East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, North East Hampshire & Farnham CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Evidence review for Surrey Prescribing Clinical Network

Medicine and proposed indication	Biosimilar Infliximab - Inflectra® and Remsima® Rheumatoid arthritis, Crohn's disease, Ulcerative colitis, Ankylosing spondylitis, Psoriatic arthritis , Psoriasis
Requested by	PCN

SUMMARY

Clinical Effectiveness

There are now three brands of infliximab available to prescribers in the UK, all licensed identically for use in ankylosing spondylitis, rheumatoid and psoriatic arthritis, psoriasis and inflammatory bowel disease.
The two new products, Inflectra® and Remsima® are known as biosimilar medicines, that is a biological medicine that is similar to a medicine that has already been authorised to be marketed in the EU (Remicade®) with respect to quality, safety and efficacy.
An authorised biosimilar can be considered to be clinically equivalent to the originator product.
Despite the two different trade names, Inflectra® (Hospira) and Remsima® (Napp) are the same biosimilar product (CT-P13) (2). Both are manufactured by Celltrion.

The totality of evidence indicated similar efficacy of the biosimilar and the reference product in all therapeutic indications of infliximab. BIOSIMILARS: THE SCIENCE OF EXTRAPOLATION: BLOOD, 20 NOV 2014 VOL 124, No 22

Safety

The totality of evidence indicates similar safety of the biosimilar and the reference product in all therapeutic indications of infliximab. BIOSIMILARS: THE SCIENCE OF EXTRAPOLATION: BLOOD, 20 NOV 2014 VOL 124, No 22

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.
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 and to avoid inadvertent switching.

Patient factors

There are no clinical reasons why patients should not be initiated on a biosimilar infliximab rather than Remicade.
South East Coast Regional Pharmacy Procurement will be able to provide patient information and consent forms for patients to change to biosimilar preparations where appropriate.

Cost implications

The list price of Remicade® is £419.62 for a 100 mg vial (excluding VAT; BNF edition 67).
NHS organisations are able to obtain at lower cost.
Both Remsima and Inflectra launched in UK Feb 15 at an NHS list price of £377.66 per 100mg vial
The Regional CMU tender for infliximab (including Remicade®, Inflectra® and Remsima®) has recently been completed. Inflectra has the lowest acquisition cost on this framework.
Actual costs are commercially confidential.

Relevant guidance / reviews

London Medicines Evaluation Network - Feb 2015 - Included in evidence review below.

NICE technology appraisal guidance [TA329] for treating moderately to severely active ulcerative colitis after

the failure of conventional therapy.
Infliximab is recommended in the TA as Remicade, Inflectra or Remsima.
In section 3, the technologies, they state; "Biosimilar versions of infliximab (Inflectra, Hospira; Remsima, Celltrion) have a marketing authorisation in the UK for the same indications. The therapeutic indications, dosage and method of administration for Remsima and Inflectra are identical to those for the reference product (Remicade). Adverse reactions are also similar."
In section 4, evidence and interpretation, when considering cost effectiveness the NICE Committee discussed that biosimilar versions of infliximab are licensed for the same indications as the reference product and discussed whether infliximab guidance would also apply to biosimilars.
The Commitee noted that the European Medicines Agency was content that the pharmacokinetics, efficacy, safety, and immunogenicity profiles of the biosimilars were similar to those of the reference product.
Section 4.16, Infliximab, reads;
"Inflectra and Remsima are biosimilar products to infliximab that were developed as a single product, CT-P13. CT-P13 was compared with Remicade (the reference proprietary product) in 2 RCTs:

- PLANET-AS: a trial comparing the pharmacokinetics, efficacy and safety of CT-P13 and Remicade in patients with ankylosing spondylitis (n=250).
- PLANET-RA: a trial comparing the efficacy and safety of CT-P13 and Remicade in patients with rheumatoid arthritis whose disease had an inadequate response to methotrexate (n=606).

The objective of these trials was to demonstrate that CT-P13 was similar to the reference product. The European Public Assessment Reports for Inflectra and Remsima acknowledged that the pharmacokinetics, efficacy, safety, and immunogenicity profiles of CT-P13 were similar to those of Remicade in PLANET-AS and PLANET-RA. Although neither of the trials was for ulcerative colitis, the European Public Assessment Reports state that the overall data comparing CT-P13 with Remicade allow for the extrapolation of the evidence generated by PLANET-AS and PLANET-RA to all other indications of Remicade."

The Committee concluded that its recommendations for infliximab could apply both to the reference product and to its biosimilars. (Ref: TA329, section 4.81, Cost Effectiveness)

NICE TA329 states that if more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose).

Likely place in therapy relative to current treatments

Hospital only in place of Remicade
All new patients when Infliximab is prescribed
Some existing patients, following informed discussion with the patient and consent

Recommendations to PCN

1. Recommendation for biosimilar versions of infliximab to be used in new patient for all indications where they have licensing authorisation in the UK.
2. Recommendation for all existing infliximab patients to be given written and verbal information and the option to change to biosimilar versions with consent.

Evidence review

London Medicines Evaluation Network - Feb 2015

Answers to commonly asked questions about biosimilar versions of infliximab

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. Despite the two different trade names, 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 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:

- 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 (Cmax 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 though to be via its binding to soluble and/or transmembrane TNFα, 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 TNFα 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).

Why is Remicade® being described as a biosimilar version of itself?
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).

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Equity / Stakeholder views (if relevant)	
Decisions of local Trusts DTCs and neighbouring APCs	BSUH – All new patients to start on biosimilar SASH – All new patients and an audited switch of existing patients in gastroenterology at East Surrey Ashford and St Peters - All new patients and looking to switch existing patients Royal Surrey - Frimley - Epsom and St Helier – not been to NDAIG yet but in discussed they are in agreement for all new patients and Rheumatology looking to switch existing patients
Recommendations from national / regional decision making groups	NICE concluded that its recommendations for infliximab in Ulcerative Colitis could apply both to the reference product and to its biosimilars.
CCG priorities	In order to make the increase in use of infliximab which will arise from implementing NICE TA 329 affordable, all CCGs need to look to using the drugs of lowest acquisition cost from the guidance.

Date: 30.03.15

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Declaration of interest: None

VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
V1	30.03.15	Liz Clark		