Canadian Agency for Drugs and Technologies in Health

COMMON DRUG REVIEW

Canadian Expert Drug Advisory Committee
Final Recommendation — Plain Language Version

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

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that Actemra, which is also called tocilizumab, be listed by Canada's publicly funded drug plans for the treatment of adults with moderate-to-severe active rheumatoid arthritis who have not improved enough after having tried both disease-modifying antirheumatic drugs (DMARDs) and a tumour necrosis factor (TNF)-alpha inhibitor.

Actemra is to be started at 4 mg/kg every four weeks and used with methotrexate or other DMARDs; Actemra may be used by itself if methotrexate cannot be used because of side effects or the patient's other health issues. The amount of improvement with Actemra should be measured after 16 weeks, and Actemra should be continued only if there is enough improvement.

Reasons for the Recommendation:

- The recommendation, which requires that patients have not improved enough with both DMARDs and TNF-alpha inhibitors, fits with the Health Canada approved indication that does not recommend the general use of Actemra in patients who do not experience enough improvement from using just DMARDs alone. One medical study of patients who did not experience enough improvement with both DMARDs and TNF-alpha inhibitors, showed that when Actemra was added to methotrexate there was some improvement in patient's American College of Rheumatology (ACR) response and physical function (measured by the Health Assessment Questionnaire Disability Index [HAQ-DI]). In this study, the improvement was shown at week 16, after which it is difficult to measure the response accurately because patients were allowed to receive other treatments if they had not improved at this point.
- The differences in results between Actemra 4 mg/kg and 8 mg/kg were small and it is not certain that the different doses would make a difference for the patient.

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Of Note

- The definition of "not enough improvement" with DMARDs and TNF-alpha inhibitors should be the definition in place at the location (city, province) where the medication is being used.

- There is no clear data on x-ray showing that Actemra slows down rheumatoid arthritis. There was only one study, with patients who had not improved enough on DMARDs only, which looked at worsening changes on x-ray. The committee was not sure if these results were accurate because of the large amount of missing data at 52 weeks.

- The time period during which the studies produced results that were thought to be accurate was short. Also, none of the studies compared Actemra with other biologic drugs, or with DMARD treatments that had been made as effective as possible.

- "Clinical response" or improvement in the studies was defined by minimum accepted standards, such as a 20% improvement in the ACR response criteria (ACR 20) or a 1.2-point improvement on the Disease Activity Score for 28 joints (DAS 28). The committee was concerned that these small improvements may not be enough for patients to notice an improvement over the short-term, and it is not known if these small improvements are useful in predicting long-term disease worsening and severity.
- The committee was concerned that liver enzymes often became higher in Actemra patients and also that there was a rare, but increased chance of stomach or intestinal tears with Actemra compared with TNF-alpha inhibitors.

Background:

Actemra is a medicine that helps keep the immune system from attacking healthy tissues in the body. A normal immune system leaves healthy body tissues alone. In people with rheumatoid arthritis, the immune system attacks normal body tissues causing damage and inflammation, especially in the tissues of the joints. Actemra interferes with an important step in this attack (by blocking a cytokine called IL-6, which is found at high levels in the joints affected by rheumatoid arthritis). By decreasing the immune system's attack on normal tissues, Actemra can reduce the symptoms of rheumatoid arthritis.

Actemra is approved by Health Canada for reducing signs and symptoms in adult patients with moderate-to-severely active rheumatoid arthritis who have not had enough improvement with one or more DMARDs and/or TNF-alpha inhibitors. However, Health Canada also recommends that use of Actemra in patients who have not had enough improvement with one or more DMARDs only, should be on a case-by-case basis.

Actemra should be used with methotrexate or other DMARDs. It may also be given by itself if patients cannot take methotrexate because of side effects or other health issues. Whether used by itself or with other medications, the starting dose of Actemra should be 4 mg/kg every four weeks; this dose may be increased to 8 mg/kg if necessary. Doses of higher than 800 mg are not recommended by Health Canada. It is available as a 20 mg/mL solution for infusion into the vein in single-dose vials of 4 mL (80 mg), 10 mL (200 mg), and 20 mL (400 mg).

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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 Actemra and a review of economic information prepared by the manufacturer of Actemra. 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 Studies
CEDAC reviewed six studies in patients with moderate-to-severely active rheumatoid arthritis. These studies were paid for by the manufacturer of Actemra, or the manufacturer's partner company. Five studies (OPTION, LITHE, TOWARD, CHARISMA, and SATORI) included patients who had not improved enough with DMARDs (usually methotrexate). One study, RADIATE, included patients who had not improved enough with both DMARDs (methotrexate) and TNF-alpha inhibitors.

Studies with patients who had not improved enough with DMARDs

- OPTION with 623 patients and LITHE with 1,196 patients were 24-week and 52-week studies respectively, which compared Actemra 4 mg/kg and 8 mg/kg every four weeks with placebo (an injection containing no active medication). All of the treatments were added to ongoing treatment with methotrexate.
- TOWARD, with 1,220 patients, was a 24-week study that compared Actemra 8 mg/kg every four weeks with placebo, both of which were added to ongoing treatment with DMARDs.
- CHARISMA, with 359 patients, was a 16-week study that compared Actemra 4 mg/kg and 8 mg/kg every four weeks with placebo. All treatments were added to ongoing treatment with methotrexate. This study also compared some patients on Actemra by itself (on 4 mg/kg and 8 mg/kg doses every four weeks) with some patients only on methotrexate treatment.
- SATORI, with 127 patients, was a 24-week study that compared patients on 8 mg/kg of Actemra every four weeks with patients on methotrexate alone.

Studies with patients who had not improved enough with DMARDs and TNF-alpha inhibitors

- RADIATE, with 499 patients, was a 24-week study that compared Actemra 4 mg/kg and 8 mg/kg every four weeks with placebo. All treatments were added to ongoing treatment with methotrexate.

More than 80% of patients finished the study in each of the six studies; however, in four studies (OPTION, LITHE, TOWARD, and RADIATE) patients were allowed to receive other treatment outside of the study (escape therapy) if there was not enough improvement by week 16. Results for patients after they received additional treatment outside the study were not reported. Therefore, there was much data missing after the 16-week point, which may have affected the results after that point.

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Outcomes

The main purposes of the studies were to measure the following:

- the percentage of patients with an ACR 20 response (20% improvement) at week 24 (in all studies except CHARISMA, which measured ACR 20 response at week 16)
- the changes in the total Genant-modified Sharp score (GmSS) at week 52 (in LITHE)
- the Health Assessment Questionnaire Disability Index (HAQ-DI) at week 52 (in LITHE).

The ACR response criteria include the following components:

- swollen joint counts
- tender joint counts
- patient global assessment of disease activity
- physician global assessment of disease activity
- patient assessment of pain
- physical function as assessed by the HAQ, HAQ-DI, or modified HAQ
- either C-reactive protein levels or erythrocyte sedimentation rates (these blood tests measure the amount of inflammation in the body).

Patients are considered ACR 20 responders if they have a 20% improvement from the start of the study in swollen and tender joint counts, plus a 20% improvement in three of the five other components.

The total GmSS measures changes on x-ray in the hands and feet, looking at damaged areas of the joints as well as narrowing of the joints. The total GmSS ranges from 0 (no damage) to 290 (worst damage), which is the sum of the scores for narrowing of the joints (0 to 145) and damaged areas of the joints (0 to 145).

The HAQ-DI is a measure of physical function based on how much difficulty patients have in dressing, getting up from a chair or bed, eating, walking, carrying out personal hygiene, reaching, gripping, and other common activities. Each of these actions contributes equally to the total score, which ranges between zero and three. Higher scores mean a higher amount of disability in physical function. The smallest change in the HAQ-DI that would still be important to patients with rheumatoid arthritis is between 0.2 and 0.25.

Other results were also defined in advance in the CDR systematic review. The committee discussed the following of these results: quality of life (based on the 36-item short form [SF-36] health survey), fatigue, serious side effects, side effects, and new infections.

Important results for patient groups included: slowing of disease progression, relief of symptoms, pain relief, ability to perform daily activities (including continuing or returning to work), improved quality of life, improved sleep, and the return of libido. The majority of the important symptoms identified by patient groups are included in the SF-36 and HAQ-DI. No data for improved sleep or return of libido were available for these studies.

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Results
Efficacy or Effectiveness

Actemra versus placebo, added to treatment with methotrexate or a DMARD, in patients who had not improved enough on DMARDs

- CADTH combined the 24-week data from OPTION, LITHE, and TOWARD. The data showed that the percentage of patients with ACR 20, ACR 50, and ACR 70 responses at 24 weeks was significantly higher for both doses of Actemra compared with placebo. Week 16 data (before escape treatment) showed similar results.
- In LITHE, patients taking Actemra (either dose) had less worsening of rheumatoid arthritis on x-ray at 52 weeks compared with patients treated with placebo. However, there was concern that these results were not accurate as there was a large amount of data missing.
- CADTH combined the 16-week data from OPTION, LITHE, and TOWARD. This data showed that there were significant short-term improvements in physical function and fatigue with both doses of Actemra compared with placebo. The improvements were considered large enough to be of importance to patients.
- When the combined 24-week data from OPTION, LITHE and TOWARD were reviewed, improvements in the physical component score of the SF-36 were greater for Actemra (both doses) compared with placebo; however, these differences were small and may not make much difference for patients. Improvements in the mental component score of the SF-36 were even smaller. The committee was concerned that the SF-36 data may not be accurate as the changes from study start were collected only at week 24, at which point there was a lot of data missing.
- The committee also felt that the DAS 28 results were not very useful because of how the data were collected and analyzed.

Actemra versus placebo, added to treatment with methotrexate, in patients who had not improved enough with a DMARD and TNF-alpha inhibitors

- In RADIATE, the percentage of patients with ACR 20 and ACR 50 responses at 24 weeks was higher for both doses of Actemra compared with placebo. Only the higher dose of Actemra (8 mg/kg) had a greater percentage of patients with an ACR 70 response compared with placebo at 24 weeks. The data at week 16 (before escape treatment) gave the same results.
- Based on week 16 data from RADIATE, short-term improvements in physical function and fatigue were greater for both doses of Actemra compared with placebo.
- In RADIATE, both doses of Actemra had greater improvements in the physical component score of the SF-36 compared with placebo at 24 weeks. There was no difference between Actemra and placebo in the SF-36 mental component score improvement. The committee was not sure if the SF-36 findings were accurate or not as the changes from study start were collected only at week 24, at which point there was a lot of data missing.
- The committee felt that the DAS 28 results were not very useful because of how the data were collected and analyzed.

Harms (Safety and Tolerability)

- A review of data up to the 24-week point (combined from all of the studies) found that

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when Actemra was added (both with 4 mg/kg and with 8 mg/kg doses) to methotrexate or DMARDs there were more side effects than with placebo. Also, more patients stopped taking part in the study because of side effects as compared with those on placebo. However, it is difficult to compare the amount of side effects accurately because patients were on Actemra or placebo for different lengths of time.

- Low white blood cell counts and infections (whether serious or not) occurred more often in patients treated with Actemra compared with other study treatments.
- Increased liver enzymes and fats in the blood were seen more often in Actemra-treated patients compared to patients treated with placebo. These changes did not seem to cause effects such as hepatitis (liver inflammation) or heart problems during the clinical studies.

Cost and Cost-Effectiveness

The manufacturer submitted economic information comparing the cost of Actemra with Orencia (abatacept), Humira (adalimumab), Enbrel (etanercept), Remicade (infliximab), and Rituxan (rituximab) in patients with moderate-to-severely active rheumatoid arthritis (who had not shown enough improvement with one or more DMARDs and/or TNF-alpha inhibitors). The yearly cost of Actemra depends on dose and patient weight. For a 75 kg patient the yearly cost of Actemra could vary from $11,348 to $17,472, based on doses of 4 mg to 8 mg per kg every four weeks. The maximum yearly cost for a patient weighing more than 100 kg and receiving the maximum dose of 800 mg per infusion would be $23,296. These costs are similar to the yearly costs for other biologics: Orencia ($18,619 to $24,825), Humira ($18,388), Enbrel ($18,942 to $20,486), Simponi (golimumab $17,364), and Rituxan ($9,348 to $28,314).

Patient Input Information:

Three national patient groups representing patients with arthritis submitted input for this review. They provided the following information:

- It is very important for people with arthritis to have access to all possible medications as individual patients respond differently to different medications. For example, Actemra may fill a need for patients who have not responded well or not improved with currently available medications.
- There are some issues with the current therapies available; special authority programs often cause delays in getting treatment, and it can be difficult to organize the daily or weekly injections.
- Patients expect Actemra to slow or stop the worsening of the disease and to relieve daily symptoms, including pain; thereby improving quality of life. Pain was included as one part of the ACR responses, rather than by itself. Also, as noted above, quality of life data from the studies (measured by the SF-36) might not be accurate.

Other Discussion Points:

- The chance of stomach or intestinal tears seems more likely with Actemra compared with TNF-alpha inhibitors.
- The benefit and harm of Actemra compared with other biologic agents is unknown. Based on a CADTH analysis, combining data from different studies, it seems that Actemra has similar ACR 50 and ACR 70 results compared with TNF-alpha inhibitors in patients who did not have enough improvement with DMARDs.

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- Four of the six studies, including the 52-week LITHE study, allowed patients to receive other treatment outside of the study (escape therapy) if there was not enough improvement by week 16. This type of study design makes it difficult to compare the benefit and harm of Actemra with placebo.
- The ACR response is a combination of a number of items, including the patient's opinion on how they are feeling as well as blood work results. It is unknown if the ACR response predicts how quickly the disease will progress or the severity of disease in the future.

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, and Dr. Lindsay Nicolle.

Regrets:

Dr. Yvonne Shevchuk

Conflicts of Interest:

CEDAC members reported no conflicts of interest related to this submission.

About this Document

The information contained within this plain language version of the 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.

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