Answers to commonly asked questions about biosimilar versions of rituximab

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The first biosimilar version of rituximab (Truxima®) was approved for use in Europe in February 2017 and was launched in the UK in April 2017. It is licensed for intravenous use in adults with rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis, non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukaemia (CLL). This briefing sheet is intended to support prescribers by providing answers to commonly asked questions about the introduction of this medicine.

What is a biosimilar medicine?

A biosimilar medicine is a biological medicine that is highly similar to a medicine that has already been authorised to be marketed in the EU (the biological reference medicine) with respect to quality, safety and efficacy.

In their position statement on biosimilar medicines the British Society of Rheumatology describe a biosimilar medicine as, "a biological medicine manufactured to be similar to an existing licensed "reference" biological medicine, **with no meaningful differences from the reference medicine in terms of quality, safety or efficacy"** (1)

A comprehensive guide to biosimilars is available from NHS England; this is intended to provide an update for stakeholders about their developing role in the NHS and can be used locally to inform finance and procurement discussions (2).

A very useful guide to biosimilar medicines (and rituximab in particular) has recently been published by the Cancer Vanguard (3). This web-based resource provides an education and engagement programme about the use of biosimilar medicines which includes access to the following resources:

- Biosimilars principles – education presentation
- Service impact study
- Education impact assessment
- Biosimilar policy
- Patient information leaflet (available soon)

What brands of biosimilar rituximab will be available for use?

A biosimilar version of intravenous rituximab (Truxima®; Napp) is licensed in the UK and was launched in April 2017 (4).

Another biosimilar version of rituximab is expected to be marketed by Sandoz later in 2017 and there are also a number of other versions under development (5). This document will be updated as these products reach the market.

Are there any differences in the licensed indications and doses between biosimilar rituximab and the reference product?

No - in common with MabThera®, 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) (6,7)

How should rituximab be prescribed?

The Medicines and Healthcare Products Regulatory Agency (MHRA) recommends that it is good practice to prescribe biological products by brand name to ensure that inadvertent substitution does not occur when the medicine is dispensed by the pharmacist (8). The use of brand names in all stages of the medicines supply chain for rituximab will be essential to allow differentiation between the two forms, which is vital for post-launch pharmacovigilance and to avoidance of *inadvertent* switching.

Pharmacists should challenge any prescriptions for rituximab that refer to its generic rather than trade name, to ensure that the product dispensed is the correct one intended for the patient.

Are there any differences in presentation of the available brands of rituximab?

At present Truxima® is only available in vials containing 500 mg of rituximab in 50ml as a concentrate for solution for intravenous infusion. The originator (MabThera®) is also available in vials containing 100 mg in 10ml as a concentrate for solution for intravenous infusion but it is likely that Truxima® will not be available in this vial size until at least July 2017 (personal communication).

Rituximab is licensed for use at a dose of 375mg/m^2 of body surface area for patients with NHL, CLL (increased to 500mg/m^2 after first dose), and granulomatosis with polyangiitis and microscopic polyangiitis (5,6). This may have some implications in the short-term in terms of potential for increased drug waste and reduced savings from using the biosimilar version instead of MabThera® for these indications. However it is likely that even if only there is a partial use of a vial of Truxima® to make up a dose of rituximab overall cost savings should still be achievable (personal communication). Alternatively, a central intravenous service could be utilised to compound individual patient doses of the biosimilar version under Section 10 of the Medicines Act 1968 if pharmacy service capacity permits. Stability data to support such use is available (personal communication).

For patients being treated with rituximab for rheumatoid arthritis it is more straight forward as the standard licensed dose is two 1000 mg IV infusions (i.e. 2x 500 mg vials per dose) (5,6).

MabThera® is also available as a solution for subcutaneous injection (1400 mg in 11.7ml) which is licensed for use in patients with NHL (9). This version is still under patent so there will not be biosimilar versions of the subcutaneous formulation available for the foreseeable future.

Specialised Pharmacy Services (SPS) will also publish an in-use risk assessment which advises on strategies to minimise the risks associated with the introduction of Truxima® to the market.

Are there any differences in the way the available brands of rituximab should be administered?

The recommended initial rate of intravenous administration of rituximab (both MabThera® and Truxima®) is 50 mg/hour; after the first 30 minutes, it can be escalated in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour (5,6). For subsequent doses, rituximab can be infused at an initial rate of 100 mg/hour, and increased by 100 mg/hour increments at 30 minute intervals, to a maximum of 400 mg/h. For rheumatoid arthritis patients who did not experience a serious infusion related reaction with their first or subsequent infusions of a dose of 1000 mg rituximab administered over the standard infusion schedule, a more rapid infusion can be administered for second and subsequent infusions.in which rituximab is given at a rate of 250 mg/hour for the first 30 minutes and then 600 mg/hour for the next 90 minutes. If the more rapid infusion is tolerated, this infusion schedule can be used when administering subsequent infusions. It is however noted that patients who have clinically significant cardiovascular disease, including arrhythmias, or previous serious infusion reactions to any prior biologic therapy or to rituximab, should not be administered the more rapid infusion.

Some centres use an off-label rapid infusion schedule for rituximab in cancer patients in which 20% of the required dose is administered over 30 minutes and the remaining 80% over the next 60 minutes (i.e. a total infusion time of 90 minutes). If these patients are switched to the new biosimilar it may be advisable to follow the recommended administration regimen outlined above to determine tolerability and this will have service capacity implications which need to be assessed.

Similarly any policy which involves switching patients from subcutaneous administration of MabThera® to intravenous administration of Truxima®, or increasing use of Truxima® in patient groups who are currently initiated on subcutaneous MabThera® will have service capacity implications that need to be quantified.

Are any clinical concerns being raised about using biosimilar versions of rituximab?

No specific concerns related to the introduction of a biosimilar version of rituximab were identified from a search of the literature. There is some discussion on the legitimacy of using overall response rate (ORR) as a primary end-point to assess clinical equivalence of biosimilar versions of rituximab with MabThera® in patients with follicular lymphoma on the basis that this was not used as a primary end-point in the trials of the reference product (10). However whilst progression-free survival or overall survival might be considered to be more

robust outcome measures it is acknowledged that they may not actually be sensitive enough to determine clinical equivalence between two versions of rituximab..

Concerns previously voiced by clinicians about biosimilars in general relate to theoretical concerns about their pharmaceutical quality, safety, and their interchangeability with the reference product. They include doubts about clinical efficacy and safety in extrapolated indications for which no formal clinical studies have been performed with the biosimilar (11). These clinical concerns have been allayed to a significant degree in rheumatology and gastroenterology following conference presentation of the results of research such as the NOR-SWITCH study in which patients were switched from branded infliximab to a biosimilar version and it was shown that it had no adverse impact on safety or effectiveness across the range of indications (12)

What evidence is required for the approval of biosimilars in the EU?

The regulatory requirements for the approval of a biosimilar are considerably more stringent than those for a generic drug. For the latter, it is usually sufficient to demonstrate pharmaceutical equivalence (identical amounts of the same active ingredient in the same dose form) and bioequivalence to the reference medicine. However for a biosimilar, a much more comprehensive analysis is required, due to the molecular complexity of these products and their manufacturing processes (2).

A legal pathway for the development of biosimilars (the 'biosimilar pathway') was established in the EU in 2005 and several biosimilars (e.g. somatropins; filgrastims; epoetins) have been licensed since this time (1). The guiding principle of the development of biosimilars is not to establish patient benefit per se (which has already been shown for the reference product), but to demonstrate high similarity to the reference product so that the experience gained with its use can be extrapolated to the biosimilar version (13).

The biosimilar development pathway involves an extensive comparability exercise, which is a head-to-head comparison of the biosimilar with the reference product in order to ensure a close resemblance in terms of physical chemistry, biological characteristics, safety and efficacy (13,14,). It is not expected that the biosimilar will be identical to the reference drug; the purpose of the comparability exercise is to show that the degree of variability is not significant. The development pathway follows a stepwise approach, with demonstration of: (14,15,16)

- Quality comparability (with regard to the molecular structure and functionality)
- Non-clinical comparability (comparative non-clinical studies)
- Clinical comparability (comparative clinical studies)

The extent of the non-clinical and clinical studies required to confirm biosimilarity will depend on the nature and the complexity of the reference product (14,15,16). The purpose of clinical data is to provide complementary information; for example the clinical relevance of any observed differences, and data on immunogenicity.

What evidence exists to support the use of a biosimilar version of rituximab?

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 (16).

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 (16).

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 (15). 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 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 (16).

Rheumatoid arthritis

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 (17). 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 (2 infusions as described above) initiated between 24 weeks and 48 weeks after the first infusion (16,18). 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 (16,19). 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) (16, 20). 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 3 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.

The ACR responses at 24 weeks are presented below

Treatment	**ACR20**	**ACR50**	**ACR70**
CT-P10	73.5%	47.7%	27.7%
Originator	75.9%	50.2%	30.5%

It is noted in the EPAR that there was no significant differences between the ACR measures at 48 weeks; although the data to support this are presented graphically the absolute data are not provided.

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.”

Follicular Lymphoma

A phase 1/3 randomized controlled trial was conducted to demonstrate the equivalence of pharmacokinetics and non-inferiority of efficacy for CT-P10 in comparison with Rituxan®. (16). Rituximab (either as CT-P10 or Rituxan®) was administered in combination with cyclophosphamide, vincristine, and prednisone (CVP) in 121 patients with previously untreated advanced CD20+ve follicular lymphoma (FL). The trial was double-blind and efficacy was determined by overall response rate (ORR) (complete response [CR] + unconfirmed complete response [CRu] + partial response [PR]) after up to 8 cycles of treatment. It is reported that 97% of patients treated with CT-P10 and 92.6% of patients treated with Rituxan® achieved an overall response. This equates to a mean difference of 4.3% in favour of CT-P10. The EMA state that the trial shows the lower bound of the 95%CI (a 4.14% difference in ORR in favour of Rituxan® lies within a pre-defined non-inferiority margin of -7%), therefore non-inferiority has been demonstrated.

Based on the results of this trial the EMA conclude that; “The objectives of study CT-P10 3.3 were to demonstrate similarity in pharmacokinetics and non-inferiority in efficacy of CT-P10 to Rituxan as primary endpoints when co-administered with CVP in patients with advanced FL; these objectives have been met and furthermore, extrapolation in the context of NHL and CLL indications is acceptable.”

At the time of writing most of the evidence discussed above remains unpublished and is only available in regulatory documents or as conference abstracts.

Is the current version of Mabthera identical to the version originally launched in 1998?

No –rituximab is a highly complex molecule produced in living cells so there will always be a minor degree of inter-batch variation. Since 1998 when MabThera® was first licensed there have been 23 manufacturing process modifications (7 low risk, 15 medium risk and 1 high risk) which have required the manufacturer to submit data to the regulator to show that those changes have not impacted adversely on the overall efficacy or safety of the product. (21).

Will there be any independent guidance available to help inform clinical practice?

NICE has explained its position with regards to the evaluation of biosimilars in a position statement (22). In terms of clarifying how existing NICE guidance for intravenous rituximab applies to any new biosimilar versions that are made available the following principles are relevant:

- The Department of Health has confirmed that a remit referred to NICE enables NICE to decide to apply the same remit, and resulting guidance, to relevant licensed biosimilar products which subsequently appear on the market.
- NICE has decided that normally all relevant published guidance that includes the originator molecule will apply to the biosimilar medicinal product at the time it is made available for use in the NHS. A funding direction will apply to a new biosimilar if the active drug substance has already been recommended by NICE.
- All existing guidance on biologics for which at least one biosimilar is available on the UK market will be amended to inform stakeholders and the public that the recommendations for the originator molecule also apply to any current and future biosimilars.
- NICE will consider appraising the evidence for any new relevant biosimilar product(s) when a published Technology Appraisal is considered for review; the introduction of a biosimilar would not automatically trigger an earlier consideration for review or an automatic decision to update the guidance.
- Biosimilars will only be appraised together with the reference products as part of a Multiple Technology Appraisal. Biosimilars will not be considered in a technology appraisal separately from the reference product.
- Recommendations will refer to the British approved name of the medicine and will not differentiate between the originator and biosimilar products. The guidance will state that treatment should be initiated with the cheapest available product. In acknowledgment of the fact that the EMA does not make recommendations on whether a biosimilar should be used interchangeably with its reference medicine, or with other biosimilar medicines, the issue of switching and interchangeability will not be considered within the technology appraisal.
- Biosimilar medicines will be considered to differ from the originator product only in terms of price.

These principles are reinforced in the NHS England document entitled “What is a biosimilar medicine”, where 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” (2). It is also stated that, “The decision to prescribe a biological medicine for an individual patient, whether an originator or biosimilar medicine, rests with the responsible clinician in consultation with the patient” and that “at the time of dispensing a biosimilar medicine should not automatically be substituted for the originator by the pharmacist”.

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 (23). 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)

For rituximab, NHS England expect these targets to be met in specialised services for oncology, rheumatology, dermatology and nephrology.

The British Society for Rheumatology (BSR) issued an updated position statement on biosimilars in January 2017 (1). The statement consists of 5 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.

The Cancer Vanguard has published a suite of resources to facilitate the uptake of biosimilar medicines but have not published explicit recommendations on initiating or switching patients to biosimilar medicines (3)

The British Oncology Pharmacists Association (BOPA) has published Guidelines on Implementation of Biosimilar Monoclonal Antibodies – Implementation of biosimilar MABs in Oncology – role of pharmacy (24).

BOPA states that biosimilar monoclonal antibodies (MABs) are therapeutically equivalent to the originator molecules and can and should be used for all commissioned indications, provided pharmacovigilance safeguards are in place, e.g. branded prescribing. They also acknowledge that although biosimilar MABS cannot be automatically substituted switching from originator to biosimilar (or biosimilar to biosimilar) is acceptable and can be recommended as part of a medicines optimisation strategy.

The BOPA Guidelines aim to facilitate the rapid uptake of biosimilar medicines by providing practical guidance on pharmacy managed introduction and switching programmes including advice on a number of practical considerations including electronic prescribing systems and the challenges of operating with two versions of every chemotherapy protocol that includes rituximab.

Are there any potential advantages to using a biosimilar version of rituximab?

As biosimilars are likely be available at lower costs than the originator, they have the potential to reduce treatment costs, expand market competition forcing originator companies to revise their pricing policies and hence increase patient accessibility. When compared to the respective branded originator products, the development of a new biosimilar medicine yields lower relative potential to decrease costs than is the case for a new generic medicine. This is because the process of manufacturing biological medicines is much more complex and the cost of generating the evidence needed to license the biosimilar medicine is much greater. Nevertheless biosimilars are already available and are expected to continue to be made available at very significantly lower acquisition cost than the corresponding originator, Since many are used to treat long-term conditions in large patient populations their use can

lead to significant absolute cost savings to healthcare systems. This will of course be contingent upon their acceptance in the marketplace (1,2).

NHS England state that they support the appropriate use of biosimilars which will drive greater competition and thereby release cost efficiencies ("headroom" to support the treatment of an increasing number of patients and the uptake of new and innovative medicines) (2)

It is not yet clear what the NHS contract price of Truxima® will be but based on current expenditure on MabThera® it is estimated that even a 50% switch to a biosimilar version marketed at 70% of the price of Mabthera® would reduce overall expenditure on this medicine by over £21m in England which equates to about £40,000 per 100,000 population.

What safeguards will be in place to ensure that post-marketing safety is being monitored?

Every biosimilar medicine authorised in the EU will have a risk management plan (RMP) in place and information on this is included in the European Public Assessment Report (7). Because similarity has been demonstrated with the reference product, the biosimilar can also refer to the safety experience gained with the reference product (16).

The EMA has approved the proposed risk management plan submitted by the marketing authorisation for Truxima® (7). This includes a commitment to complete ongoing studies which will provide more detailed information on safety concerns including risks of acute infusion reactions, infections, impaired immune response and progressive multifocal leucoencephalopathy (PML).

The marketing authorisation holder has undertaken to provide a physician education document for non-oncology indications which covers the following:

- The need for close supervision during administration in an environment where full resuscitation facilities are immediately available
- The need to check prior to Truxima® treatment, for infections, immunosuppression, prior/current medication affecting the immune system and recent history of, or planned, vaccination.
- The need to monitor patients for infections, especially PML, during and after Truxima® treatment.
- Detailed information on the risk of PML, the need for timely diagnosis of PML and appropriate measures to diagnose PML
- The need to advise patients on the risk of infections and PML, including the symptoms to be aware of and the need to contact their doctor immediately if they experience any.
- The need to provide patients with the Patient Alert Card with each infusion

The marketing authorisation holder will also provide patient information for non-oncology indications which will cover the following:

- Detailed information on the risk of infections and PML•
- Information on the signs and symptoms of infections, especially PML, and the need to contact their doctor immediately if they experience any.

- The importance of sharing this information with their partner or caregiver•
- Information on the Patient Alert Card

Clinicians working in oncology will be provided with material to ensure that they are aware that the product should be only be administered by the intravenous route.

What other biosimilar medicines are expected over the next few years?

Biosimilar versions of the following medicines are currently in development and are expected to be available in the UK over the next few years: trastuzumab (Herceptin®); adalimumab (Humira®); bevacizumab (Avastin®) and pegfilgrastim (Neulasta®).

What information is available for patients?

Truxima® – an EPAR summary for the public available via: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/004112/WC500222696.pdf

Patient Information Leaflet- Truxima® available via eMC website http://www.medicines.org.uk/emc/medicine/33187

A Q&A on biosimilar medicines from the EMA available via: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf

A specimen patient information leaflet will also be made available from the Cancer Vanguard

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