CEDAC FINAL RECOMMENDATION

ABATACEPT RESUBMISSION
(Orencia – Bristol-Myers Squibb)
Indication: Rheumatoid Arthritis

This recommendation supersedes the CEDAC recommendation for this drug and indication dated June 27, 2007.

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that abatacept be listed for patients with moderately to severely active rheumatoid arthritis in a similar manner to tumor necrosis factor (TNF) alpha inhibitor therapies.

Reason for the Recommendation:
In seven randomized controlled trials, abatacept in combination with disease-modifying antirheumatic drugs (DMARDs), was statistically significantly better than placebo plus DMARDs with respect to the proportion of patients achieving an American College of Rheumatology (ACR) response, as well as other outcomes measuring improvement in the symptoms of moderate-to-severe rheumatoid arthritis in patients with an inadequate response to DMARDs or TNF-alpha inhibitor therapies.

Background:
Abatacept is a selective co-stimulation modulator that selectively modulates a key co-stimulatory signal required for full activation of T lymphocytes expressing CD28. At the time of this resubmission, abatacept had a Health Canada indication for reducing signs and symptoms, inducing clinical responses, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who had experienced an inadequate response to one or more DMARDs, or to tumor necrosis factor (TNF) antagonists, or to both. It may be used as monotherapy or in combination with DMARD therapy.

Abatacept is administered as a 30-minute intravenous infusion at weeks zero, two, and four, followed by an infusion every four weeks thereafter. Dosing is based on weight as follows: patients who are < 60 kg receive 500 mg of abatacept, 60 kg to 100 kg receive 750 mg of abatacept, and > 100 kg receive 1 g of abatacept. It is supplied as a lyophilized powder for reconstitution; each 15 mL vial contains 250 mg of abatacept.

Submission History:
Abatacept was previously reviewed for the treatment of patients with moderately to severely active rheumatoid arthritis and received a recommendation to be listed for use in combination with DMARDs (when these agents are not contraindicated) for the treatment of patients with severely active rheumatoid arthritis who have failed to respond to an adequate trial of an anti-TNF agent. Abatacept should not be used in combination with an anti-TNF agent (see Notice of CEDAC Final Recommendation, June 27, 2007).

The original Common Drug Review (CDR) systematic review of abatacept included five double-blind (DB) randomized placebo-controlled trials, including 2,854 patients with moderate-to-severe rheumatoid arthritis. Three studies were conducted in patients with rheumatoid arthritis who had failed DMARD therapy (IM101-100, AIM, ATTEST), one study was conducted in patients with rheumatoid arthritis who had failed TNF inhibitors (ATTAIN), and one study was conducted in patients with rheumatoid arthritis who had failed DMARDs and/or biologics (ASSURE). All patients were maintained on background DMARD therapy. These trials provided evidence that abatacept is more effective than placebo in patients with rheumatoid arthritis who have failed DMARDs and in patients who have failed anti-TNF therapy. The Committee concluded, at that time, that there was insufficient evidence that abatacept was superior to other biologic therapies (e.g., anti-TNF therapies, rituximab) for rheumatoid arthritis and that there was more clinical experience with anti-TNF therapies.

This manufacturer's resubmission was submitted under a CDR pilot project that allows resubmissions to be filed using non-randomized controlled trial (RCT) data when the basis for the resubmission is improved efficacy or safety that addresses the specific issues raised in the CEDAC Recommendation document. The basis of this resubmission is greater clinical experience gained with abatacept since the initial CEDAC recommendation and the resubmission included two new studies, ARRIVE and AGREE, and new long-term extension data of up to seven years that provides information on greater clinical experience with abatacept. The manufacturer also provided a new economic evaluation.

Summary of CEDAC Considerations:

The Committee considered the following information prepared by CDR:

- The original CDR systematic review of DB RCTs of abatacept in patients with moderately to severely active rheumatoid arthritis who had an inadequate response to one or more DMARDs or TNF antagonists, or to both.
- Two new placebo-controlled DB RCTs that evaluated abatacept, IM101-124 (N = 113) and IM101-071 (N = 195), and met the CDR systematic review protocol. These studies were conducted in Korean and Japanese populations respectively, which limited the generalizability of the studies' results.
- Long-term uncontrolled extension data from the five trials included in the original CDR systematic review (IM101-100, AIM, ATTEST, ATTAIN, and ASSURE).
- The AGREE and ARRIVE studies were not included in the CDR systematic review because AGREE was conducted in methotrexate-naive patients and ARRIVE was an uncontrolled, non-randomized study; however, harms data from these studies were considered by the Committee.

- The most recent periodic safety update report for abatacept reporting approximately 11,000 patient-years of exposure during a six-month period and 30,000 patient-years of cumulative exposure.
- A critique of the manufacturer's pharmacoeconomic evaluation of abatacept.

The Committee focused on the results of the original CDR systematic review and the long-term extension data that provided additional evidence on clinical experience with abatacept.

Results

Efficacy or Effectiveness

- Statistically significant improvements for abatacept plus methotrexate compared with placebo plus methotrexate were observed in ACR response, Health Assessment Questionnaire-Disability Index (HAQ-DI) scores, and SF-36 scores at six months in the two new studies, IM101-124 and IM101-071, which is consistent with the original CDR systematic review.

Harms (Safety and Tolerability)

- Overall, adverse events and withdrawals due to adverse events were similar between abatacept and placebo in the original CDR systematic review and the two new studies. No new harms issues were identified in the two new trials.
- In all the trials, the most common infections included nasopharyngitis, upper respiratory tract infection, bronchitis, sinusitis, urinary tract infection, and influenza. Pneumonia was the most common serious infection.

Additional Clinical Experience

- Up to seven years of total exposure data for patients who were DMARD or TNF inhibitor experienced, or both, were available from long-term extension studies (duration range of 4.5 to seven years). The overall exposure-adjusted incidence rates for serious adverse events, infections, serious infections, malignancies, and autoimmune disorders did not increase during the open-label extension phases compared with the double-blind phases of each study, and exposure-adjusted rates were found to be stable over time.
- All serious adverse events reported during the six-month period of the most recent periodic safety update report were previously part of the abatacept risk management plan and no actions related to harms were taken during this time period.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing abatacept with etanercept, infliximab, adalimumab, and methotrexate, in patients with moderately to severely active rheumatoid arthritis and inadequate response to DMARDs over a 10-year time horizon. Patients' response to treatment was based on changes in HAQ-DI score, which were obtained from an indirect mixed treatment comparison. The manufacturer reported that abatacept is associated with an incremental cost per quality-adjusted life-year of $93,649 compared with methotrexate, which is similar to or more cost-effective than TNF-alpha inhibitors compared with methotrexate, where incremental cost-utility ratios range from $96,032 to $171,179.

The annual cost of abatacept ranges from $11,440 for a 60 kg patient to $22,880 for a patient > 100 kg, which is similar to the annual cost of certolizumab pegol ($17,277; 200 mg every two weeks), golimumab ($17,364; 50 mg monthly), adalimumab ($18,388; 50 mg every other week), and etanercept ($18,943; 50 mg weekly or $20,486; 25 mg twice weekly). Abatacept may be more or less costly than infliximab depending on patient weight, dosing of infliximab, and potential vial wastage.

Other Discussion Points:

- The Committee discussed the lack of evidence assessing the sequential use of abatacept and TNF-alpha inhibitor therapies. It is uncertain whether the effect of using abatacept before a TNF-alpha inhibitor would differ from the effect of using abatacept following a TNF-alpha inhibitor.
- The Committee considered whether or not there were patients with an inadequate response to DMARDs for whom abatacept would be preferred compared with a TNF-alpha inhibitor therapy. It was noted that the route of administration, clinician experience with specific agents, and contraindications to TNF-alpha inhibitors (e.g., demyelinating disease, risk of tuberculosis) may be considered when selecting a therapy.
- In February 2010, the Health Canada indication for abatacept was expanded to include methotrexate-naive patients; however, this new indication was not considered by the Committee at this time.

CEDAC Members Participating:
Dr. Robert Peterson (Chair), Dr. Michael Allan, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

Regrets:
Dr. Anne Holbrook (Vice-Chair), Dr. Ken Bassett, and Dr. Lindsay Nicolle.

Conflicts of Interest:
One CEDAC member reported a conflict of interest and did not participate in the vote.

About this Document:
CEDAC 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 CEDAC made its recommendation.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The CEDAC 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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