



## CDEC FINAL RECOMMENDATION

### RITUXIMAB

(Rituxan – Hoffman-La Roche Ltd.)

**New Indication: Granulomatosis with Polyangiitis and Microscopic Polyangiitis, Remission Induction (adults)**

#### Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that rituximab be listed for the induction of remission in patients with severely active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) who have a severe intolerance or other contraindication to cyclophosphamide, or who have failed an adequate trial of cyclophosphamide.

#### Reasons for the Recommendation:

1. In one double-blind randomized controlled trial (RCT; the RAVE trial), rituximab was reported to be non-inferior, but not superior to oral cyclophosphamide for inducing remission in patients with severely active GPA or MPA, based on the percentage of patients who achieved complete remission at six months.
2. At recommended doses, the treatment drug cost for rituximab (\$12,687; 375 mg/m<sup>2</sup> weekly for four weeks) is greater than oral cyclophosphamide (\$128 to \$341; 2 mg/kg daily for three to six months), intravenous (IV) cyclophosphamide (\$115 to \$173; 15 mg/kg for six to nine doses), and IV immunoglobulin (IVIG) \$8,287 (0.5 g/kg for four doses) – assuming a body surface area of 1.8 m<sup>2</sup> and a body weight of 70 kg.

#### Of Note:

1. The Committee considered an adequate trial of cyclophosphamide to be six IV pulses, or three months of oral therapy.
2. The Committee noted that jurisdictions may wish to consider funding rituximab for patients who desire to preserve ovarian or testicular function, or fertility.

#### Background:

This submission for rituximab is for the new Health Canada indication for the induction of remission in adult patients with severely active GPA (also known as Wegener's granulomatosis) and MPA.

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Rituximab is a monoclonal anti-CD20 antibody that binds to the surface of B-lymphocytes to promote their depletion. Rituximab is available as a 10 mg/mL solution in 100 mg and 500 mg vials and the Health Canada-approved dose is 375 mg/m<sup>2</sup> body surface area administered as an IV infusion once-weekly for four weeks.

### **Submission History:**

Rituximab was previously reviewed by the Canadian Expert Drug Advisory Committee (CEDAC) for the treatment of rheumatoid arthritis and received a recommendation to “list with criteria/condition” (see Notice of CEDAC Final Recommendation, February 14, 2007).

### **Summary of CDEC Considerations:**

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of rituximab in patients with severely active GPA or MPA, a critique of the manufacturer’s pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

### **Clinical Trials**

The systematic review included two multicentre RCTs of patients with severely active GPA or MPA.

- RAVE (n = 197) was a double-blind, double-dummy, non-inferiority RCT that enrolled patients with newly diagnosed or relapsing disease. Of patients with relapsing disease, 78% had been previously treated with cyclophosphamide. RAVE consisted of a six-month remission-induction phase followed by a 12-month remission maintenance phase. Patients were randomized to rituximab 375 mg/m<sup>2</sup> IV once weekly for four weeks or oral cyclophosphamide for three to six months at a dose of 2 mg/kg daily. Patients randomized to cyclophosphamide were switched to azathioprine during months four to six.
- RITUXVAS (n = 44) was an open-label, superiority RCT of 12 months duration that enrolled newly diagnosed patients with renal involvement. Patients were randomized to one of two groups. Group 1 received rituximab 375 mg/m<sup>2</sup> IV once weekly for four weeks plus IV cyclophosphamide 15 mg/kg administered at the time of the first and third rituximab doses; patients who had progressive disease in the first six months could receive a third dose of IV cyclophosphamide. Group 2 received IV cyclophosphamide for three to six months, at a dose of 15 mg/kg every two weeks for three doses, then every three weeks; patients were switched to azathioprine during months four to six.

In both trials, patients received concomitant corticosteroid treatment with IV methylprednisolone followed by a tapered regimen of oral prednisone. In both trials rituximab-treated patients did not receive maintenance immunosuppressive therapy unless they experienced disease flare; cyclophosphamide-treated patients received azathioprine for maintenance therapy as described above.

In RAVE, the percentage of patients completing the six-month induction phase was similar for rituximab and cyclophosphamide groups; 94% and 93% respectively. In RITUXVAS, 82% of patients randomized to rituximab completed the 12-month study, compared with 91% of patients randomized to cyclophosphamide.

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### **Outcomes**

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: remission, severe flare or major relapse, corticosteroid use, quality of life, and serious and total adverse events.

The primary efficacy outcome in the RAVE trial was the percentage of patients who achieved complete remission at six months; defined as a score of zero on the Birmingham Vasculitis Activity Score for Wegener's granulomatosis (BVAS/WG) plus discontinuation of prednisone. Rituximab would be considered non-inferior to cyclophosphamide if the lower limit of the 95.1% confidence interval (CI), for the between-treatment difference, was above -20%.

The primary efficacy outcome in the RITUXVAS trial was the percentage of patients who achieved sustained remission at 12 months, defined as a BVAS (version 3.0) score of zero for six months.

The BVAS (version 3.0) and the BVAS/WG are scales used to measure disease activity based on signs and symptoms in relevant organ systems. The BVAS/WG is a tool specifically tailored for patients with WG; it includes a section to document clinical manifestations of WG not included in the original BVAS and BVAS (version 3.0), and omits features from the BVAS and BVAS (version 3.0) that are less commonly observed in patients with WG. In all versions of the BVAS, a score of zero indicates inactive disease, with higher scores indicating greater disease activity. The Vascular Damage Index (VDI) is a scale used to measure irreversible damage based on 11 organ systems, with higher scores indicating greater damage. The minimal clinically important difference for any of the above scales (BVAS [version 3.0], BVAS/WG, or VDI), is uncertain.

In the RAVE trial, a severe flare was defined as a BVAS/WG score of  $\geq 3$  or the occurrence of at least one major item, and a limited flare was defined as the new occurrence or worsening of one or more minor BVAS/WG items. In the RITUXVAS trial, a major relapse was defined as the recurrence or new appearance of a major BVAS (version 3.0) item.

In both trials, quality of life was assessed using the 36-item Short-Form Health Survey.

### **Results**

#### ***Efficacy or Effectiveness***

- In the RAVE trial, rituximab was non-inferior but not superior to cyclophosphamide based on the percentage of patients achieving complete remission at six months; 63.6% versus 54.7% respectively; treatment difference (95.1% CI), 9.5% (-4.3 to 23.4). A pre-specified subgroup analysis indicated that, for patients with relapsing disease, the percentage of patients achieving complete remission at six months was statistically significantly higher in the rituximab group compared with cyclophosphamide; 67% versus 42% respectively.
- In the RITUXVAS trial, the percentage of patients with sustained remission at 12 months was not statistically significantly different between rituximab and cyclophosphamide groups; 76% versus 82% respectively.
- There were no statistically significant between-treatment differences in the percentage of patients having either a severe flare or a limited flare in the RAVE trial, or in the percentage of patients having a major relapse in the RITUXVAS trial.

- In both RAVE and RITUXVAS, there were no statistically significant between-treatment differences in irreversible damage as measured by the VDI or in corticosteroid usage.
- There were no notable between-treatment differences in quality of life in either trial.

### **Harms (Safety and Tolerability)**

- The incidence of adverse events and serious events was not statistically significantly different between treatment groups in either trial
- In RAVE, confirmed malignancies were identified in 5% of rituximab-treated patients compared with 2% for cyclophosphamide. In RITUXVAS, malignancy was reported for two patients in the rituximab group compared with none for cyclophosphamide.
- In the RAVE trial, the incidence of leukopenia (grade  $\geq 2$ ) was statistically significantly higher in the cyclophosphamide group compared with rituximab; 17% versus 5%.
- The incidence of serious infection or any infection was not statistically significantly different between treatment groups in either trial.

### **Cost and Cost-Effectiveness**

The manufacturer conducted a cost analysis comparing rituximab with treatments included in the 2009 European League Against Rheumatism recommendations (e.g., IVIG, antithymocyte globulin, infliximab, and mycophenolate mofetil). The manufacturer did not include cyclophosphamide as a comparator in their economic analysis. *[Confidential information related to the manufacturer's requested reimbursement criteria was removed at the manufacturer's request, pursuant to the CDR Confidentiality Guidelines.]* The rationale for the type of analysis used was based on the lack of treatments specifically indicated for the induction of remission in adult patients with severely active GPA or MPA and the absence of any comparative clinical data.

Based on recommended doses, the treatment drug cost for rituximab (\$12,687; 375 mg/m<sup>2</sup> weekly for four weeks) is greater than oral cyclophosphamide (\$128 to \$341; 2 mg/kg daily for three to six months), IV cyclophosphamide (\$115 to \$173; 15 mg/kg for six to nine doses), and IVIG \$8,287 (0.5 g/kg for four doses) — assuming a body surface area of 1.8m<sup>2</sup> and body weight of 70 kg.

### **Patient Input Information:**

The following is a summary of information that was provided by four patient groups that responded to the CDR Call for Patient Input:

- Symptoms of particular concern to patients include pain, fatigue, difficulty breathing, and depression. Symptoms and the unpredictable nature of disease flare were noted to negatively impact patients' quality of life. Patients also expressed concerns regarding adverse events associated with current treatments.
- Patients desire treatments that will reduce the need for current therapies, including corticosteroids, and that will reduce flares and improve quality of life.

### **Other Discussion Points:**

- The Committee considered the results of RITUXVAS to be of limited generalizability given that the treatment regimen (i.e., concomitant rituximab and cyclophosphamide) is neither consistent with the Health Canada-approved use of rituximab for the induction of remission in GPA or MPA, nor reflective of accepted clinical practice.
- The Committee noted that the efficacy and safety of subsequent courses of rituximab for GPA and MPA has not been established.

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**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.

**July 18, 2012 Meeting****Regrets:**

None

**Conflicts of Interest:**

None

**About this Document:**

CDEC 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 CDEC made its recommendation. 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 requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CDEC 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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