

CEDAC FINAL RECOMMENDATION and REASONS for RECOMMENDATION

RITUXIMAB (Rituxan[®] – Hoffmann-La Roche Ltd.)

Description:

Rituximab is a monoclonal antibody against B lymphocytes and is approved for use in non-Hodgkin's lymphoma and rheumatoid arthritis. The submission to the Common Drug Review was solely for the approved indication to reduce signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more anti-tumour necrosis factor (anti-TNF) therapies.

Dosage Forms:

100 mg and 500 mg vials for intravenous injection. In the treatment of rheumatoid arthritis, the recommended dose is 1000 mg followed two weeks later by the second 1000 mg.

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that rituximab, when used in combination with methotrexate, be listed for the treatment of adult patients with severely active rheumatoid arthritis who have failed to respond to an adequate trial of an anti-TNF agent. Rituximab should not be used concomitantly with anti-TNF agents.

Reasons for the Recommendation:

1. The Committee considered the results of a 24 week randomized controlled trial (RCT) which compared rituximab with placebo in 499 patients with rheumatoid arthritis who had an inadequate response to previous treatment with anti-TNF therapies. All patients received concomitant methotrexate therapy. Compared to placebo, rituximab resulted in significantly more patients achieving 20%, 50% and 70% improvements in the American College of Rheumatology response criteria (ACR 20, ACR 50 and ACR 70), with numbers needed to treat (NNT) to achieve these responses of 3, 5 and 9, respectively. Quality of life was also significantly improved with rituximab.
2. The RCT evaluated response to a single dose of rituximab and there is insufficient evidence on the effectiveness and safety of repeated doses. Re-treatment with rituximab should only be considered for patients who have achieved a response, followed by a subsequent loss of effect and, after an interval of no less than six months since the previous dose. Response is defined by criteria such as ACR 20 or a 1.2 point improvement on the Disease Activity Score on 28 joints (DAS28).

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3. A treatment course of rituximab costs \$9,060 which is significantly more than traditional disease modifying anti-rheumatic drugs (DMARDs) but similar in cost to anti-TNF therapies, when the interval to re-treatment with rituximab is 6-12 months.

Summary of Committee Considerations:

Based on current evidence, including the results of the 24 week RCT noted above, there is insufficient evidence on the effect of rituximab on structural damage to joints in rheumatoid arthritis.

Rituximab causes depletion of B-lymphocyte cells and serious infections can occur during therapy with rituximab. Although there was no difference in the incidence of serious adverse events or infections between rituximab and placebo in the RCT, it was of limited duration. Further investigation on the effectiveness and safety of more than one treatment course of rituximab is required.

In patients with moderate to severe rheumatoid arthritis who have failed DMARDs and etanercept, the economic evaluation submitted by the manufacturer reported an incremental cost per quality adjusted life year (QALY) of \$18,400 when rituximab was used followed by a standard sequence of treatments (rituximab plus methotrexate, followed by adalimumab plus methotrexate, infliximab plus methotrexate, leflunomide plus methotrexate, gold, cyclosporine and lastly palliative care) compared to the standard sequence without rituximab. However, this was based on key assumptions including that a change in the Health Assessment Questionnaire score for patients receiving rituximab results in a change in survival and that the re-treatment interval with rituximab is nine months. Given the lack of long-term studies, there is uncertainty regarding the true incremental cost-effectiveness of rituximab in rheumatoid arthritis. For example, if the re-treatment interval with rituximab was assumed to be only six months, the incremental cost effectiveness becomes less attractive at \$53,400 per QALY.

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.

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.