



CEDAC FINAL RECOMMENDATION and REASONS for RECOMMENDATION

ABATACEPT

(Orencia™ – Bristol-Myers Squibb Canada)

New Indication: Juvenile Idiopathic Arthritis

Description:

Abatacept is a protein that selectively modulates a key co-stimulatory pathway required for full activation of T lymphocytes. Abatacept is indicated for reducing signs and symptoms of moderate to severe active polyarticular juvenile idiopathic arthritis (JIA)/juvenile rheumatoid arthritis in pediatric patients 6 years of age and older who have had an inadequate response to one or more disease modifying anti-rheumatic drugs, such as methotrexate. Abatacept has not been studied in children under 6 years of age.

Previous CEDAC Recommendation for Abatacept:

- Rheumatoid arthritis in adults (see Notice of CEDAC Final Recommendation, June 27, 2007)

Dosage Forms:

Supplied as abatacept 250 mg sterile powder for reconstitution. Abatacept is administered as a 30-minute intravenous infusion for children 6 to 17 years of age with JIA. Abatacept is given every two weeks for the first four weeks and then every four weeks thereafter.

Recommendation:

The Canadian Expert Drug Advisory Committee recommends that abatacept be listed for children with juvenile idiopathic arthritis who are intolerant to, or have not had an adequate response from etanercept. Initial treatment should be limited to a maximum of 16 weeks. Retreatment should only be permitted for children who had an adequate initial treatment response and subsequently experience a disease flare.

Reasons for the Recommendation:

1. In the single study included in the systematic review, initial response was determined after 16 weeks of exposure to abatacept. Children who responded were randomized to continued abatacept or placebo in the double-blind phase of the trial. Children who received abatacept were more likely to have a longer time to flare compared with children randomized to receive placebo. The Committee noted that many children who were withdrawn from abatacept during the double-blind phase continued without flare for a significant period of time (median time to flare was 6 months in the placebo group).

2. The daily cost of abatacept in children ranges from \$15.67 to \$47.01 which is similar to the cost of etanercept of \$18.88 to \$54.93.
3. The risk of harm associated with long-term abatacept use in children with juvenile idiopathic arthritis, is largely unknown. The withdrawal trial methodology and short trial duration does not allow harms to be adequately assessed for maintenance use. Although there was no difference in the incidence of serious adverse events between abatacept and placebo in this study, a carry-over effect from the lead-in phase, in which all children received abatacept, may have resulted in the underestimation of harms associated with abatacept. The Committee had concerns regarding uninterrupted, long-term use of abatacept given the manner in which this drug modulates immune function.

Summary of Committee Considerations:

The Committee considered a systematic review that included the results of one withdrawal trial evaluating the effects of abatacept in children with JIA who responded initially to abatacept therapy. Of the 190 children entering a four month open-label abatacept treatment phase, 122 children, who responded to abatacept were randomized to receive either continued therapy with abatacept or placebo for an additional six months. The primary outcome of this double-blind phase was the time to disease flare, defined as worsening of 30% or more in at least 3 of 6 ACR-Pedi core response variables and at least 30% improvement in no more than one of the other variables. Children who (i) completed period A with inadequate response, (ii) completed period B without flare, or (iii) had disease flare during period B were offered open-label treatment with abatacept (N=153). This open-label follow up phase is ongoing and has a mean (standard deviation) follow up of 833 (326) days as of May 2008.

Median time to flare was six months in the placebo group and was not estimable in the abatacept group, because less than half of children taking abatacept experienced flare during the randomized phase. However, children randomized to continued abatacept were more likely to have a longer time to flare compared with placebo [HR=0.3 (95% CI: 0.2 to 0.6)]. Response rates for ACR-Pedi 50, 70 and 90 were statistically significantly higher in the abatacept group, compared to placebo, but the ACR-Pedi 30 response rates were not. The increase (worsening) in pain scores measured by a visual analog scale from 0-100 mm, was statistically significantly less for abatacept compared with placebo; mean difference -7.2 (95% CI: -14.4 to -0.1). Overall quality of life, as measured by the physical and psychosocial summary scores of the Child Health Questionnaire (CHQ), was not statistically significantly different between abatacept and placebo. Children's Health Assessment Questionnaire (CHAQ)-disability index scores worsened in the placebo group compared with the abatacept group and although statistically significant, the clinical significance of this small difference is uncertain. The effectiveness endpoints used in the trial were subject to bias due to higher attrition in the placebo group, use of last observation carried forward technique to impute missing data, and carry-over effects of treatment inherent in the withdrawal trial design.

During the lead-in phase, children who had previously discontinued anti-tumour necrosis factor therapy (primarily due to treatment failure) had a lower ACR-Pedi 30 response rate compared to those who had no history of having discontinued anti-TNF therapy (39% versus 76%, respectively). This suggests that some children achieve a response on abatacept after unsuccessful treatment with etanercept, albeit at a lower rate than children with no history of having discontinued anti-TNF therapy.

Serious adverse events among abatacept-treated participants included one report of acute lymphocytic leukemia (ALL) during the lead-in phase which resulted in the patient discontinuing the trial. The incidence of adverse events was similar in children taking abatacept or placebo during the double-blind phase, however selection bias and/or carryover effects from Period A to Period B confound assessment of this finding. Infections and infestations were commonly reported and there were two reports of serious

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infections that included encephalitis and varicella. Other common adverse events among abatacept-treated children included nausea, abdominal pain, vomiting, and pyrexia.

The daily cost of abatacept ranges from \$15.67 to \$47.01 and the daily cost of etanercept ranges from \$18.88 to \$54.93. These costs are based on a range of patient weights observed at baseline in the clinical trial (21 kg to 77 kg). While the range of costs for abatacept is similar to etanercept, abatacept has additional costs associated with its intravenous route of administration, whereas administration costs are minimal for subcutaneously administered etanercept.

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.
2. The Committee is aware that the open label phase of the abatacept trial is ongoing and that the manufacturer is planning to collect data on at least 500 children for 10 years in a registry. Future results from these studies may provide additional insight on the long term use and safety of the drug in the pediatric population.
3. The manufacturer has reviewed this document and has not requested the removal of any confidential information, in conformity with the [CDR Confidentiality Guidelines](#).

Background:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication's effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.

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