

## 5.14 RITUXIMAB

**Solution for I.V. infusion 100 mg in 10 mL**

**Solution for I.V. infusion 500 mg in 50 mL**

**Truxima<sup>®</sup>, Celltrion Healthcare Australia Pty Ltd**

### 1 Purpose of Application

- 1.1 The minor submission sought a Section 100 Efficient Funding of Chemotherapy (EFC) listing for a new biosimilar of rituximab (Truxima<sup>®</sup>) for the treatment of:
- CD20 positive, previously untreated, stage III/IV follicular, B-cell non-Hodgkin's lymphoma (NHL); and
  - CD20 positive, relapsed or refractory low grade or follicular, B-cell NHL.

### 2 Requested listing

- 2.1 Truxima<sup>®</sup> was proposed for PBS listing as a biosimilar of the rituximab reference brand MabThera<sup>®</sup>. Rituximab is currently PBS-listed for the treatment of NHL, severe active granulomatosis with polyangiitis, severe active microscopic polyangiitis, CD20 positive lymphoid cancer, CD20 positive acute lymphoblastic leukaemia and severe active rheumatoid arthritis.
- 2.2 The submission requested listing for 100 mg per 100 mL and 500 mg per 50 mL injection vial forms of Truxima<sup>®</sup> for NHL, which is the only TGA-approved indication for this brand of rituximab.
- 2.3 The submission requested Truxima<sup>®</sup> be considered equivalent ('a' flagged) with MabThera<sup>®</sup> for the purposes of the substitution at the point of dispensing for the treatment of NHL.
- 2.4 Rituximab for NHL is currently listed as an Authority Required (STREAMLINED) benefit.
- 2.5 The submission proposed identical restrictions to the existing listing for MabThera<sup>®</sup>, for which the intravenous (IV) formulation is listed on the Section 100 EFC but these have not been reproduced in full below.

Name, Restriction, Manner of administration and form	Max. amount	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
RITUXIMAB				
100 mg/10 mL injection, 2 x 10 mL vial	800 mg	7	Refer to Table 2	Truxima <sup>®</sup> Celltrion Healthcare Australia Pty Ltd
500 mg/50 mL injection, 50 mL vial		11		

- 2.6 The PBAC noted the sponsor sought TGA registration for four brands of its biosimilar rituximab (i.e. the same drug with four brand names, including Tuxella<sup>®</sup>, Rituzena<sup>®</sup>, Ritemvia<sup>®</sup> in addition to Truxima<sup>®</sup>). These brands of the biosimilar are registered for different sets of indications.

- 2.7 The PBAC noted advice from the sponsor that it is intending to request the listings of the different brands of the rituximab biosimilar sequentially, with the fourth (and final) brand to include all PBS-listed indications for rituximab.
- 2.8 As part of consideration for this biosimilar, the PBAC expressed concern regarding the complexity in prescribing and dispensing the same biosimilar under different brand names with different TGA approved indications (further detail under “Quality Use of Medicines”).

*For more detail on PBAC’s view, see section 6 PBAC outcome.*

### **3 Background**

- 3.1 The Truxima® brand of rituximab was TGA registered on 29 November 2018 for both 100 mg/10 mL and 500 mg/50 mL forms for the treatment of NHL.
- 3.2 This brand of rituximab was previously submitted to the PBAC Secretariat for consideration at the July 2018 PBAC meeting as a minor submission however, the sponsor withdrew it before the meeting.
- 3.3 The PBAC has not previously considered an application for this biosimilar rituximab.
- 3.4 At its March 2018 meeting, the PBAC considered a submission for another biosimilar rituximab, Riximyo®, which requested a range of biosimilar uptake drivers be applied to the listings for rituximab. Riximyo® received a positive PBAC recommendation and the PBAC advised there were no clinical or other concerns about appropriate use of medicines, if the policy decision were made to apply biosimilar uptake measures to rituximab, provided certain recommendations are followed. The PBAC considered that the oncology indications for rituximab should remain unchanged as a streamlined authority as it considered a change to a Restricted Benefit would have minimal effect on prescribing behaviours and may inadvertently lead to an increase in prescribing beyond the current restrictions (Riximyo, Public Summary Document, March 2018).
- 3.5 In its March 2018 consideration of Riximyo®, the PBAC also recommended a note encouraging prescribing of the biosimilar brand to treatment naïve patients for all indications as part of its consideration of biosimilar uptake drivers.

*For more detail on PBAC’s view, see section 6 PBAC outcome.*

### **4 Comparator**

- 4.1 The minor submission nominated the reference brand of rituximab (MabThera®) as the comparator, which was appropriate. The submission also stated that the Riximyo® brand of rituximab is an alternative comparator. The PBAC noted that Riximyo® was not PBS listed at the time of consideration.

*For more detail on PBAC’s view, see section 6 PBAC outcome.*

### **5 Consideration of the evidence**

### **Sponsor hearing**

5.1 There was no hearing for this item as it was a minor submission.

### **Consumer comments**

5.2 The PBAC noted that there were no consumer comments for this submission.

### **Clinical trials**

5.3 The submission presented two clinical trials supporting the safety and efficacy of Truxima® with the reference brand as outlined below.

**Table 1: Trials and associated reports presented in the submission**

<b>Trial ID/First Author</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
<b>Direct randomised trial(s)</b>		
Study CT-P10 3.2 NCT 02149121	A Randomized, Controlled, Double-Blind, Parallel-Group, Phase 3 Study to Compare the Pharmacokinetics, Efficacy and Safety Between CT-P10, Rituxan and MabThera in Patients With Rheumatoid Arthritis	CSR CT-P10 3.2 Addendum 14 November 2016 (Celltrion Healthcare, Nov 2016)
Study CT-P10 3.3 NCT 02162771	Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 compared with rituximab in patients with previously untreated advanced-stage follicular lymphoma: a randomised, double-blind, parallel-group, non-inferiority phase 3 trial.	Kim WS et al. Lancet Haematol 2017; 4: e362-73. (Kim, 2017)

5.4 As a minor submission, no evaluation of the clinical data was undertaken.

### **Comparative effectiveness**

5.5 The approved Product Information (PI) states that the comparability of Truxima® with MabThera® has been demonstrated with regard to physicochemical characteristics and efficacy and safety outcomes for the listed indications.

5.6 The PI considered the physicochemical, pharmacological, clinical and safety properties of Truxima® to be very similar to MabThera® and was of the view that Truxima® was highly similar to MabThera®.

### **Comparative harms**

5.7 The TGA approved product information (PI) stated that the overall safety profile of Truxima® in clinical trials was similar to that of MabThera®.

5.8 The most common reported adverse events were infections and infusion related reactions. The frequencies and nature of the adverse events were similar to those reported for MabThera®.

### **Clinical claim**

5.9 The approved Product Information states that Truxima® is a biosimilar rituximab, and equivalent in terms of efficacy and safety to the reference brand, MabThera®.

5.10 There has been limited data on switching between the different brands of rituximab. Twenty subjects with RA switched from MabThera® to Truxima® in a phase 1 open label extension study which aimed to investigate the long-term safety of Truxima® (up

to 2 years). No significant difference in B-cell responses was observed between the Truxima® maintenance and switch cohort over the whole study period. Efficacy data (ACR 20, ACR 50 and ACR 70) were also similar in the switch cohort compared to the Truxima® maintenance cohort. There was no notable difference in the safety profile in the switch cohort. Park et al 2017 concluded that comparable efficacy and safety profiles were observed in patients who switched from MabThera® to Truxima® and those maintained on Truxima® throughout treatment<sup>1</sup>. ***Estimated PBS usage & financial implications***

- 5.11 As the Riximyo® brand of rituximab was not listed on the PBS at the time of the submission, Truxima® may be the first biosimilar rituximab brand to be listed on the PBS and, in accordance with division 3A of Part VII of the *National Health Act 1953*, rituximab may be subject to a statutory price reduction. The sponsor also acknowledged this in the submission.

**Table 2: Proposed DPMA for both private and public hospital**

Indication	DPMA
CD20 positive, previously untreated, Stage III/IV follicular, B-cell non-Hodgkin's lymphoma	\$ [REDACTED]
CD20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma	\$ [REDACTED]

DPMA: dispensed price for maximum amount

- 5.12 Based on this assumption, the sponsor estimated a cost saving to Government because of the listing of Truxima® for the requested NHL indications in excess of \$30 to \$ 60 million over a six-year period.

*For more detail on PBAC's view, see section 6 PBAC outcome.*

### **Quality Use of Medicines (QUM)**

- 5.13 As part of the consideration for this biosimilar, the PBAC expressed concern regarding the complexity in prescribing the same biosimilar under different brand names with different sets of TGA approved indications. The PBAC noted there were practical implementation challenges particularly in the hospital setting, as individual hospitals are unlikely to stock multiple brands of rituximab and dispense them across a range of specific indication subsets.
- 5.14 The PBAC considered having multiple brands of the same biosimilar rituximab would lead to confusion for both prescribers and patients, particularly if a change in brand was incorrectly considered to be a treatment switch, and this would ultimately impact on quality use of medicines and could discourage the use of biosimilars in a long term.

## **6 PBAC Outcome**

- 6.1 The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy), Authority Required (STREAMLINED) listing of Truxima® brand of rituximab, for the treatment of stage III or IV CD20 positive follicular B-cell non-Hodgkin's lymphoma (NHL) as a biosimilar of the intravenous (IV) infusion presentation of the reference

<sup>1</sup> Park W et al. *BioDrugs* (2017) 31:369-377

- brand of rituximab (MabThera®). In making this recommendation, the PBAC noted the approved Product Information states that Truxima® is biosimilar to the reference brand, MabThera®.
- 6.2 The PBAC noted that the submission only requested listing for NHL indications at this time. The PBAC noted there are other brands of the rituximab biosimilar that are TGA registered by the same sponsor for different subsets of indications for which the reference brand is currently listed on the PBS. The PBAC considered the listing of numerous different brands of this biosimilar with different indications could cause significant brand confusion for consumers, prescribers and dispensers.
- 6.3 Although the submission requested listing only for Truxima® brand for NHL, the PBAC was satisfied that it was sufficiently able to extrapolate, in principle, the recommendation to all indications for which rituximab is currently PBS-listed, including additional brands of the identical TGA registered rituximab product manufactured by the same sponsor.
- 6.4 The PBAC indicated a strong preference to minimise brand proliferation of the same rituximab biosimilar(s) to minimise the risks of quality use of medicines (QUM) issues including patient and prescriber confusion, where a change in brand is incorrectly considered a treatment switch. The PBAC requested the Department investigate implementation options to minimise the impact of these QUM issues, stating a preference for Ritemvia® brand alone to be PBS listed as this is TGA registered for all indications for which the reference biologic is currently PBS listed.
- 6.5 The PBAC noted the minor submission did not propose the application of biosimilar uptake drivers for the Truxima® brand of rituximab, however considered that issues previously identified relating to biosimilar uptake drivers for the S100 EFC listings of the Riximyo® brand of rituximab (March 2018) continued to apply. As such, the Committee reiterated its position that lowering the authority level for oncology indications of rituximab may have minimal effect on prescribing behaviours and potentially increase the risk of leakage beyond the current restrictions.
- 6.6 The PBAC advised that under Section 101(4AACD) of the National Health Act, that Truxima® brand of rituximab (or any other identical brand of rituximab sponsored by Celltrion Healthcare Australia) and MabThera® brand of rituximab should be considered equivalent for the purposes of substitution (i.e., 'a' flagged in the Schedule) at the pharmacy level. The Committee recalled it had previously noted concerns professional groups raised regarding multiple treatment switches. The PBAC noted that switches between more than two brands of rituximab could possibly occur in practice but had no reason to consider this a major QUM concern, noting that prescriber and patient choice remained paramount.
- 6.7 The PBAC noted that another rituximab biosimilar, Riximyo® was recommended for PBS listing at the March 2018 PBAC meeting. At the time, the PBAC advised that Riximyo® and MabThera® should be marked as equivalent for the purposes of substitution ('a' flagged). Therefore, the PBAC considered it would be appropriate for all three brands of rituximab (MabThera® IV, Riximyo® and Truxima®/Ritemvia® or any

other identical brand of rituximab sponsored by Celltrion Healthcare Australia) to be marked as equivalent ('a' flagged) to each other for the indication of NHL, when all brands are PBS listed.

- 6.8 The PBAC reiterated its previous position from the March 2018 consideration of Riximyo® that although brand substitution at the pharmacy level has been recommended, the uptake of this biosimilar brand of rituximab will largely be driven by which brand of rituximab hospitals choose to keep in stock via tendering and formulary arrangements.
- 6.9 The PBAC advised that rituximab remains unsuitable for prescribing by nurse practitioners.
- 6.10 The PBAC recommended that the Early Supply Rule should not apply.
- 6.11 The PBAC noted the restriction is considered complex, and that the resolution of issues outlined in paragraph 6.4 above may need to be factored into timeframes for the implementation of this positive recommendation.
- 6.12 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 7 Recommended listing

Add new brand to item codes 10179R, 10193L, 4613T, 7258B. No changes to current restriction wording.

Name, Restriction, Manner of administration and form	Max. amount	No. of Rpts	Proprietary Name and Manufacturer	
RITUXIMAB				
100 mg/10 mL injection, 2 x 10 mL vial	800 mg	7	Truxima®	Celltrion Healthcare Australia Pty Ltd
500 mg/50 mL injection, 50 mL vial		11		

## 8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## 9 Sponsor's Comment

Celltrion Healthcare Australia agrees with the position of PBAC to PBS list a single brand (Truxima®) for all indications for which reference rituximab is currently PBS listed.