CDEC FINAL RECOMMENDATION

TOCILIZUMAB
(Actemra — Hoffmann-La Roche Limited)
Indication: Rheumatoid Arthritis

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that subcutaneous (SC) tocilizumab be listed for the treatment of patients with moderately to severely active rheumatoid arthritis (RA) who have an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs), tumour necrosis factor (TNF) antagonists, or both DMARDs and TNF antagonists, if the following conditions are met:

Conditions:
- List in a manner similar to intravenous (IV) tocilizumab.
- The overall drug plan cost of treatment with SC tocilizumab should not exceed the overall drug plan cost of treatment with IV tocilizumab.

Reasons for the Recommendation:

1. One double-blind randomized controlled trial (RCT) (SUMMACTA; N = 1,262) demonstrated that SC tocilizumab (162 mg once per week) was non-inferior to IV tocilizumab (8 mg/kg once every four weeks) for achieving an American College of Rheumatology (ACR) 20 response in patients receiving non-biologic DMARDs. A second double-blind RCT (MUSASHI; N = 348) demonstrated that tocilizumab SC (162 mg once every two weeks) was non-inferior to tocilizumab IV (8 mg/kg every four weeks) in patients who were not receiving concomitant DMARDs.
2. One double-blind RCT (BREVACTA; N = 656) demonstrated that SC tocilizumab (162 mg once every two weeks) was superior to placebo for achieving ACR20, ACR50, and ACR70 responses, inducing remission, and improving physical functioning and quality of life.
3. The comparative cost of tocilizumab SC with tocilizumab IV will depend on the proportion of patients who receive weekly versus every-other-week treatment and patients' body weight. At the submitted price ($355.00 per 162 mg/0.9 mL pre-filled syringe), assuming a weight of 75 kg, for the first year of treatment, tocilizumab SC is more costly than tocilizumab IV (4 mg/kg and 8 mg/kg every four weeks).

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Background:
Tocilizumab is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody indicated for use in the treatment of RA, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis. This CADTH Common Drug Review (CDR) submission is for the SC formulation of tocilizumab, for the treatment of adult patients with moderately to severely active RA who have an inadequate response to one or more DMARDs, tumour necrosis factor (TNF) antagonists, or both DMARDs and TNF antagonists.

Tocilizumab is available as a 162 mg/0.9 mL solution for SC injection, in a single-use pre-filled syringe, and in single-use vials containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL of tocilizumab for IV infusion. The product monograph recommends the following dosage regimen for the SC formulation: 162 mg administered every other week, followed by an increase to every week based on clinical response for patients weighing less than 100 kg, and 162 mg administered every week for patients at or above a weight of 100 kg.

Summary of CDEC Considerations:
CDEC considered the following information prepared by 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 that are important to individuals living with RA.

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:

- Patient groups emphasized that having a range of treatment options increases the likelihood that individuals with RA will have access to an affordable and effective medication with fewer side effects.
- Patients reported a preference for SC administration because the drug can be self-administered, which would enhance their freedom and control over the management of their disease. Being able to take the drug at home rather than having to travel to a clinic for IV infusion appeals particularly to patients in rural and remote areas. In addition to greater convenience, patients also indicated that SC administration could be more comfortable than IV administration, especially for patients with hard-to-access veins.
- Currently available therapies are limited by adverse effects, high cost, and a significant paperwork burden required by provincial drug plans to receive approval for drug coverage.

Clinical Trials
The systematic review included three multi-centre, randomized, double-blind, phase 3 trials:

- The SUMMACTA trial (N = 1,262) was a double-dummy non-inferiority trial comparing tocilizumab SC 162 mg once weekly in combination with non-biologic DMARDs to tocilizumab IV 8 mg/kg every four weeks in combination with non-biologic DMARDs.
- The MUSASHI trial (N = 348) was a double-dummy non-inferiority trial comparing tocilizumab SC 162 mg monotherapy once every two weeks to tocilizumab IV 8 mg/kg monotherapy every four weeks.
- The BREVACTA trial (N = 656) was a superiority trial comparing tocilizumab SC 162 mg every two weeks in combination with non-biologic DMARDs to placebo every two weeks in combination with non-biologic DMARDs.

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Adult patients with moderately to severely active RA who had an inadequate response to DMARD therapy were included in the trials, with the percentage of patients who had failed at least one TNF inhibitor capped at approximately 20%. All studies were blinded during the first 24 weeks, after which all patients were re-randomized to an open-label treatment period.

Outcomes

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

- ACR 20 response — improvement of 20% or more from baseline in both the tender joint count (68 joints) and swollen joint count (66 joints), as well as for three of the additional five ACR core set variables: patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, Health Assessment Questionnaire (HAQ), and acute-phase reactant (either C-reactive protein or erythrocyte sedimentation rate).
- ACR 50 and 70 response — 50% or 70% improvement from baseline in swollen and tender joint counts, plus a 50% or 70% improvement in three of the five other ACR components.
- Disease Activity Score (DAS) 28-ESR — a measure of disease activity based on tender and swollen joint counts, patient global assessment, and erythrocyte sedimentation rate (ESR). A DAS 28 score of 5.1 or greater indicates high disease activity, while a score of less than 3.2 is defined as low disease activity and a score of less than 2.6 is defined as remission.
- The HAQ Disability Index (DI) — an instrument composed of the following eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. The average score of all eight categories represents the overall HAQ-DI and can range from 0 to 3 to describe no disability to completely disabled, respectively.
- The Short-Form 36-Item Health Survey (SF-36) — a generic HAQ that is used to study the impact of chronic disease on health-related quality of life. The SF-36 consists of eight sub-domains: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations due to physical and emotional problems. The SF-36 also provides two component summaries, the physical component score (PCS) and mental component score (MCS).

The primary efficacy end point for all three studies was the proportion of patients achieving an ACR 20 response at week 24. The SUMMACTA and MUSASHI trials employed a non-inferiority design for the primary efficacy end point, with pre-specified non-inferiority margins of 12% and 18%, respectively.

Efficacy

Tocilizumab in combination with non-biologic DMARDs

Tocilizumab SC once per week versus tocilizumab IV (SUMMACTA)

- The proportion of patients achieving an ACR 20 response at week 24 was 69.4% in the tocilizumab SC group and 73.4% in the tocilizumab IV group, resulting in a between-treatment difference of −4.0% (95% confidence interval [CI], −9.2 to 1.2) in the per-protocol analysis and −2.7% (95% CI, −7.6 to 2.2) in the intention-to-treat analysis, which met pre-specified non-inferiority criteria.
- There was no statistically significant difference between the tocilizumab SC and IV groups for the proportion of patients with ACR 50 or ACR 70 responses at 24 weeks.
- The proportion of patients achieving DAS 28-ESR–defined remission was not statistically significantly different between the tocilizumab SC and IV groups.

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- The proportion of patients achieving a minimum 0.3 improvement in the HAQ-DI was not statistically significantly different between the tocilizumab SC and IV groups.
- Changes in SF-36 scores were similar between the tocilizumab SC and IV groups for both the MCS and PCS domains.
- Subgroup analysis by body weight (< 60 kg, 60 to 100 kg, ≥ 100 kg) indicated that the proportion of patients achieving an ACR 20, ACR 50, and ACR 70 response in the heaviest weight category (≥ 100 kg) was lowest overall.

Tocilizumab SC once every two weeks versus placebo (BREVACTA)

- A statistically significantly greater proportion of patients treated with tocilizumab SC achieved an ACR 20 response at week 24 compared with patients who were treated with placebo.
- The proportion of patients achieving ACR 50, ACR 70, DAS 28-ESR < 2.6, DAS 28-ESR < 3.2, a minimum 0.3 and 0.22 improvement in the HAQ-DI was statistically significantly higher in patients receiving tocilizumab SC versus placebo.
- The mean changes from baseline to week 24 in SF-36 PCS and MCS were statistically significantly higher in the tocilizumab SC group than the placebo group. The change in scores from baseline exceeded the lower bound of the established minimal clinically important difference (MCID) of 2.5 to 5 points for both treatment groups; however, the upper bound of the MCID was exceeded only by the tocilizumab SC group.

Tocilizumab without non-biologic DMARDs

Tocilizumab SC once every two weeks versus tocilizumab IV (MUSASHI)

- The proportion of patients achieving an ACR 20 response at week 24 was 79.2% in the tocilizumab SC group and 88.5% in the tocilizumab IV group, resulting in a between-treatment difference of −9.4% (95% CI, −17.6 to −1.2) in the per-protocol analysis and −7.0% (95% CI, −15.0 to 1.0) in the intention-to-treat analysis, which met pre-specified non-inferiority criteria. However, in the per-protocol analysis, the 95% CI was below 0, indicating that tocilizumab SC was statistically significantly worse than tocilizumab IV.
- There was no statistically significant difference between the tocilizumab SC and IV groups for the proportion of patients with ACR 50 or ACR 70 responses at 24 weeks.

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one serious adverse event was:
  - SUMMACTA: 4.6% and 5.2% in the tocilizumab SC and IV groups, respectively
  - MUSASHI: 7.5% and 5.8% in the tocilizumab SC and IV groups, respectively
  - BREVACTA: 4.6% and 3.7% in the tocilizumab SC and placebo groups, respectively.
- Infections and infestations were the most commonly reported serious adverse events in patients treated with tocilizumab.
- In BREVACTA, three deaths occurred in tocilizumab SC group (one from lower respiratory tract infection and two from sepsis) and no deaths occurred in the placebo arm.
- The incidence of patients reporting adverse events in SUMMACTA and MUSASHI was balanced between the tocilizumab SC and tocilizumab IV groups (76.2% versus 77.0% in SUMMACTA; 89.0% versus 90.8% in MUSASHI). A slightly higher proportion of patients reported adverse events in the tocilizumab SC group versus placebo (62.7% versus 57.8%, respectively) in BREVACTA.
- There was a higher rate of injection-site reactions in the tocilizumab SC group (10.1% and 12.1%, respectively) compared with the tocilizumab IV group (2.4% and 5.2%, respectively)

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in SUMMACTA and MUSASHI. In BREVACTA, there was a slightly higher rate of injection-site reactions in the tocilizumab SC group (7.1%) compared with the placebo group (4.1%).
- In SUMMACTA and MUSASHI, withdrawals due to adverse events were slightly more frequent in the tocilizumab IV groups (6.5% and 5.2%, respectively) than in the tocilizumab SC groups (4.8% and 1.7%, respectively). In BREVACTA, the incidence of withdrawals due to adverse events was similar between tocilizumab SC and placebo.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing tocilizumab SC with tocilizumab IV and other biologic DMARDs over a one-year time frame. The assumption of similar efficacy for tocilizumab SC was based on the SUMMACTA trial and on a network meta-analysis (NMA). For tocilizumab IV, the manufacturer assumed that [redacted]% of patients would receive 4 mg/kg every four weeks and [redacted]% would receive 8 mg/kg every four weeks, based on utilization data from the manufacturer's patient assistance program. For tocilizumab SC, however, the manufacturer assumed that [redacted]% of patients would receive an injection every other week and [redacted]% would receive weekly dosing, based on market research. The manufacturer included the first and subsequent years in determining the range of costs by averaging the costs over a three-year period. Costs were based on a patient weight of 75 kg with different body weights used in sensitivity analyses.

CDR identified the following key limitations with the manufacturer's economic submission:
- The proportion of patients who will receive tocilizumab SC weekly versus every-other-week is uncertain and will affect the cost of treatment with tocilizumab SC.
- There is no head-to-head trial that compared low doses of tocilizumab IV (i.e., 4 mg/kg every four weeks) with SC (i.e., 162 mg every other week).
- Although two NMAs support similar efficacy of tocilizumab 8 mg/kg IV every four weeks with most biologics, none of the NMAs included the SC formulation of tocilizumab. Without any evidence that compares tocilizumab SC with other biologics, whether tocilizumab SC is similar to other biologic DMARDs remains uncertain.

The submitted price for tocilizumab SC is $355 per 162 mg pre-filled syringe. The average cost of tocilizumab SC will depend on the proportion of patients who receive weekly versus every-other-week treatment and patients' body weight. When the same split between tocilizumab SC weekly and every-other-week and tocilizumab IV 4 mg/kg and 8 mg/kg is applied, tocilizumab SC is more costly than tocilizumab IV for patients weighing 50 kg or 75 kg and less costly for a patient weighing 100 kg or more.

For the first year of treatment, assuming a patient weight of 75 kg, tocilizumab SC administered every other week ($9,230) is less costly than tocilizumab IV (savings of $1,253 versus 4 mg/kg and $8,242 versus 8 mg/kg every four weeks) and less costly than all other biologic DMARDs (savings ranging from $8,137 to $14,471), with the exception of one course of rituximab ($168 more costly). However, if administered weekly, for the first year of treatment, tocilizumab SC ($18,460) is more costly than tocilizumab IV (incremental cost of $7,977 versus 4 mg/kg and $988 versus 8 mg/kg every four weeks), anakinra, golimumab SC, infliximab (Inflectra), and rituximab (incremental cost ranging from $217 to $9,398), but less costly than abatacept (SC and IV), adalimumab, etanercept, and infliximab (Remicade), with cost savings ranging from $203 to $5,241.

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Other Discussion Points:
CDEC noted the following:

- SC administration is more convenient than IV administration for patients; however, SC was associated with more injection-site reactions than IV in the SUMMACTA trial.
- All CDR-participating drug plans require patients with RA to have inadequate disease control with at least two non-biologic DMARDs before receiving a treatment with a biologic DMARD.
- Data from the open-label extension phase of SUMMACTA suggested that response rates were maintained when patients were switched from SC to IV or from IV to SC.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- There are no direct or indirect comparisons of SC tocilizumab with other biologic drugs for the treatment of RA.

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, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

January 21, 2015 Meeting
Regrets:

Two CDEC members were unable to attend this portion of 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. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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