For all indications for which rituximab originator (MabThera®) is approved for use across Hertfordshire, in line with HMMC recommendations

RED – NOT RECOMMENDED FOR USE IN PRIMARY CARE. PRESCRIBING RESPONSIBILITY TO BE RETAINED IN SECONDARY CARE

<table>
<thead>
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<th>NAME: GENERIC (TRADE)</th>
<th>WHAT IT IS</th>
<th>INDICATIONS</th>
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| Rituximab (Truxima®)  | Monoclonal anti-CD20 antibody | For which CCGs are responsible commissioner:  
  - Licensed – Rheumatoid arthritis (adults)  
  - Unlicensed – Immune (Idiopathic) thrombocytopenic purpura (adults) | June 2017 | Final | NICE – no guidance specifically relating to Truxima®, however recommendations set out in original TAs will apply to the appropriate biosimilar(s). |

HMMC recommendation following consultation with local specialists:
Truxima® is recommended for introduction into the local health economy, in line with HMMC-approved indications for rituximab originator as:
  - It has been approved by the European Medicines Agency (EMA) which has shown it to be equivalent to the originator medicine in terms of quality, safety and efficacy.
  - It has been launched in the UK.
  - The acquisition cost is less than that of the originator medicine.
  - The originator is accepted for use within the local health economy (i.e. not classified as ‘double-red’).

Currently, rituximab is approved for restricted use within Hertfordshire for the following indications:
  - Rheumatoid arthritis (adults)
  - Immune (idiopathic) thrombocytopenic purpura (adults)

For any future indications for rituximab approved for use by HMMC, Truxima® will be considered as approved for those indications.

All rituximab products must be identified within the drug formulary and prescribed by brand, in line with MHRA guidelines that state that biological medicines, including biosimilar medicines, must be prescribed by brand name to support on-going pharmacovigilance.
**HERTFORDSHIRE MEDICINES MANAGEMENT COMMITTEE**  
Rituximab biosimilar (Truxima®)

**HMMC Recommendation**

Truxima® is recommended for introduction into the local health economy, in line with HMMC-approved indications for rituximab originator.

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**Background Information**

A biosimilar medicine is a biological medicine that is developed to be similar to an existing biologic in terms of quality, safety and efficacy. Biosimilars are not the same as generics – the manufacture of biologic medicines is highly complex and no two batches of any given product are identical. This presents a huge regulatory challenge but it is one that has been successfully overseen by the EMA for several decades. In order to gain regulatory approval, the variability between the biosimilar and the reference medicine will have been shown to have no effect on safety or efficacy. The aim of development is to convincingly demonstrate high similarity to the reference product. This will then allow the biosimilar to rely on, in part, the existing efficacy and safety experience with the originator product. Copies of existing biologics (biosimilars) have been approved for use for many years (e.g. somatropin, epoetin, filgrastim).

**Biosimilar rituximab**

- Rituximab biosimilar (Truxima®) recently became available on the UK market (April 2017). It is manufactured by Napp Pharmaceuticals and currently is available only as a 500mg concentrate for solution for infusion with a 100mg presentation due to launch in the next few weeks.
- Another rituximab biosimilar is expected to be marketed by Sandoz in late June 2017 and there are also a number of other versions under development.
- As with originator rituximab (MabThera®, Roche) intravenous Truxima® is licensed for use in adults with rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis, non-Hodgkin’s lymphoma (NHL) and chronic lymphocytic leukaemia (CLL). Licensed indications of the Sandoz rituximab biosimilar are expected to match those of MabThera®.
- There are no differences in the way the available brands of rituximab should be administered.
- The issue around the lack of a 100mg preparation being available currently will impact more on the oncology indications for this drug where doses are modified according to body surface area and the 100mg vial is therefore more likely to be involved in the manufacture of a dose. For rheumatology patients requiring this drug (the majority of CCG-funded patients), the lack of the 100mg vial will not be an issue as the standard dose is two 1g doses given two weeks apart.
- A comprehensive comparability exercise was performed for the biosimilar against reference product (MabThera®). The initial stage consisted of numerous physiochemical tests and studies comparing biological activity and the biosimilar was deemed to be comparable to the reference product from a quality perspective. The non-clinical exercise consisted of studies evaluating their similarity in terms of pharmacology, pharmacokinetics and toxicology and again Truxima® was considered to be comparable to the reference product.
- In addition to the overarching biosimilars guideline, the EMA has also produced a number of class-specific guidelines, including one on the development of monoclonal antibodies. This states that the most sensitive model and study conditions (pharmacodynamic or clinical) should be used in a homogeneous patient population. In cases where comparative pharmacodynamic studies are claimed to be most suitable to provide the pivotal evidence for similar efficacy, applicants will have to choose clinically relevant markers, justify these markers, and also provide sufficient reassurance of clinical safety, particularly immunogenicity. To demonstrate clinical similarity between Truxima® and MabThera® the manufacturers chose to demonstrate equivalence in a population of patients with moderate to severe rheumatoid arthritis (RA) using the American College of Rheumatology (ACR)-20 response and in a population of patients with Follicular Lymphoma using overall response rate (ORR) as markers of disease response and this was accepted as valid by the EMA.
- The Medicines and Healthcare Products Regulatory Agency (MHRA) recommends that it is good practice to prescribe biological products by brand name to ensure that substitution of a biosimilar product does not occur when the medicine is dispensed by the pharmacist.
- Local clinical experience in HVCCG/WHHT with a different biosimilar, infliximab, has been positive, in terms of efficacy and safety compared with originator.
- Gain share arrangements in regards to uptake of biosimilars are in place between Provider organisations and host Commissioners in a variety of guises, both nationally and locally. Implementation of biosimilar rituximab use...
Current statements from clinical bodies

- NICE issued a position statement on biosimilars in January 2015. This states that similar biological medicinal products will usually be considered in the context of a Multiple Technology Appraisal in parallel with their reference products in the indication under consideration. In general, biosimilars will not undergo new Technology Appraisals (TA) as NICE considers them similar enough to the reference product, therefore recommendations set out in original TAs will apply to the appropriate biosimilar(s).
- In the NHS England document entitled 'What is a biosimilar medicine', it is stated that, “where NICE has already recommended the originator biological medicine the same guidance will normally apply to a biosimilar of the originator”.
- Within the Revised Specialised Commissioning CQUINS for 2017/18 and 2018/19 NHS England aim to support the faster adoption of best value medicines with a particular focus on the uptake of best value generics, biological medicines and use of CMU procurement frameworks as they become available. There are specific targets which are relevant to uptake of new biosimilar medicines as follows:
  - Adoption of best value generic / biologic products in 90% of new patients within one quarter of guidance being made available.
  - Adoption of best value generic / biologic products in 80% of applicable existing patients within one year of being made available (except if standard treatment course is < 6 months).
- The British Society for Rheumatology (BSR) issued an updated position statement on biosimilars in January 2017. The statement consists of five recommendations and is supportive of biosimilars being used in treatment naïve patients. In terms of switching, BSR recommend that the decision to switch patients currently receiving a reference product to a biosimilar should be on a case-by-case basis until further data are available to support safe switching. They recommend that strong safeguards are required to ensure that patients who have responded well to existing medicine and are switched for non-clinical reasons are closely monitored to ensure efficacy and safety, and that if such patients fail to maintain the efficacy achieved on a reference product then they should have the option of reverting to it.

Risks vs. benefits

- Based on the equivalency studies, prescribing of biosimilar rituximab in place of originator is expected to provide cost opportunities for the local health economies without detriment to patient services or outcomes.
- The majority of the rituximab spend in both ENH and HV CCGs is for rheumatology patients, with a much smaller proportion of spend in haematology (100mg vials). The use of biosimilar rituximab in place of originator gives a potentially substantial cost avoidance opportunity. If the use of rituximab biosimilar is not implemented, the local health economy will miss out on savings which could be utilised to develop local health services to benefit these and other groups of patients.

Evidence of Clinical Effectiveness

- A fully published randomised study was conducted in which 154 patients with active RA despite taking methotrexate and having previously shown an inadequate response or intolerance to an anti-TNF agent. Following randomisation patients received two intravenous infusions of 1000 mg of either CT-P10 (biosimilar version of rituximab and now marketed as Truxima®, n=103)) or reference product (n=51) whilst continuing methotrexate. The main objective of the study was to demonstrate pharmacokinetic equivalence but efficacy was also assessed. In this study the groups were well balanced at baseline in terms of potential confounding variables. After 24 weeks the ACR response rates were highly similar between the two groups (63% vs. 66.7% achieved ACR20, 37% vs. 31.1% achieved ACR50 and 16% vs. 14.6% achieved ACR70 for CT-P10 and reference product respectively). Similarly, no differences were shown in mean time to achieve ACR20 (58 vs. 60 days), the proportions of patients achieving good or moderate European League against Rheumatism (EULAR) responses, or in decreases in mean scores from baseline in Disease Activity Scores in 28 joints (DAS28). Improvements in the 36-item Short Form Health survey (SF-36) and physical and mental health summary scores were also shown to be similar between the two groups. Anti-drug antibodies were detected in 17.6% and neutralising antibodies in 2% of patients in both groups at week 24. In terms of safety, adverse events were reported in 51% and 74.5% of the CT-P10 and reference groups respectively – these were classified as serious in 4.9% and 5.9%, and were infusion-related in 16.7% and 19.6% respectively. The presence of anti-drug antibodies did not appear to affect the safety of either form of rituximab.
- If residual disease activity remained, or if disease activity returned within 48 weeks from the date of the first dose, patients could be retreated with the second course of study drug (two infusions as described above) initiated between 24 weeks and 48 weeks after the first infusion. In an unpublished abstract it is reported that 60
patients received a second course of CT-P10 and 23 patients received a second course of reference product. After 24 weeks follow up, the DAS28-CRP score decreased by 2.4 and 2.5 and the DAS28-ESR scores decreased by 2.0 and 2.0 in the CT-P10 group and the reference product groups respectively.

- Eighty seven patients (58 who received CT-P10 and 29 who received MabThera®) that completed 72 weeks follow up entered an open-label extension study. In this phase their disease was monitored and they were treated with CT-P10 if there was evidence of worsening disease activity – during 56 weeks of follow up 38 (65.5%) and 20 (69%) of patients required further treatment with CT-P10. Again in an unpublished abstract it is reported that the DAS28-CRP and ESR improvement were similar in the two treatment groups – a 2.2 and 2.7 point reduction respectively in the group maintained on CT-P10 and a 2.2 and 2.4 point reduction in the group switched to CT-P10. No significant differences in toxicity were noted. This study provides some reassurance about the feasibility of switching patients previously treated with MabThera® to Truxima®.

- In a larger unpublished Phase III trial (n= 372) the pharmacokinetics and efficacy of CT-P10 was compared with the reference products MabThera® and Rituxan® (the branded version of rituximab available in the US). Efficacy was determined by clinical response assessed by change from baseline activity measured by DAS28-CRP at week 24 followed by an extended study period so that in total patients were followed up for up to 76 weeks. The dosage regimen was as described for the study above and patients received up to three courses of treatment. The trial was powered to demonstrate therapeutic equivalence which was defined as there being a no more 0.6 point difference in the upper and lower limits of the 95% confidence interval for the estimate of treatment difference as assessed by DAS28-CRP at week 24. The authors report that the treatment difference was 0.05 (a decrease of 2.13 vs. 2.09 in favour of CT-P10) and the 95% CI around this estimate was (-)2.9 to (+)0.2. As these figures are both less than 0.6, it was accepted that the treatments were therapeutically equivalent according to this definition.

- Based on the results of these trials the EMA concluded that; “Biosimilarity of CT-P10 and MabThera® is considered demonstrated based on the efficacy data. In the pivotal RA trial, efficacy results in terms of DAS28 and ACR were shown to be comparable between CT-P10 and MabThera®. In addition, PK data discussed support the extrapolation to the autoimmune indications MPA/GPA.”

Cost Effectiveness
- Current biosimilar rituximab cost represents a significant dose for dose cost saving compared with originator (actual costs are commercial in confidence).
- Truxima® has demonstrated equivalence by EMA definition to the originator product.
- Rituximab originator has been recommended by NICE as a cost effective treatment option for the following CCG-commissioned indication: rheumatoid arthritis after failure of TNF-inhibitor in adults. This NICE approval would apply equally to the biosimilar product.
- Locally across Hertfordshire, rituximab originator is also recommended for the following indications: rheumatoid arthritis (first line) in adults; chronic immune thrombocytopenic purpura (ITP) in adults. These local recommendations would apply equally to the biosimilar product.

The needs of the population
The needs of the population are low as originator rituximab meets the clinical requirements of the existing patient group.

The needs of the community
The reduced cost of biosimilar rituximab in comparison with originator would result in more resource available to treat other patients / conditions.

Policy Drivers
- Specialist clinical bodies have produced position statements relating to biologics (see above).
- Patient numbers for biologics are increasing year on year, and there is a need for the local health economies to continue to deliver care within the allocated financial resources.

Equity
No equity issues identified.
Implementability
Governance arrangements are required within Provider Trusts to ensure that biosimilar rituximab is prescribed by brand. This is in line with MHRA guidelines that state that biological medicines, including biosimilars, must be prescribed by brand name to support on-going pharmacovigilance.

References