

## London Medicines Evaluation Network Review

### Answers to commonly asked questions about biosimilar versions of infliximab

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The first biosimilar versions of infliximab were approved for use in Europe in October 2014 and are due to be launched in the UK in late February 2015. This means that there will be three brands of infliximab available to prescribers in the UK and they will all be licensed identically to the originator product for use in ankylosing spondylitis, rheumatoid and psoriatic arthritis, psoriasis and inflammatory bowel disease (Crohn's disease and ulcerative colitis). This briefing sheet is intended to support prescribers by providing answers to commonly asked questions about the introduction of these medicines.

#### What is a biosimilar medicine?

A biosimilar medicine is a biological medicine that is 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. Information on biosimilar medicines and the background to their licensing and clinical use are discussed in an open access article from the Drug & Therapeutics Bulletin entitled; [What are biosimilars and are they important?](#) (1).

#### What brands of infliximab will be available for use?

Two infliximab biosimilars are licensed in the UK and will be marketed once the patents on Remicade® expire (end of Feb 2015). Despite the two different trade names (and two marketing authorisation applications), Inflectra® (Hospira) and Remsima® (Napp) are the same biosimilar product (CT-P13) (2). Both are manufactured by Celltrion.

The therapeutic indications, dosing regimen, pharmaceutical form (powder for concentrate for solution for infusion) and strength (100mg infliximab per vial) of the biosimilars are the same as those of the reference medicine Remicade® (3, 4).

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 (5). The use of brand names in all stages of the medicines supply chain for infliximab will be essential to allow differentiation between the various forms, which is vital for post-launch pharmacovigilance (discussed later) and to ensure patient safety (avoidance of inadvertent switching).

#### What objections are being raised about using biosimilar versions of infliximab?

Various medical societies have raised concerns about the use of biosimilars. Their main objections include the lack of clinical trials available in general and the use of extrapolation, whereby the licensed indications go beyond those studied for the biosimilar. In the case of the infliximab biosimilars, the European Medicines Agency (EMA) granted approval of their use for all Remicade® indications, based on clinical efficacy data for rheumatoid arthritis only. These issues are discussed further below.

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

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 (6). 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 (1, 7).

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 (1, 8). This follows a stepwise approach, with demonstration of: (8, 9)

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

The foundation of biosimilar development is the extensive characterisation and comparison of the physiochemical properties and biological activity of the biosimilar and the originator, and the subsequent requirement for non-clinical and clinical data will depend on the observed similarity in these aspects (6). The purpose of clinical data is to provide complementary information; for example the clinical relevance of any observed differences, and data on immunogenicity (6).

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

A comprehensive and state-of-the art comparability exercise was performed for the infliximab biosimilar with the reference product (Remicade®), with multiple batches of each product used for each analysis. The first part of the exercise consisted of numerous physiochemical tests and studies comparing biological activity. Although lower levels of afucosylation were identified in the biosimilar (discussed later), this was not considered to be clinically meaningful, and it was concluded that biosimilarity had been demonstrated (3, 4).

The second part of the comparability exercise consisted of pharmacodynamic, pharmacokinetic and toxicological studies (nonclinical) and clinical studies in humans. The two clinical studies included a Phase 1 pharmacokinetic study in ankylosing spondylitis and a Phase III study evaluating efficacy in rheumatoid arthritis. The key results from these were as follows (please see Table 1 in the Appendix for further details):

- PLANETRA (Phase III RCT; n=606): The biosimilar was equivalent to Remicade® in terms of ACR20 response rates at week 30 in patients with active RA despite methotrexate (61% vs. 59% respectively; 95% CI of the difference: -6% to 10%) (10). The study only evaluated a 3mg/kg dose of infliximab; a 5mg/kg dose was however used in the PLANETAS study.
- PLANETAS (pharmacokinetic study; n=250): Steady state pharmacokinetics (C<sub>max</sub> and AUC) were shown to be equivalent for the biosimilar and Remicade® in patients with ankylosing spondylitis. Clinical efficacy (secondary endpoint) was also similar; for example ASAS20 response rates were 70.5% and 72.4%, respectively (11)

Both studies were extended at week 54, at which point half of the patients who had been randomised to Remicade® were crossed over to the biosimilar. The results suggest continued safety and efficacy in these patients (12, 13).

The PLANETRA study evaluated infliximab in combination with methotrexate; it is therefore unknown if the demonstrated comparability would reflect outcomes in conditions in which it is used as monotherapy or in combination with other drugs (14). It was however evaluated as monotherapy in the AS pharmacokinetic study (11).

The evaluation of the safety profile of the biosimilar was supported mainly by the results from these two clinical studies. The type and incidence of adverse drug reactions observed with the biosimilar and Remicade® were generally similar and no new safety concerns were identified. There were no marked differences in the immunogenicity profile of the two products up to 54 weeks and the impact of antibodies on efficacy and safety was comparable (3, 4).

It is worth pointing out that Remicade® was originally licensed for the treatment of Crohn's disease in the EU under "exceptional circumstances", as there were limited safety and efficacy data available at the time (15). The license was extended to cover further indications following subsequent applications made to the EMA.

### **What evidence exists to support extrapolation of evidence to support use in one indication to use in another indication?**

Extrapolation is the regulatory and scientific process of granting a clinical indication to a medicine without its own clinical efficacy and safety data to support that indication (16). This is an already established scientific and regulatory principle that has been exercised for many years. Examples of its application include the introduction of a new subcutaneous formulation of an intravenous product (e.g. trastuzumab [Herceptin®]) and changes to the manufacturing processes of biologicals (discussed below). In both these cases, clinical data are typically generated in one indication only, with extrapolation to the other indications based on information gained from a comparability exercise (16). The principles of extrapolation have recently become the focus of heightened interest following the introduction of biosimilars.

If biosimilarity has been demonstrated in one indication, the EMA considers that extrapolation of efficacy and safety data to all other indications of the reference product may be acceptable with appropriate scientific justifications (9). Although concerns have been expressed about this, the Working Party on Similar Biologic Medicinal Products of the EMA stress that extrapolation will only be approved on the basis of sound scientific justification, and only when the following requirements have been fulfilled (6):

- Similarity with the reference product must be convincingly demonstrated based on the totality of evidence from the comparability exercise
- If the mechanism of action involved in the extrapolated indication(s) is different or unknown, additional convincing data (e.g. on pharmacodynamic parameters and/or functional assays reflecting the respective pharmacological action(s)) must be available for further reassurance that the biosimilar and the reference product will behave alike in these indications [this applied to approvals of biosimilars for somatropin, epoetin and filgrastim]
- The safety profile of the biosimilar must have been properly characterised and unacceptable immunogenicity excluded

Taking the above considerations into account, the extrapolation of data to other indications following demonstration of clinical similarity in a key indication, without the lack of a formal clinical trial, does not imply less reassurance with regards to safety and efficacy of the biosimilar (6). The principles of extrapolation have been applied to the approval of all biosimilars currently licensed in the UK (e.g. growth hormone; G-CSF), with no significant incidents reported to date.

### **What data is there to support the extrapolation of infliximab?**

The mechanism of action of infliximab in rheumatological indications and psoriasis is thought to be via its binding to soluble and/or transmembrane TNF $\alpha$ , and such binding (and the functions mediated by this binding) was comparable for the biosimilar and Remicade®. The Fc region of infliximab may however be involved in other potential mechanisms (e.g. antibody-dependent cellular cytotoxicity [ADCC]) that have been suggested to play a role in IBD (3, 4).

Analytical studies conducted as part of the comparability exercise identified lower levels of afucosylation in the infliximab biosimilar compared to Remicade®, and this led to lower levels of binding to specific Fc receptors. In one assay this appeared to result in lower ADCC activity, which raised concerns about the extrapolation of data from rheumatoid arthritis to Crohn's and ulcerative colitis. However no difference could be detected in a number of experimental models regarded as more relevant to the pathophysiological conditions in patients, and the observed difference in afucosylation was therefore not considered to be clinically meaningful (3, 4).

Supplementary tests showed similar inhibition of the direct effects of TNF $\alpha$  on epithelial cells that play an important role in Crohn's disease and there was similar induction of regulatory macrophages (implicated as a mode of action in IBD). Preliminary clinical data from a small cohort of South Korean patients with Crohn's disease and ulcerative colitis indicate similar response to CT-P13 compared with historical data on Remicade® (6). Based on the totality of the data presented, the EMA considered that biosimilarity of the biosimilar to Remicade® had been demonstrated, and that the data were sufficient to allow for extrapolation to all other indications of Remicade® (3, 4).

Post-authorisation registries and studies will provide further efficacy data for CT-P13 in the treatment of IBD (3, 4). A further study comparing CT-P13 and Remicade® in patients with active Crohn's disease is currently underway and is due to complete in 2017 (2).

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

NICE has recently clarified its position with regards to the evaluation of biosimilars. These 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 other circumstances, where it is considered a review of the evidence for a similar biological medicinal product is necessary, NICE will consider producing an 'Evidence summary new medicine'. Evidence summaries do not make recommendations hence the decision regarding the choice of biosimilar or originator biologic for an individual patient rests with the responsible clinician in consultation with the patient (17).

NICE is currently updating its guidance on the use of infliximab in ulcerative colitis. Based on the conclusions of the EMA regarding the demonstration of similarity, the Appraisal Committee concluded that its recommendations for infliximab could apply both to the reference product and to its biosimilars (18). Currently draft recommendations are available in the Final Appraisal Determination; final guidance is awaited.

The Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG) are both reviewing the infliximab biosimilars and the final assessments and recommendations are due for publication soon (19, 20).

The British Society of Gastroenterology issued a statement on biosimilars in 2014 (21). Although this is broadly positive, it notes the lack of published data for the infliximab biosimilar in the treatment of IBD and advises caution until such are available. A paper by the Working Party on Similar Biologic Medicinal Products of the EMA comments that such 'absolute certainty' called for in a number of such position papers is impossible to reach in any drug development. The weighing of benefits and risks of a medicine at the time of its approval always involves some uncertainty, which is much less for biosimilars than it is for innovative products (16).

### **Is Remicade® still the same product as the one used in the original clinical trials?**

Any biological product is likely to be modified several times throughout its life cycle, with various changes in manufacturing processes that may be quite substantial (16). In the case of Remicade®, there have been 40 listed changes made to the manufacturing process for the active substance or the final product since its original authorisation (1999-2011) (22).

The similarity of the product before and after such changes in manufacturing process must be demonstrated in order for the product to retain its license. This procedure involves the same scientific principles that underlie the comparability exercise for the purpose of demonstrating biosimilarity (in fact the data requirements for the latter are higher). Therefore from a scientific and regulatory point of view, the active substance of the biosimilar is just another version of the active substance of the originator (16).

### **Are there any potential advantages to using a biosimilar version of infliximab?**

Biological drugs are expensive and biosimilars are seen as a cost-saving alternative; those marketed are currently 5-20% cheaper than the originator products (23). Inflectra® and Remsima® have not yet been launched in the UK and their price has yet to be confirmed. Celltrion have however stated that 'the price of Remsima® will be more than 30% cheaper than those of the original drugs' in Europe (2). A statement by the British Society of Gastroenterology recommends that a substantial discount in line with that introduced in Norway (39%) and Poland (31%) will help to facilitate market access in order to gain real-world experience (21).

### **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](#). Based on similarity being demonstrated with the reference product, the biosimilar can also refer to the safety experience gained with the reference product (6).

In addition to routine pharmacovigilance activities, such as collecting adverse event reports, the RMP for the infliximab biosimilars includes several long-term extensions of pre-authorisation studies, two additional RCTs in Japan and Russia (both in rheumatoid arthritis), and additional observational studies to assess safety and efficacy in rheumatoid arthritis, Crohn's disease and ulcerative colitis (3, 4, 24). The companies will also contribute to various existing European registries, including the British Society for Rheumatology Biologics Register (BSR-BR) and Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT). Despite the EMA's approval of extrapolation of the biosimilar to cover all indications of Remicade®, the RMP additionally includes a RCT to study the safety and efficacy of the biosimilar in patients with active Crohn's disease (3, 4, 24).

Celltrion will be partnering with the BSR-BR in order to enter patients into the RA registry and will be actively recruiting patients from launch. Celltrion will also be creating an IBD registry as part of the risk management plan to include Crohn's disease and ulcerative colitis patients across the EU and South Korea; the details pertaining to the UK are however currently being determined (25). Hospira have confirmed that they are currently in late-stage discussions with various IBD registries (26).

In accordance with the reference product Remicade®, additional risk minimisation measures will address a number of important identified risks (3, 4). Celltrion have produced material for patients and healthcare professionals and this has been adapted by Hospira and Napp for UK customers, in collaboration with the MHRA (25, 26). There will be Patient Alert Cards addressing the risks of HBV reactivation, congestive heart failure, opportunistic infections, serious infections (including sepsis), and TB. Educational material for healthcare professionals will additionally cover the risks of serum sickness (delayed hypersensitivity reactions), lymphoma, HSTCL, serious infusion reactions during a re-induction regimen following a disease flare, and paediatric malignancy (3, 4). This material will ensure that prescribers are aware of the risks of treatment and will provide guidance on the appropriate screening and selection of patients (26). The healthcare professional information will include a specific section referring to the management of children with inflammatory bowel disease, as this was an additional risk minimisation measure identified in the EPAR (3, 4).

In view of the molecular complexity of biologicals and the subtle differences that are likely to exist between biosimilar products, it is important that adverse drug reactions (ADRs) are properly assigned to the suspect product. The MHRA therefore advises that care is taken to report the product name rather than the



substance name when reporting ADRs for biosimilars (5). The risk minimisation measures will communicate the importance of recording both the brand name and batch number of the product received by the patient wherever possible, particularly in cases of ADRs (26).

### **Will there be any support material produced to help minimise patient risk?**

UKMi will be producing an In-Use Product Safety Assessment Report on infliximab biosimilars in due course. This will use the UKMi validated tool to determine the potential safety issues associated with their introduction into the UK market and will include recommendations on the steps to be taken to help mitigate any identified risks. This will be available on the UKMi website and will be featured in the NICE Medicines Awareness Daily bulletin once published.

### **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®); etanercept (Enbrel®); rituximab (MabThera®); adalimumab (Humira®); bevacizumab (Avastin®); insulin glargine (Lantus®) and pegfilgrastim (Neulasta®) (2, 23).

### **What information is available for patients?**

A [Q&A](#) on biosimilar medicines is available from the EMA (27).

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## APPENDIX

**Table 1: Main results of two clinical studies of the infliximab biosimilar (CT-P13)**

Study	Population and treatment	Primary endpoint(s)	Key secondary endpoints	Adverse effects
Randomised, double-blind Phase III efficacy study ( <b>PLANETRA</b> ) (10)	606 patients with active RA despite MTX randomised to 3mg/kg CT-P13 or Remicade® at weeks 0, 2, 6, then every 8 weeks up to week 30	<b>ACR20 response at week 30:</b> <ul style="list-style-type: none"> <li>60.9% ITT (73.4% PP) for CT-P13</li> <li>58.6% ITT (69.7% PP) for Remicade®</li> </ul> <p>Equivalence determined as 95% CI of the difference (-6% to 10% ITT; -4% to 12% PP) within the predefined margin of <math>\pm 15\%</math></p> <p>At week 54 (n=457), ACR20 seen in 57% and 52%, respectively (95% CI -3% to 13%) (28)</p>	<b>ACR50:</b> 35.1% CT-P13 and 34.2% Remicade® <b>ACR70:</b> 16.6% and 15.5%, respectively  <p>Comparable findings for other efficacy measures and PK/ PD endpoints</p> <p>Antibodies to IFX in 25.4% CT-P13 and 25.8% Remicade® at week 30; 52% v 50% at week 54</p>	Comparable safety profiles TEAEs in 60.1% CT-P13 and 60.8% Remicade®; 35.2% v 35.9% considered related to treatment. Latent TB and increased ALT/AST most frequent Serious TEAEs reported in 10% v 7%*
<b>PLANETRA open-label extension</b> (12) (302 of 455 who completed scheduled visits up to 54 weeks): - 158 continued CT-P13 - 144 switched from Remicade® to CT-P13 for further 48 wks		<p>Through week 102, ACR20/50/70 rates were maintained and were similar in each group: 72.2%/48.3%/24.5% for the maintenance group and 71.8%/51.4%/26.1% for the switch group.</p> <p>Proportion of patients positive for antibody was comparable between the groups and did not increase significantly during the second year (46% and 50% at week 102, for maintenance and switch groups, respectively)</p>		
Randomised, double-blind Phase 1 pharmacokinetic study ( <b>PLANETAS</b> ) (11)	250 patients with AS randomised to 5mg/kg CT-P13 or Remicade® at weeks 0, 2, 6, then every 8 weeks up to week 30	<b>AUC</b> (ratio of geometric means: 104.5% [90% CI 94% to 116%])  <b>Cmax</b> (ratio of geometric means: 101.5% [90% CI 95% to 109%])  <p>Steady state PK shown to be equivalent as 90% CIs within the predefined equivalence margin (80-125%)</p>	<b>ASAS20 response at week 30:</b> <ul style="list-style-type: none"> <li>70.5% of CT-P13</li> <li>72.4% of Remicade®</li> </ul> <p>(OR 0.91; 95% CI 0.51 to 1.62)</p> <b>ASAS40 response at week 30:</b> <ul style="list-style-type: none"> <li>51.8% of CT-P13</li> <li>47.4% of Remicade®</li> </ul> <p>(OR 1.19; 95% CI 0.7 to 2.0)</p>	Comparable safety profiles TEAEs in 64.8% CT-P13 and 63.9% Remicade® ; most commonly increased AST/ALT; similar incidence for both arms
<b>PLANETAS open-label extension</b> (13) (n=174) – 88 continued CT-P13 and 86 switched from Remicade® to CT-P13 for 1 year		<ul style="list-style-type: none"> <li>ASAS20: 70.1% maintenance and 77.1% switch at wk 78; 80.7% v 76.9% at wk 102</li> <li>ASAS40: 57.5% maintenance and 51.8% switch at wk 78; 63.9% v 61.5% at wk 102</li> <li>ASAS partial remission rates and proportion with antibodies also similar</li> </ul>		

AS: ankylosing spondylitis; RA: rheumatoid arthritis; AUC: area under the concentration-time curve; Cmax: maximum steady state serum concentration; PK: pharmacokinetics; PD: pharmacodynamic; TEAE: treatment-emergent adverse effects; IFX: infliximab; PP: per protocol; IIT: intention-to-treat

\*Although there was a numerical imbalance in serious adverse events observed in PLANETRA, with a higher number of serious infections (including active TB) in the CT-P13 arm, the numbers were low and the CHMP considered this was most likely a chance finding (3, 4).