Biosimilar Rituximab
Frequently Asked Questions

BCRenal
Provincial Health Services Authority

1. What is a biosimilar rituximab?

Rituximab is a genetically engineered chimeric murine/human immunoglobulin G1 kappa-type (IgG1) antibody that binds to the CD20 receptor on B lymphocyte cells (B-cells). It is produced in mammalian cell cultures (Chinese hamster ovary), which is the gold standard culture for the production of biologics.

B-cells produce antibodies (e.g. ANCA), and they are part of the inflammatory cells recruited to an area of the body (e.g. kidneys) when an immune response is required.

When rituximab binds to the CD20 receptor on B-cells in the systemic circulation, lymphatic system and bone marrow, B-cell numbers in the blood, and lymph nodes (including those in the kidney) are significantly reduced; which may result in complete elimination of B-cells in the blood and lymphoid tissues.

A biosimilar rituximab is highly similar to the original biologic drug (aka. the originator rituximab) but not identical. To be approved in Canada, a biosimilar must be proven to have no clinically meaningful differences from the originator.

2. Why is BC Renal changing coverage from the originator rituximab (Rituxan®) to a biosimilar rituximab?

This decision follows our partner organizations (BC Cancer and BC PharmaCare) who have already switched from the originator rituximab (Rituxan®) to a biosimilar rituximab.

In 2016, Canada spent $241 million on Rituxan® – making it one of the top 10 highest biologic expenditures in the country. For BC Renal, Rituxan accounts for between 20 to 25% of the entire annual expenditure for the Glomerulonephritis Formulary.

Savings from changing coverage from Rituxan® to a biosimilar rituximab will be reinvested into other treatments for patients with kidney disease.

3. Which biosimilar rituximab is covered by BC Renal?

There are three biosimilar rituximabs available in Canada - Riximyo™, Ruxience™ and Truxima™. Currently, the BC Renal Glomerulonephritis formulary only reimburses Riximyo™. The use of Riximyo™ will be closely monitored and the funding policy will be re-evaluated periodically.

4. Is there data that a biosimilar rituximab is as safe and effective as the originator rituximab (Rituxan®)?

To be approved in Canada, a biosimilar must be proven to have no clinically meaningful differences from the originator. Health Canada provides guidance on the data required for this; in short, a biosimilar must demonstrate equivalence on the following:

- Physiochemical properties
- Biological activity
- Immunochemical properties
- Purity and impurity
- Specifications (tests or analytical procedures with numerical limits, ranges, or other criteria to inform acceptance criteria)
- Stability

With regards to the biosimilar rituximabs, the evidence to support similarity in safety and efficacy with the originator is based on data that the antibody protein structure is highly similar, there is equivalent depletion of B-cells in human or animal models, and patients have equivalent outcomes in clinical trials (see Table 1).

Given the treatment of glomerulonephritis is an off-label indication for rituximab, there is currently no high-quality efficacy data with the biosimilar rituximabs identified in a systematic review conducted by the Glomerulonephritis committee on June 20, 2020. However, there are several clinical trials demonstrating equivalent outcomes in patients with rheumatoid arthritis, which provides some reassurance that biosimilar rituximabs will also provide equivalent outcomes in patients with glomerulonephritis.

5. Will patients be required to switch to the biosimilar if they are in the middle of a treatment cycle?

No, patients in the middle of a treatment cycle with the originator rituximab (Rituxan®) should finish therapy with Rituxan®. Patients newly starting on therapy, patients who have received Rituxan® previously but are not in the middle of a treatment cycle, and patients currently receiving maintenance therapy with Rituxan® will be provided the biosimilar rituximab (Riximyo™).

6. Will BC Renal be evaluating the impact of switching to a biosimilar rituximab on patients?

Yes, the BC Renal Glomerulonephritis committee will closely monitor the use of the rituximab biosimilar and this funding policy will be re-evaluated periodically.

Table 1: references for safety and efficacy of biosimilar rituximab

Safety and efficacy markers that must be equivalent	References
1. Primary protein structure (i.e. sequence of amino acids in a polypeptide chain) 2. Secondary protein structure (i.e. folding of the polypeptide chains) 3. Tertiary protein structure (i.e. final 3-D structure) 4. CD20 receptor binding and subsequent B-cell depletion	**Riximyo™:** 1. Visser et al. Physicochemical and functional comparability between the proposed biosimilar rituximab GP2013 and originator rituximab. BioDrugs. 2013 Oct;27(5):495-507. 2. Silva et al. Target-directed development and preclinical characterization of the proposed biosimilar rituximab GP2013. Leuk Lymphoma. 2014 Jul;55(7):1609-17. **Ruxience™:** 1. Ryan et al. Comparative nonclinical assessments of the proposed biosimilar PF-05280586 and rituximab (MabThera®). Toxicol pathol. 2014 Oct;42(7):1069-81. **Truxima™:** 1. Lee at al. Analytical similarity assessment of rituximab biosimilar CT-P10 to reference medicinal product. MAbs. 2018 Apr;10(3):380-396.
5. Outcomes in clinical trials in patients with rheumatoid arthritis	**Riximyo™:** 1. Smolen JS et al. A randomized double-blind trial to demonstrate bioequivalence of GP2013 and reference rituximab combined with methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis 2017;76:1598–1602. 2. Tony HP et al. Safety and Immunogenicity of Rituximab Biosimilar GP2013 After Switch from Reference Rituximab in Patients with Active Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2019 Jan;71(1):88-94. **Ruxience™:** 1. Cohen S, Emery P, Greenwald M, Yin D, Becker JC, Melia LA, et al. A phase I pharmacokinetics trial comparing PF-05280586 (a potential biosimilar) and rituximab in patients with active rheumatoid arthritis. Br J Clin Pharmacol. 2016;82(1):129-38. 2. Williams JH, Hutmacher MM, Zierhut ML, Becker JC, Gumbiner B, Spencer-Green G, et al. Comparative assessment of clinical response in patients with rheumatoid arthritis between PF-05280586, a proposed rituximab biosimilar, and rituximab. Br J Clin Pharmacol. 2016;82(6):1568-1579 3. Cohen SB, Burgos-Vargas R, Emery P, Jin B, Cronenberger C, Vazquez-Abad MD. Extension Study of PF-05280586, a Potential Rituximab Biosimilar, Versus Rituximab in Subjects With Active Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2018;70(11):1598-606. **Truxima™:** 1. Park W, Suh C-H, Shim SC, et al. Efficacy and Safety of Switching from Innovator Rituximab to Biosimilar CT-P10 Compared with Continued Treatment with CT-P10: Results of a 56-Week Open-Label Study in Patients with Rheumatoid Arthritis. BioDrugs: clinical immunotherapeutics, biopharmaceuticals and gene therapy 2017;31:369-77. 2. Park W, Bozic-Majstorovic L, Milakovic D, et al. Comparison of biosimilar CT-P10 and innovator rituximab in patients with rheumatoid arthritis: a randomized controlled Phase 3 trial. MAbs 2018;10:934-43. 3. Suh C-H, Yoo DH, Berrocal Kasay A, et al. Long-Term Efficacy and Safety of Biosimilar CT-P10 Versus Innovator Rituximab in Rheumatoid Arthritis: 48-Week Results from a Randomized Phase III Trial. BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy 2019;33:79-91