

## Rituximab (for rheumatoid arthritis)

**Product:**  
RITUXIMAB (Rituxan®)  
10 mg/mL injection

**Class of drugs:**  
Antineoplastics / Biologics

**Indication:**  
Treatment of rheumatoid arthritis

**Manufacturer:**  
Hoffman-La Roche Limited

### CED Recommendation

The CED recommended that rituximab (Rituxan) be funded through the Exceptional Access Program for the treatment of rheumatoid arthritis according to specific criteria. The CED's recommendation was made on the basis that rituximab (Rituxan) has been shown to be an effective treatment option in rheumatoid arthritis patients who have failed other therapies.

### Executive Officer Decision

Based on the CED's recommendation, the Executive Officer decided to fund rituximab (Rituxan) through the Exceptional Access Program for the treatment of rheumatoid arthritis according to specific criteria.

### Status

Funding available through the Ontario Public Drug Programs via the Exceptional Access Program.

### Highlights of Recommendation:

- ◆ Rituximab (Rituxan) is indicated for the treatment of rheumatoid arthritis in patients who have not responded to, or cannot tolerate, other standard treatments. It belongs to a group of drugs called biologic response modifiers, or biologics.
- ◆ A study in patients with rheumatoid arthritis who had failed standard therapies (both traditional anti-rheumatic drugs and other biologic treatments) found that rituximab (Rituxan) lessened disease activity and improved quality of life.
- ◆ However, this study only evaluated the use of a single course of rituximab (Rituxan). There are insufficient data to adequately assess the safety and effectiveness of repeat courses of this treatment.
- ◆ Rituximab (Rituxan) costs approximately \$10,000 per treatment course. It is significantly more expensive than traditional anti-rheumatic drugs, such as methotrexate and leflunomide; but it is similar in cost to other biological treatments for rheumatoid arthritis.
- ◆ **Overall, the Committee noted the lack of long-term efficacy and safety data, but acknowledged that rituximab (Rituxan) provides a treatment option in patients who have failed standard therapies.**

### Background:

Rheumatoid arthritis (RA) is a chronic disease in which the body's immune system attacks the joints and surrounding tissues. This leads to swelling, pain, and stiffness in the joints, and can restrict patients' movement and ability to carry out the tasks of daily living. The disease can also affect other organs, such as the skin, heart, lungs, blood vessels, and muscles.

The cause of RA is unknown. This disease usually requires life-long treatment, including medications, physical therapy, exercise, education, and possibly surgery. Anti-inflammatory medications are usually used to help with symptoms of pain and swelling. Current standard therapies used to modify the disease process and to delay joint destruction are known as disease-modifying anti-rheumatic drugs (DMARDs). Methotrexate, leflunomide and sulfasalazine are traditional DMARDs that are usually effective as first-line treatment.

Biologic agents are a group of disease-modifying drugs designed to target specific components of the immune system that play an important role in RA. There are various groups of biologic treatments for RA: tumor necrosis factor (TNF) inhibitors (etanercept, infliximab, and adalimumab); human interleukin-1 receptor antagonist (anakinra); selective co-stimulation modulator (abatacept); and B-cell targeted therapy (rituximab). Due to safety and cost-effectiveness reasons, biological therapies are considered after traditional DMARDs have failed.

Rituximab (Rituxan) is indicated for the treatment of moderate to severe rheumatoid arthritis in adult patients who have had an inadequate response to, or cannot tolerate, one or more TNF inhibitor therapies. It is also indicated for certain cancers of the lymph system. This review considered the use of rituximab (Rituxan) only in the treatment of rheumatoid arthritis.

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## Detailed Discussion:

- ◆ The funding of rituximab (Rituxan) for the treatment of rheumatoid arthritis was initially reviewed in February 2007. At that time, the Committee recommended that funding be provided in patients who have failed to respond to an adequate trial of two TNF inhibitors. In July 2008, the Committee conducted a second review to consider revising the funding criteria to require the failure of only one TNF inhibitor.
- ◆ The Committee reviewed a single randomized controlled study that compared rituximab (Rituxan) to placebo in patients who experienced an inadequate response or intolerance to one or more TNF inhibitors. The study reported that, compared with placebo, rituximab (Rituxan) resulted in significantly more patients achieving disease response, as measured by the American College of Rheumatology (ACR) response criteria, ACR 20, ACR 50 and ACR 70. (ACR response denotes the percentage reduction in various measures of disease activity and symptoms. ACR 20, 50 and 70 signifies a 20%, 50% and 70% reduction, respectively.) In the study, patients who were on rituximab (Rituxan) also experienced a greater improvement in their quality of life.
- ◆ The study only evaluated the use of a single course of therapy, rituximab (Rituxan) 1000mg administered on day 1 and day 15. There are insufficient data to adequately assess the effectiveness and safety of additional doses beyond the first treatment course. Moreover, there is some concern of lung toxicity with repeated use, as suggested by studies using multiple doses of rituximab (Rituxan) as a component of lymphoma therapy.
- ◆ There are no trials comparing rituximab (Rituxan) to other biological agents for the treatment of rheumatoid arthritis. Therefore, the relative efficacy of rituximab (Rituxan) versus other biological treatments is unknown.
- ◆ Common side effects of rituximab (Rituxan) include headache, nausea, facial flushing, dizziness, fatigue, weakness, decreased urine output, fever, chills, joint or muscle pain, stomach pain, and sore throat. Rare but serious infections, such as reactivation of hepatitis B and progressive multifocal leukoencephalopathy (a viral infection in the central nervous system), have also been reported with rituximab (Rituxan) treatment.

- ◆ Rituximab (Rituxan) costs approximately \$10,000 per treatment course. It is significantly more expensive than traditional DMARDs, but is similar in cost to other TNF inhibitor therapies.
- ◆ Overall, the Committee noted the lack of long-term efficacy and safety data but acknowledged that rituximab (Rituxan) provides a treatment option in patients who had an inadequate response to one or more TNF inhibitors.

## EAP Criteria:

- ◆ The CED recommended that rituximab (Rituxan) be funded through the Exceptional Access Program (EAP) according to the following revised criteria:
  - *For the treatment of adult patients with severe active rheumatoid arthritis who have failed to respond to an adequate trial of one anti-TNF agent. (Rituximab should not be used concomitantly with anti-TNF agents.)*
  - *The patient should have also failed, or been unable to tolerate, adequate trials of DMARDs.*
  - *The patient should be rheumatoid-factor positive OR have radiographic evidence of rheumatoid joint damage; AND have at least five swollen joints.*
  - *The approved dosing for rituximab is 1000mg, to be followed by the second 1000mg dose two weeks later.*
  - *Re-treatment with rituximab therapy will be considered on a case-by-case basis for patients who have achieved an initial response, followed by a subsequent loss of effect and after an interval of no less than six months since the previous dose.*

## CEDAC Recommendation:

(<http://www.cadth.ca/index.php/en/cdr/recommendations>)

The Canadian Expert Drug Advisory Committee recommended that rituximab (Rituxan) 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 (Rituxan) should not be used concomitantly with anti-TNF agents.



Ministry of  
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