Technology Guidance

Rituximab

for treating non-Hodgkin's lymphoma and chronic lymphocytic leukaemia

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Rituximab biosimilar (Truxima) 100 mg/10 ml and 500 mg/50 ml concentrate for infusion for treating:
  - CD20-positive diffuse large B-cell non-Hodgkin's lymphoma,
  - Indolent B-cell non-Hodgkin's lymphomas,
  - Stage III-IV follicular lymphoma, or
  - CD20-positive chronic lymphocytic leukaemia

  in line with its registered indications; and

- ✓ The removal of rituximab reference biologic 100 mg/10 ml and 500 mg/50 ml concentrate for infusion (MabThera) from the Medication Assistance Fund (MAF) for all indications.

Subsidy status

Truxima 100 mg/10 ml and 500 mg/50 ml concentrate for infusion is recommended for inclusion in the MOH Standard Drug List (SDL) for the abovementioned indications from 18 January 2021. The MAF listing of MabThera will cease on 19 July 2021.

SDL subsidy **does not** apply to any other rituximab biosimilars (such as Rixathon), or to any formulations or strengths of MabThera.

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Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1. The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of intravenous (IV) rituximab biosimilars, Rixathon and Truxima, for treating non-Hodgkin's lymphoma (NHL, specifically diffuse large B-cell lymphoma, follicular lymphoma and indolent B-cell lymphoma) and chronic lymphocytic leukaemia (CLL). The Agency for Care Effectiveness conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for Rixathon and Truxima was considered in line with their registered indications.

1.2. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3. Additional factors, including social and value judgments, may also inform the Committee's subsidy considerations.

Clinical need

2.1. A biosimilar is a biological therapeutic product with proven similar physicochemical characteristics, biological activity, safety and efficacy to the reference biological product. Rixathon and Truxima are biosimilars of rituximab and its reference biologic is MabThera. The Committee acknowledged that MabThera IV was already listed on the MAF for NHL but use for CLL had not been previously assessed for subsidy consideration. Furthermore, the Committee noted that the subcutaneous formulation of MabThera, which is not subsidised, was not within the scope of this evaluation.

2.2. The Committee acknowledged that rituximab-based regimens are routinely used in local practice for NHL and are also a preferred treatment option in select patients with CLL. They noted that MabThera IV accounted for SG$13 million of drug expenditure in the public sector in 2019 and agreed that the availability of cheaper biosimilar products could improve treatment affordability for patients and lead to cost savings for the healthcare system.

2.3. Local clinical experts confirmed that they would prescribe a rituximab biosimilar if the clinical evidence showed that it was non-inferior to the reference biologic and it was more affordable for their patients. They advised that a 6-month overlap period for subsidy should be put in place to allow sufficient time for patients to switch products.

Clinical effectiveness and safety

3.1. Non-Hodgkin's lymphoma

The Committee noted that equivalence or non-inferiority trials for rituximab biosimilars have only been conducted in patients with follicular lymphoma. Results from these studies showed no statistically significant differences in efficacy and safety between rituximab biosimilars (Rixathon and Truxima) and the reference biologic (MabThera). The Committee acknowledged that surrogate endpoints such as overall response rate (ORR) were used in the clinical trials in view of the long median progression free survival for follicular lymphoma (approximately seven years).

3.2. Observational studies in diffuse large B-cell lymphoma showed no statistically significant differences in ORR between Truxima and MabThera. No evidence for Rixathon was identified for this indication.

3.3. Chronic lymphocytic leukaemia

No clinical studies on the use of rituximab biosimilars to treat CLL were available. The Committee noted that pivotal studies supporting the use of reference rituximab (MabThera) to treat CD20 positive CLL showed that rituximab in combination with fludarabine and cyclophosphamide (FC) led to statistically significant improvements in survival outcomes but more adverse events (including neutropenia and leukocytopenia) compared with FC alone when used as first-line treatment or after relapse following one prior therapy.

3.4. The Committee acknowledged that local and international regulatory agencies had concluded that there was sufficient evidence to support therapeutic similarity between the rituximab biosimilars and the reference biologic and to also approve Rixathon and Truxima for all of the same indications as MabThera, including CLL, diffuse large B-cell lymphoma and indolent B-cell lymphoma despite a lack of clinical evidence.

Cost effectiveness

4.1. No local economic evaluations of rituximab biosimilar were identified. The Committee reviewed budget impact analyses from overseas jurisdictions which estimated substantial cost savings from the introduction of rituximab biosimilars in their local contexts (assuming a 30% to 45% price discount from the reference biologic).

4.2. Manufacturers of all IV rituximab products offered discounts, contingent on subsidy listing, as part of their value-based pricing (VBP) proposals for the Committee's consideration. The prices proposed for the biosimilars were lower than for MabThera.

4.3. Committee agreed that a cost-minimisation approach was appropriate to assess the cost-effectiveness of Truxima and Rixathon in view of their comparable efficacy and safety with MabThera. At the price proposed by the manufacturer, the Committee considered that Truxima represented the most cost-effective IV rituximab product for all registered indications.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact was estimated to be less than SG$1 million in the first year of listing Truxima on the SDL for all registered indications, taking into consideration cost savings associated with removing MabThera IV from the MAF.

Additional considerations

6.1. In view of the potential cost savings to patients who use Truxima instead of MabThera, as well as the well-established role of rituximab for treating NHL and CLL, and low risk of inappropriate use, the Committee considered that an SDL listing for Truxima was appropriate to encourage uptake.

Recommendations

7.1. Based on available evidence, the Committee recommended rituximab biosimilar (Truxima) 100 mg/10 ml and 500 mg/50 ml concentrate for infusion be listed on the SDL for treating NHL and CLL in line with its registered indication, in view of its therapeutic similarity and favourable cost effectiveness compared to the reference biologic (MabThera).

7.2. The Committee also recommended that MabThera 100 mg/10 ml and 500 mg/50 ml concentrate for infusion be removed from the MAF for all indications in view of unfavourable cost-effectiveness compared with Truxima. Clinicians should actively assess each patient's suitability for switching from MabThera to Truxima and provide relevant counselling to patients. The Committee advised that switching to Truxima or to an alternative treatment should be done within six months, before subsidy for MabThera is completely withdrawn.

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government subsidy decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is based on the evidence available to the MOH Drug Advisory Committee as at 19 August 2020. It is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at www.ace-hta.gov.sg/about

Principal Head (HTA)
Agency for Care Effectiveness
Email: ACE_HTA@moh.gov.sg