CDEC FINAL RECOMMENDATION

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

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that subcutaneous (SC) abatacept be listed for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) if all of the following conditions are met:

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

Reasons for the Recommendation:
1. One six-month, double-blind, randomized controlled trial (RCT) (ACQUIRE; N = 1457) demonstrated that SC abatacept, administered at 125 mg weekly with an IV loading dose and concomitant methotrexate, was non-inferior to IV abatacept, as measured by the proportion of patients achieving an ACR 20 response. ACQUIRE also demonstrated similar ACR 50 and ACR 70 response rates between the SC abatacept and IV abatacept treatment groups.

2. At the submitted price, SC abatacept represents an increased cost relative to IV abatacept for patients weighing less than 60 kg.

Background:
Abatacept is a soluble fusion protein that selectively modulates a key co-stimulatory signal required for full activation of T lymphocytes that express CD28. It is approved by Health Canada 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 RA who have had inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs) or to tumour necrosis factor (TNF) antagonists, or to both. Abatacept may be used as monotherapy or in combination with non-biologic DMARDs.

Abatacept SC is administered weekly as a 125 mg injection, with or without an IV loading dose. Abatacept is available as a 125 mg/mL solution for SC injection in single-dose, pre-filled syringes, and in 15 mL vials containing 250 mg abatacept for IV infusion. Dosing for the IV

formulation is based on weight as follows: patients who are less than 60 kg receive 500 mg of abatacept, 60 kg to 100 kg receive 750 mg of abatacept, and greater than 100 kg receive 1 g of abatacept.

This submission is for the SC formulation of abatacept, with or without an initial loading dose of IV abatacept, for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs, TNF antagonists, or both.

Submission History:
The IV formulation of abatacept was originally reviewed by the Canadian Expert Drug Advisory Committee (CEDAC) for the treatment of patients with moderately to severely active RA and received a recommendation to "list with criteria/condition" (see Notice of CEDAC Final Recommendation, June 27, 2007). Abatacept IV was subsequently reviewed in 2010 for the same indication and received a recommendation to "list in a similar manner" to TNF inhibitors (see Notice of CEDAC Final Recommendation, June 17, 2010). The IV formulation of abatacept has also been reviewed by CEDAC for the treatment of juvenile idiopathic arthritis and juvenile RA, and received a recommendation to "list with criteria/condition" (see Notice of CEDAC Final Recommendation, April 22, 2009).

Summary of CDEC Considerations:
CDEC considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs for abatacept, a critique of the manufacturer's pharmacoeconomic 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 two patient groups that responded to the CDR call for patient input:

- Pain due to severe inflammation has an impact on every aspect of a patient's life.
- IV abatacept is an option for patients no longer responsive to TNF antagonists, but may be inconvenient for some patients due to the need for monthly infusions and the difficulty inserting needles due to vein scarring.
- SC abatacept may offer patients the prospect of a greater degree of self-management of their condition.

Clinical Trials
The systematic review included one manufacturer-sponsored, six-month, double-blind, double-dummy, non-inferiority RCT. ACQUIRE (N = 1457) evaluated the efficacy and safety of SC abatacept (125 mg SC per week with an IV loading dose) compared with IV abatacept (monthly weight-based dosing) for the treatment of moderately to severely active RA; all patients concomitantly received methotrexate. ACQUIRE excluded patients that had discontinued anti-TNF therapy due to lack of efficacy in the past.

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

- ACR 20 response — 20% improvement from baseline in swollen and tender joint counts, plus a 20% improvement in three of the five other components: patient global assessment of disease activity, physician global assessment of disease activity, patient assessment of

pain, physical function, and either C-reactive protein levels or erythrocyte sedimentation rates.
- ACR 50 and ACR 70 responses — 50% or 70% improvement from baseline in swollen and tender joint counts, plus a 50% or 70% improvement in three of the five other components.
- HAQ-DI — a measure of physical functional status, which assessed the difficulty experienced by patients in dressing, arising, eating, walking, maintaining hygiene, reaching, gripping, and other common activities. Each function contributes equally to the total score, with a range between zero (no difficulty) and three (unable to do).
- DAS28-CRP — a measure of disease activity based on tender and swollen joint counts, patient global assessment, and C-reactive protein levels. A DAS28 score of 5.1 or greater indicates high disease activity; whereas, a score of less than or equal to 3.2 is defined as low disease activity and a score of less than 2.6 is defined as remission.

The primary efficacy outcome in the ACQUIRE trial was the proportion of patients achieving an ACR 20 response at day 169. The ACQUIRE trial employed a non-inferiority design for the primary efficacy endpoint, with a pre-specified non-inferiority margin of 7.5%, allowing for a maximum point estimate of –2.1% (95% confidence interval [CI], –7.5 to 3.2).

Results

Efficacy
- The proportion of patients achieving an ACR 20 response at day 169 was 76.0% in the SC abatacept group and 75.8% in the IV abatacept group, resulting in a between-treatment difference of 0.3% (95% CI, –4.2 to 4.8) in the per-protocol analysis and 0.5% (95% CI, –4.0 to 4.9) in the intention-to-treat analysis, which met pre-specified non-inferiority criteria.
- ACR 50 and ACR 70 response rates were similar between the SC abatacept and IV abatacept treatment groups.
- There were no statistically significant differences between the SC abatacept and IV abatacept treatment groups for the proportion of patients achieving a HAQ-DI response, DAS28-CRP-defined low disease activity, and DAS28-CRP-defined remission.
- Pre-specified subgroup analyses based on body weight (> 100 kg, < 60 kg, and 60 kg to 100 kg), demonstrated that ACR 20 and HAQ-DI response rates were similar between the SC abatacept and IV abatacept treatment groups in each weight class. In both treatment groups, ACR 20 and HAQ-DI responses rates were lowest for patients in the heaviest weight class.

Harms (Safety and Tolerability)
- The proportion of patients reporting at least one adverse event was balanced between the SC abatacept and IV abatacept treatment groups (67.0% versus 65.2%). The most commonly reported adverse events were upper respiratory tract infections, bronchitis, diarrhea, and headache.
- The proportion of patients reporting at least one serious adverse event was similar between SC abatacept and IV abatacept treatment groups (4.2% versus 4.9%). Infections were the most commonly reported serious adverse events.
- Withdrawals due to adverse events were slightly greater in the IV abatacept group compared with the SC abatacept group (3.5% versus 2.0%).

Cost and Cost-Effectiveness
The manufacturer submitted a cost-minimization analysis comparing drug costs for SC abatacept with IV abatacept over a two-year time horizon. Adequate evidence was presented to support the assumption of similar clinical efficacy and safety, based on five studies of SC abatacept: one direct comparison against IV abatacept, one direct comparison against adalimumab, one crossover study against IV abatacept, and two single-arm studies.

The daily cost of SC abatacept (125 mg weekly; $50.13 to $53.98 per day) is similar to that of IV abatacept (750 mg every 4 weeks; $50.13 to $53.98 per day) and other biological DMARDs: adalimumab (40 mg every 2 weeks; $51.96 per day), etanercept (50 mg weekly; $53.99 per day), certolizumab pegol (200 mg every 2 weeks; $51.36 to $59.26 per day), golimumab (50 mg monthly; $51.62 per day), tocilizumab (4 mg to 8 mg per kg every 4 weeks; $44.49 to $61.97 per day), infliximab (3 mg per kg every 8 weeks; $54.08 to $61.81 per day), rituximab (1,000 mg every 4 to 6 months; $56.16 to $84.25 per day), and anakinra (100 mg daily; $46.77 per day). Whether SC abatacept is cost-saving compared with IV abatacept depends on the price of IV abatacept, which varies among jurisdictions, and the weight of patients given the weight-based dosing for IV abatacept (where lower doses of IV abatacept are required [< 60 kg], SC abatacept represents an increased cost).

Research Gaps:
CDEC noted that there is an absence of evidence regarding the following:
- There is no evidence addressing the efficacy of SC abatacept for patients with an inadequate response to TNF antagonists.

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 19, 2013 Meeting

Regrets:
None

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 not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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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