



COMMON DRUG REVIEW

CEDAC FINAL RECOMMENDATION

CERTOLIZUMAB PEGOL (Cimzia – UCB Canada Inc.) Indication: Rheumatoid Arthritis

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that certolizumab pegol not be listed.

Reason for the Recommendation:

The Committee considered that the quality of the certolizumab pegol randomized controlled trials was limited and that other therapeutic options are available.

Background:

Certolizumab pegol is a human monoclonal antibody to TNF-alpha. It has a Health Canada indication for use in combination with methotrexate for reducing signs and symptoms, inducing major clinical response, and reducing the progression of joint damage as assessed by x-ray, in adult patients with moderately to severely active rheumatoid arthritis. It may be used alone for reducing signs and symptoms in patients with moderately to severely active rheumatoid arthritis who do not tolerate methotrexate.

The Health Canada approved dosing regimen for certolizumab pegol is 400 mg (given as two subcutaneous injections of 200 mg) at weeks zero, two, and four, followed by certolizumab pegol 200 mg every other week. For maintenance dosing, certolizumab pegol 400 mg every four weeks may be considered. It is supplied as a 200 mg/mL solution and packaged in a single-use prefilled glass syringe.

Summary of CEDAC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind randomized controlled trials of certolizumab pegol and a critique of the manufacturer's pharmacoeconomic evaluation.

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Clinical Trials

The CDR systematic review included five manufacturer-sponsored, double-blind, placebo-controlled trials (RAPID 1, RAPID 2, Study 014, FAST4WARD, and Study 004) in patients with moderately to severely active rheumatoid arthritis. Study 004 and Study 014 are unpublished.

RAPID 1 (N = 992, 52 weeks) and RAPID 2 (N = 619, 24 weeks) evaluated a loading dose of 400 mg at weeks zero, two, and four, followed by a maintenance dose of 200 mg every two weeks. Study 004, FAST4WARD, and Study 014 did not use a loading dose as indicated by Health Canada, therefore, the Committee focused on RAPID 1 and RAPID 2. Both studies also evaluated higher unapproved doses of certolizumab pegol. In both studies, any patient who did not achieve an American College of Rheumatology 20 (ACR 20) response was withdrawn from the study at week 16 and was offered enrolment in an uncontrolled, open-label extension study.

The quality of RAPID 1 and RAPID 2 was compromised by the high and differential proportion of withdrawals that occurred prior to measurement of the primary or co-primary outcome at week 24. In RAPID 1, 35% of the 200 mg certolizumab pegol group compared with 78% of the placebo group withdrew by 54 weeks. In RAPID 2, 29% of the 200 mg certolizumab pegol group compared with 87% of the placebo group withdrew by 24 weeks. From the time of their withdrawal, patients were treated as non-responders.

Outcomes

The co-primary outcome in RAPID 1 and the primary outcome in RAPID 2 was the proportion of patients with an ACR 20 response at 24 weeks. The other co-primary outcome in RAPID 1 was the change from baseline in the van der Heijde modified total Sharp score (mTSS) at 52 weeks.

The mTSS measures radiographic progression and has scores ranging from zero to 440, with higher scores indicating greater disease severity.

The ACR 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 Health Assessment Questionnaire (HAQ), and either C-reactive protein levels or erythrocyte sedimentation rates. Patients are considered ACR 20 responders if they have a 20% improvement from baseline in swollen and tender joint counts, plus a 20% improvement in three of the five other components.

Other outcomes were also defined a priori in the CDR systematic review protocol. Of these outcomes, the Committee discussed the following: ACR 50, ACR 70, functional outcomes measured by the HAQ-DI, quality of life as measured by the Short Form-36 (SF-36).

Results

Efficacy or Effectiveness

- Statistically significant improvements in ACR response, HAQ-DI, SF-36 and inhibition of radiographic progression were observed for certolizumab pegol 200 mg compared with placebo in both trials at 24 weeks. However, due to the high and differential proportion of withdrawals in RAPID 1 and RAPID 2, interpretation of these results was limited.

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Harms (Safety and Tolerability)

- At Health Canada approved doses, there was a statistically significantly greater proportion of patients reporting serious adverse events in the certolizumab pegol group compared with the placebo group in RAPID 1 but not in RAPID 2. However, the high withdrawals in the control groups of RAPID 1 and RAPID 2 led to less information on harms being available for placebo patients and, therefore, uncertainty in interpreting these results.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing certolizumab pegol with three TNF alpha inhibitors: etanercept, adalimumab, and infliximab. In the first year of treatment, the annual cost of certolizumab pegol (\$19,271) is more than adalimumab (\$18,388; 50 mg every other week) and similar to etanercept (\$18,943; 50 mg weekly or \$20,486; 25 mg twice weekly). In subsequent years, the annual cost of certolizumab pegol (\$17,277) is less than adalimumab (\$18,388) and etanercept (\$18,943 or \$20,486). Certolizumab pegol 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 that withdrawals in the placebo group of the certolizumab pegol trials were higher than those of all other trials included in the CADTH therapeutic review on biologics for rheumatoid arthritis.
- It was noted that the concomitant methotrexate dose used in RAPID 1 and RAPID 2 was low based on current standards and was not likely optimized. Low methotrexate doses in these patients may have contributed to the higher than expected withdrawal rates and may have biased the results toward the certolizumab pegol group as placebo responses in these trials were lower than expected. Interpretation of data from the certolizumab pegol trials was challenging given the low control group responses.
- Certolizumab pegol differs from other TNF alpha inhibitors in that it lacks the Fc portion of the antibody, which is associated with antibody-dependent cellular toxicity and complement fixation. There is no evidence that these characteristics influence clinical outcomes.

CEDAC Members Participating:

February 17: Dr. Robert Peterson (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, Dr. Lindsay Nicolle, and Dr. Kelly Zarnke.

May 19: 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. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

Regrets:

February 17: Dr. Anne Holbrook (Vice-Chair) and Dr. Yvonne Shevchuk.

May 19: Dr. Anne Holbrook (Vice-Chair) and Dr. Ken Bassett.

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Conflicts of Interest:

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

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 Final 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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