocilizumab with methotrexate in the base-case analysis over a 16-year time horizon. The manufacturer considered a cohort of patients two years of age, who were followed until they were 18, with disease severity similar to that observed in the TENDER trial. ACR scores from the 12-week TENDER trial were correlated with changes in the CHAQ, assuming CHAQ is equivalent to the HAQ (adult measure), and mapped to the European Quality of Life-5 Dimension (EQ-5D) scale. The manufacturer reported an incremental cost per quality-adjusted life-year (QALY) of $69,845 for tocilizumab (with or without methotrexate) compared with methotrexate.

CDR noted the following limitations with the manufacturer's analysis: correlations between ACR scores with quality of life have not been validated; the 12-week TENDER trial was used to predict long-term efficacy; harms were not considered in the model; and, the patient population considered may reflect a more severe patient population. CDR estimates that if the average age of patients that initiate treatment is older (with greater body weight), the incremental cost per QALY would increase to $99,631, given weight-based dosing for tocilizumab.

The average daily cost of tocilizumab is $44.80 to $108.80, depending on the weight of the patient (12 mg/kg for patients < 30 kg and 8 mg/kg for patients ≥ 30 kg).

Patient Input Information:

The following is a summary of information provided by two patient groups that responded to the CDR Call for Patient Input.

- Symptoms of concern to patients and caregivers include pain and joint inflammation. These, coupled with the unpredictable nature of flares, were noted to negatively affect school attendance, and participation in recreational and social activities, resulting in reduced quality of life.
- Patients and their caregivers are concerned with the adverse effects of long-term use of NSAIDs, opioid pain medications, acetaminophen, corticosteroids, and methotrexate.

Other Discussion Points:

- The Committee expressed concern regarding the cost and the cost-effectiveness estimates which exceed generally accepted thresholds.

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. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

June 20, 2012 Meeting

Regrets:
None

Conflicts of Interest:
None

About this Document:
CDEC 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 CDEC made its recommendation. 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 not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CDEC 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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