Infliximab Biosimilars
(Reimsima® & Inflectra®)

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Summary

- Infliximab (Remicade®) is a monoclonal antibody that plays a major role in the management of many inflammatory autoimmune diseases. In February 2015, a biosimilar formulation of infliximab known as CT-P13 was launched under two different brand names: Inflectra®▼ (Hospira), and Remsima®▼ (Napp). Despite two separate marketing authorisations, they are essentially the same biosimilar product and are both manufactured by Celltrion. The licensed therapeutic indications, dosing regimen, pharmaceutical form, and strength for both biosimilar products are identical to those of the originator infliximab.

- In extensive product characterisation exercises all major physicochemical characteristics and biological activities of CT-P13 were comparable to those of Remicade®.

- The clinical data demonstrating similarity between CT-P13 and Remicade® consisted of two main clinical trials (PLANETRA and PLANETAS). The studies showed that up to 54 weeks there were no clinically meaningful differences in the efficacy, safety or pharmacokinetic profile between CT-P13 and Remicade® in patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Preliminary data from 48-week open-label extensions showed that patients who switched from Remicade® to CT-P13, efficacy was sustained, and comparable to those maintained on CT-P13.

- Although clinical studies were only performed in patients with RA and AS, efficacy and safety for other indications is assumed from the demonstration of equivalence to the reference product in accordance with regulatory procedures. Based on the totality of evidence, the EMA concluded that similarity has been convincingly demonstrated enabling extrapolation of CT-P13 approval to all other indications for which the reference product Remicade® is approved, including ulcerative colitis, Crohn’s disease, psoriatic arthritis and psoriasis.

- Overall, the type and incidence of treatment-emergent adverse events observed in the clinical studies was generally similar between the two treatment groups and were in line with the well-characterised safety profile of Remicade®. There were no marked differences in the immunogenicity profile and the impact of antibodies on efficacy and safety was comparable between treatment arms.

- Both Inflectra®▼ and Remsima®▼ have a NHS list price of £377.66 per 100 mg vial, which is 10% lower than the list price of Remicade® (£419.62 per 100 mg vial). However, the actual cost of Remicade® and the biosimilar products differs substantially from list prices due to locally negotiated procurement discounts. Based on the CMU contract price, Inflectra®▼ and Remsima®▼ would be cost saving in all indications compared with Remicade® at its current price. Depending on actual usage of each product, cost savings of up to may be achieved. Local CCGs should contact NTAG if more detail is required.
Introduction and background

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of tumour necrosis factor alpha (TNF-α). Inhibition of TNF with biologic agents such as infliximab plays a major role in the management of many inflammatory autoimmune diseases. Infliximab was first authorised in the EU in 1999 under the brand name of Remicade® (MSD), and is approved for the following indications:

- Rheumatoid arthritis
- Ankylosing spondylitis
- Psoriatic arthritis
- Psoriasis
- Adult Crohn’s disease
- Paediatric Crohn’s disease
- Adult ulcerative colitis
- Paediatric ulcerative colitis

A biosimilar is a biological medicine that is developed to be highly similar to an existing licensed biological medicine (the ‘reference medicine’) in terms of quality characteristics, biological activity, safety, and efficacy. Biosimilars are not the same as generic medicines, which have simpler chemical structures and are considered to be identical to their reference medicines.

Biosimilars are typically large, complex molecules manufactured using living organisms. Although the active substance of a biosimilar and its reference medicine are essentially the same biological substance, the characteristics of biologic drugs cannot be reproduced exactly due to their complex nature and production methods. Like the reference medicine, the biosimilar will have a degree of natural variability, and minor quality differences are expected to be observed between a biosimilar and its reference product. To gain approval in the EU, such variability and any differences between the biosimilar and its reference medicine must have been shown not to affect safety or effectiveness.

In September 2013, the European Medicines Agency (EMA) approved a biosimilar formulation of infliximab known as CT-P13, which was subsequently marketed under two different brand names: Inflectra® (Hospira), and Remsima® (Napp). Despite two separate marketing authorisations, Inflectra® and Remsima® are essentially the same biosimilar product (CT-P13), and are both manufactured by Celltrion. The licensed therapeutic indications, dosing regimen, pharmaceutical form, strength and composition for both biosimilar products are identical to those of the originator infliximab (Remicade®). Both biosimilars were launched in the UK in February 2015, after the patent for Remicade® expired.

This document will review the comparability, efficacy, safety and cost of Inflectra® and Remsima®, with respect to the reference product Remicade®.
Guidance and related advice

The National Institute for Health and Care Excellence (NICE) has updated its position and process for providing guidance and advice on biosimilar medicines within the NHS. These products will usually be considered in the context of a Multiple Technology Appraisal (MTA) in parallel with their reference products in the indication under consideration. NICE technology appraisals will use the name of the active drug substance, including reference products and brand named similar biological medicinal products in its documentation. In other circumstances, where it is considered a review of the evidence for similar biological medicinal product is necessary, NICE will consider producing an ‘Evidence summary new medicine’. Evidence summaries will use the brand names of the medicines because substitutability and interchangeability cannot be assumed. 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.

NICE has recently updated its guidance on the use of infliximab in ulcerative colitis. The Appraisal Committee noted that the EMA was content that the pharmacokinetics, efficacy, safety, and immunogenicity profiles of the biosimilars were similar to those of the reference product. The Committee concluded that its recommendations for infliximab could apply both to the reference product and to its biosimilars.

The Scottish Medicine Consortium (SMC) have accepted Inflectra® and Remsima® for restricted use within NHS Scotland. Both products were accepted for restricted use for the treatment of rheumatoid arthritis; adult and paediatric Crohn’s disease and ulcerative colitis; adult ankylosing spondylitis; psoriatic arthritis and psoriasis. Both are restricted for use in line with the current SMC and Healthcare Improvement Scotland advice for the reference product Remicade®.

The All Wales Medicines Strategy Group (AWMSG) has recommended Inflectra® and Remsima® as an option for restricted use within NHS Wales. Both products should be prescribed within its licensed indications in accordance with NICE or AWMSG guidance for Remicade®, the reference product. Inflectra® and Remsima® should be prescribed by brand name to avoid automatic substitution and therefore help with pharmacovigilance.

The British Society for Rheumatology (BSR) issued a position statement on biosimilar medicines in February 2015. Although the BSR broadly supports the use of biosimilars in clinical rheumatology, it sets out some of the concerns on the use of biosimilars, and outlines measures on how to address these. It recommends that all biologics and biosimilars should be prescribed by brand name rather than by International Non-proprietary Name (INN); prescribing should be based on clinical reasons, and decisions made in partnership with the patients; substitution should only be with the consent of the prescribing clinician; all patients starting or switching to biosimilars should be registered with the BSR Biologic Register; raising awareness of biosimilars in patients and healthcare professionals; biosimilars should undergo robust technology appraisals; better information sharing across the care pathways; and that local tenders involving biosimilars seek to source a range of products.
The British Society for Gastroenterology (BSG) issued a statement on biosimilar medicines in 2014, in which it welcomed the introduction of new agents for the treatment of inflammatory bowel disease (IBD). However, it noted a lack of published evidence for biosimilars in the treatment of IBD, and urged caution until such data are available. It recommends prescribing by brand name; avoidance of switching from parent drug to biosimilar, or vice versa; registering all biologic use in an IBD register; and discussion with patients about the choice of anti-TNF.

Non-clinical evidence

To gain approval in the EU, biosimilar medicines must demonstrate that they are as safe and as effective as the reference medicine, and have the same quality characteristics. The EU regulatory process demands an extensive comparability exercise is performed through a stepwise process that begins with structural, physicochemical and biological analysis, non-clinical, then pharmacokinetic and pharmacodynamic studies, followed by clinical safety and efficacy trials. In the comparability exercise it was shown that all major physicochemical characteristics and biological activities of CT-P13 are comparable to those of Remicade® except for small difference in the amount of afucosylated infliximab, which translates in a lower binding affinity towards specific Fc receptors and lower and a lower ex vivo antibody-dependent cellular cytotoxicity (ADCC) activity in the most sensitive ADCC assay. However, this difference was not considered clinically relevant as it does not affect the activities of CT-P13 in the experimental models that are most relevant to the pathophysiological conditions.

Clinical evidence

The clinical program demonstrating biosimilarity between CT-P13 (subsequently marketed as Inflectra® and Remsima®), and the reference product infliximab (Remicade®) consisted of a phase III efficacy and safety study in patients with active rheumatoid arthritis (PLANETRA), and a phase I pharmacokinetic (PK) study in patients with ankylosing spondylitis (PLANETAS). Both studies were randomised, double-blind, multi-centre, parallel-group trials lasting 54-weeks. Patients who completed each of the studies had the option to continue on an open-label, 48-week extension phase, in which they either continued on CT-P13, or were switched from Remicade® to CT-P13.

PLANETRA

The PLANETRA trial recruited patients aged 18 to 75 years with active rheumatoid arthritis for ≥1 year despite receiving methotrexate for ≥3 months. Participants were required to have ≥6 swollen and ≥6 tender joints, and at least two of the following: morning stiffness (≥45 mins), CRP >2.0 mg/dl, and ESR >28 mm/h. Patients were randomised to a two-hour IV infusion of 3 mg/kg of CT-P13 (n=302) or Remicade® (n=304) with methotrexate (12.5 to 25 mg once weekly) and folic acid...
(≥5 mg once weekly) at Weeks 0, 2, and 6 then once every 8 weeks up to 54 weeks. This corresponds to three loading doses and six maintenance doses. Oral corticosteroids and NSAIDs were permitted if dose had been stable for ≥4 weeks prior to screening. The primary endpoint was the proportion of patients achieving a clinical response according to American College of Rheumatology (ACR) definition of a 20% improvement (ACR20) at week 30 in the intention-to-treat (ITT) and per-protocol (PP) populations. Equivalence was demonstrated if the 95% confidence interval (95% CI) for treatment difference was within the predefined margin of ±15%. Secondary endpoints included individual components of ACR criteria, ACR50, ACR70, European League Against Rheumatism (EULAR) response criteria, change in Disease Activity Score 28 (DAS28), Medical Outcomes Study Short-Form Health Survey (SF-36), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI).

In the ITT population, the proportion of ACR20 responders at week 30 was similar in the CT-P13 and Remicade® groups (60.9% and 58.6%, respectively). The 95% CI for the treatment difference was -6% to 10%, indicating therapeutic equivalence between treatment groups. The corresponding results in the PP population were 73% and 70%, respectively (95% CI -4% to 12%). The results of all secondary endpoints were consistent with the results of the primary endpoint. Good or moderate EULAR responses (C reactive protein (CRP)) at week 30 were 85.8% and 87.1%, respectively. ACR50 and 70 responses at week 30 were 42.3% vs. 40.6%, and 20.2% vs. 17.9%, respectively. The mean changes in individual ACR criteria, SDAI, CDAI and SF-36 components were similar in the CT-P13 and Remicade® groups. After each infusion, all pharmacokinetic and pharmacodynamic endpoints were comparable.

Among the 457 patients who received treatment up to week 54, an ACR20 response was achieved in 57% and 52% of patients in each group, respectively (95% CI -3% to 13%). ACR50 and 70 responses were also comparable between groups at 33.1% vs. 43.1.6%, and 16.2% vs. 15.1%, respectively.

**PLANETAS**

The PLANETAS trial recruited patients aged 18 to 75 years with active ankylosing spondylitis for ≥3 months, a Bath Ankylosing Spondylitis Disease Activity Index (BASADI) score of ≥4, and a visual analogue score for spinal pain of ≥4 were eligible for randomisation. Patients received a two-hour IV infusion of 5 mg/kg of CT-P13 (n=125) or infliximab (n=125) at Weeks 0, 2, and 6 then once every 8 weeks up to week 54. This corresponds to three loading doses and six maintenance doses. The primary objective of this study was to demonstrate comparable PK at steady state (area under the concentration-time curve (AUC) over the dosing-interval and observed maximum serum concentration (C\text{MAX,SS})) between Weeks 22 and 30. Equivalence was demonstrated if the 90% CI was within the predefined margin of 80-125%. Secondary endpoints included additional PK, and efficacy endpoints including 20% and 40% improvement in Ankylosing Spondylitis International Working Group criteria (ASAS20 and ASAS40), BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI), and SF-36.
The steady-state PK profiles of CT-P13 and Remicade® were shown to be equivalent. The ratio of geometric means was 104.10 (90% CI; 94 to 116) for AUC, and 101.47 (90% CI; 95 to 109) for CMAX,SS. The values for the 90% CI of the ratio were within the predefined margins, thereby satisfying the criteria set for PK equivalence. The results of secondary PK analyses (CMAX, CMIN and TMAX) were supportive of the primary PK result. Clinical efficacy was also similar between the two treatment groups. An ASAS20 was reported in 70.5% of CT-P13 recipients and 72.4% of Remicade® recipients (OR 0.91; 95% CI 0.51 to 1.62). An ASAS40 response was achieved in 51.8% and 47.4% of patients, respectively (OR 1.91; 95% CI 0.7 to 2.0). All other efficacy endpoints were comparable with both products eliciting improvements in clinical response.

Among the 213 patients who received treatment up to week-54, PK parameters were shown to be equivalent, with the 90% CI for the ratio of geometric means entirely contained within the pre-defined comparability margins. Response rates were also comparable, with an ASAS40 achieved in 54.7% and 49.1%, and an ASAS partial remission in 19.8% and 17.6%, respectively.

In both PLANETRA and PLANETAS the efficacy results were also analysed according to anti-drug antibodies (ADA) status. Data from each study shows that the efficacy response in both treatment groups was less robust in ADA positive patients than in those who had remained ADA negative throughout 54 weeks of treatment. However, in both studies, the impact of the immune response was comparable, with no statistically significant differences observed between the CT-P13 and Remicade® groups in efficacy analyses at week 30 based on ADA status.

**Switching from reference infliximab (Remicade®) to CT-P13**

A total of 302 patients who completed PLANETRA entered the open-label extension phase for an additional 48-weeks treatment, of whom, 158 were maintained on CT-P13 (maintenance group) and 144 were switched from Remicade® to CT-P13 (switch group). Efficacy assessments including ACR20/50/70 were assessed at weeks 54, 78 and 102. At all time points ACR20/50/70 response rates were comparable between the maintenance group and the switch group. Good or moderate EULAR responses and changes in DAS28 were also comparable.

A total of 174 patients who completed PLANETAS entered the open-label extension phase for an additional 48-weeks treatment, of whom, 88 were maintained on CT-P13 (maintenance group) and 86 were switched from Remicade® to CT-P13 (switch group). Comparable efficacy as demonstrated by ASAS20/40 and partial response rates was maintained up to 102 weeks in both the maintenance and the switched groups.
Safety

The size of the safety database and duration of exposure is appropriate for an assessment of the overall safety profile of CT-P13 in comparison to the reference product infliximab (Remicade®). During clinical studies, 302 patients with rheumatoid arthritis (PLANETRA) and 128 patients with ankylosing spondylitis (PLANETAS) received treatment with CT-P13. An additional 9 patients with rheumatoid arthritis were exposed as part of a pilot study to investigate the initial PK, safety, and efficacy of CT-P13. The data includes a safety update at week 54 after all patients had completed the comparative treatment phase of the trials which was submitted upon request of the Committee for Medicinal Products for Human Use (CHMP).

Overall, the type and incidence of treatment-emergent adverse events (TEAEs) observed in the clinical studies was generally similar between the two treatment groups and were in line with the well-characterised safety profile of Remicade® as outlined in the Summary of Product Characteristics. The majority of TEAEs were of mild to moderate severity, and no significant new safety signals, which had not been observed previously with Remicade®, were reported. A summary of the safety findings up to week 54 for each of the studies is presented below.

PLANETRA

In PLANETRA, the proportion of patients reporting at least one TEAEs was 70.2% (212) in the CT-P13 group and 70.3% (211) in the Remicade® group. The most frequently reported TEAEs (≥5% of patients in any treatment group) were latent tuberculosis (8.9% vs. 8.3% patients, respectively), upper respiratory tract infection (8.9% vs. 5.3%), nasopharyngitis (7.9% vs. 5.7%), urinary tract infection (6.0% vs. 7.0%), ALT increased (5.0% vs. 5.7%), bronchitis (4.3% vs. 5.7%), headache (4.3% vs. 5.3%), rheumatoid arthritis (5.0% vs. 3.7%), and hypertension (5.0% vs. 3.3%). Infusion-related reactions were reported for 3.3% and 3.7% of patients, respectively. Serious TEAEs occurred in 13.9% (42) of patients in the CT-P13 group and 10.0% (30) in the Remicade® group. The numerical imbalance was mainly due to a higher incidence of serious infections, including active tuberculosis. However, the numbers involved are small and a thorough review of all available data by the EMA suggests that the observed difference was most likely a chance finding.

PLANETAS

In PLANETAS, TEAEs were experienced by 72.7% (93) of patients treated with CT-P13 and 67.2% (82) patients treated with Remicade®. The most common TEAEs (≥5% in any group) were ALT increased (14.8% vs. 15.6%), AST (12.5% vs. 10.7%), upper respiratory tract infection (7.8% vs. 10.7%), nasopharyngitis (9.4 vs. 8.2), headache (7.8% vs. 5.7%), latent tuberculosis (6.3% vs. 4.1%), Blood CPK increased (6.3% vs. 4.1%), pharyngitis (3.1% vs. 5.7%), GGT increased (3.1% vs. 5.7%), and urinary tract infection (6.3% vs. 0.8%). The incidence of serious TEAEs in each treatment group was comparable at (6.3% (8) and 6.6% (8), respectively.

In the pilot study in patients with rheumatoid arthritis, the incidence of TEAEs was similar in the two treatment groups at 6.3% (6) and 6.6% (5), respectively. Only hypersensitivity, dizziness and pruritus were observed in more than one patient (all in the Remicade® group). Serious TEAEs were experienced by one patient in each treatment group.
Switching from reference infliximab (Remicade®) to CT-P13

In the open-label, 48 week extension of PLANETRA, the proportion of patients with at least one TEAEs by week 102 in the group maintained on CT-P13 and the group who switched from Remicade® to CT-P13 was similar (53.5% (85) vs. 53.8% (77), respectively).19 (44) of the maintenance group and 71.4% (60) of the switch group at week 102.21 These were classified as severe in 4.4% and 5.6%, respectively. The incidence of serious TEAEs in each treatment group was comparable at (7.5% (12) and 9.1% (13), respectively. Infusion-related reactions were seen in 6.3% (10) in the maintenance group and in 2.8% (4) in the switch group (p=0.1781). Rates of infection were similar between the two groups at (31.4% (50) and 32.9% (47), respectively. There were no reports of tuberculosis infections in either group.

In the extension phase of PLANETAS, TEAEs were reported in 48.9% (44) of the maintenance group and 71.4% (60) of the switch group at week 102.21 These were classified as severe in 3.3% (3) and 6.0% (5) of patients, respectively. Serious TEAEs were almost identical at 4.4% (4) and 4.8% (4), respectively. Infusion-related reactions or hypersensitivity were reported in 5.7% (5) in the maintenance group and in 2.3% (2) in the switch group. Rates of infection were 25.6% (23) and 34.5% (29), respectively. There was one case of tuberculosis in each group.

Immunogenicity

The number of patients with positive immunogenicity test results was examined in each treatment group at each time point in PLANETRA and PLANETAS. Overall, the detection of anti-drug antibody (ADA) was broadly similar in the CT-P13 and Remicade® treatment groups in both trials.

In PLANETRA, the proportion of patients positive for ADA in the CT-P13 and Remicade® groups was 25.4% (69) and 25.8% (70), respectively at week 14, 48.4% (122) and 48.2% (122) at week 30,17 and 52.3% and 49.5% at week 50.18 In the open-label extension phase (n=302), ADA positivity did not increase significantly during year two when both groups were receiving CT-P13. At week 102, 46.4% (64) of those who continued CT-P13 and 49.6% (64) of those who were switched from Remicade® to CT-P13 were ADA positive.19

Among patients in PLANETAS, the proportion who were ADA positive was 9.1% (11) in the CT-P13 group and 11.0% (13) in the Remicade® group, respectively at week 14, 27.4% (32) and 22.5% (25) at week 30,20 and 22.9% (25/109) and 49.5% (28/109) at week 50.22 In the extension phase (n=172), the proportion of patients who were ADA positive at week 102 was 25.0% (21) in the maintenance group and 30.7% (23) in the switch group, respectively.21

Pharmacovigilance and Risk Management Plan

All known risks associated with infliximab (Remicade®) treatment have been included in the Inflectra®▼ and Remsima®▼ Summary of Product Characteristics.5,6 The identified safety concerns include risk of infection (tuberculosis, bacterial infections, including sepsis and pneumonia, invasive fungal, viral, and other opportunistic infections), congestive heart failure, malignancies and
lymphoproliferative disorders. In collaboration with the MHRA, the manufacturers have produced educational materials for healthcare professionals and information for patients, including Patient Alert cards addressing these risks.24

In order to facilitate the safe introduction of infliximab biosimilars to the NHS, brand name prescribing, identification, recording and traceability needs to be in place.25 Brand name prescribing is vital if products are to be identified appropriately at the points of dispensing and/or administration. In addition, for each patient, a traceable record of the brand, batch number, and other vital details of the product used should be made.

Robust postmarketing pharmacovigilance is essential to ensure that the biosimilars are both safe and effective in the treatment of each of the indications for which it has been approved. As with all new medicines, the safety of Inflectra® and Remsima® are subject to continuous monitoring after authorisation. In order that all suspected adverse drug reactions (ADRs) are assigned to the correct product, care must be taken to report the brand name rather than the non-proprietary name when reporting ADRs for biosimilars.26

In addition to routine pharmacovigilance activities, a Risk Management Plan that includes several post-authorisation studies and registries that will provide further long-term efficacy data, including in the treatment of inflammatory bowel diseases (IBD), and further characterise the long-term safety profile of Inflectra® and Remsima®.15,16 Serious infections, including tuberculosis will be closely monitored on a longer-term and in larger patient cohorts through the use of several prospective registries in different patient populations, including IBD. Rare ADRs, such as malignancies and lymphoproliferative disorders, will also be closely monitored as part of these registries. Post-authorisation studies, including a randomised double-blind comparison of CT-P13 vs. Remicade® in active CD will provide essential efficacy and safety data in the treatment of IBD.

Extrapolation of efficacy and safety
Extrapolation is an established scientific and regulatory principle that has been exercised for many years. The EMA guideline on biosimilar monoclonal antibodies states that extrapolation of clinical efficacy and safety data to other indications of the reference antibody, not specifically studied during the clinical development of the biosimilar antibody, is possible based on the overall evidence of comparability provided from the comparability exercise and with adequate justification. This includes at least one clinical study in the most sensitive patient population measuring the most sensitive clinical endpoints.2

In extensive product characterisation exercises all major physicochemical characteristics and biological activities of CT-P13 were comparable to those of Remicade®.15,16 Clinical data from two comparative trials have shown that there are no clinically meaningful differences in the pharmacokinetics, efficacy, safety and immunogenicity profiles between CT-P13 and Remicade®. Based on the totality of evidence the EMA concluded that similarity has been convincingly demonstrated enabling extrapolation of CT-P13 approval to all other indications for which the reference product is approved, including ulcerative colitis, Crohn’s disease, psoriatic arthritis and psoriasis.
Dosage and administration

As with Remicade®, both Inflectra® and Remsima® are supplied as lyophilised concentrate for intravenous injection, in individually boxed single-use vials containing 100 mg infliximab. However, shelf-lives differ between the products: Remicade® has a 36 months shelf-life; Inflectra® 51 months and Remsima® 57 months. The reconstitution and dilution steps for Inflectra® and Remsima® are the same as those for Remicade®.

Both products are administered as an intravenous infusion, usually over a 2-hour period. Depending upon the indication, a loading dose regimen of 3 or 5 mg/kg are administered at 0, 2 and 6 weeks, typically followed by a maintenance dose regimen of the same dose every 6 or 8 weeks. The approved therapeutic indications and posology for Inflectra® and Remsima® are identical to those for Remicade®.

Cost analysis

Infliximab is a specified high-cost medicine and represents a significant expenditure for the NHS. Both Inflectra® and Remsima® have a NHS list price of £377.66 per 100 mg vial, which is 10% lower than the list price of Remicade® (£419.62 per 100 mg vial). However, the actual cost of Remicade® and the biosimilar products differs substantially from list prices due to locally negotiated procurement discounts.

On 1st April 2015, a new Commercial Medicines Unit (CMU) contract which covers all three infliximab products will start in the NTAG area. Under the CMU contract the negotiated price for each of the products are as follows:

- Remicade® (MSD) – based on usage the price ranges from band A: £419.62 (list price) to £335.70. Usage will be monitored by MSD every three months and the price adjusted accordingly. Current North East usage equates to £358.78.

- Remsima® (Napp) – based on usage the price ranges from £266.08 to £220.20. Current NE usage is zero, which equates to £266.08.

- Inflectra® (Hospira) £208.63 for any usage.

Therefore, regardless of actual usage the cheapest product is Inflectra®.

As the usage of the biosimilar increases then the price of the Remicade® will increase (as its usage decreases) and initially any cost savings from use of the biosimilar products will be outweighed by the increase in price of Remicade® until around 30% of usage is the biosimilar.

Based on the CMU contract price, Inflectra® and Remsima® would be cost saving in all indications compared with Remicade® at its current price. The exact level of cost savings depends on the price difference, together with the number of patients treated with each product and any differences in dosing and scheduling for the licensed indications.
The table below shows a cost minimisation analysis comparing Inflectra®▼ and Remsima®▼ with the reference product Remicade® in all licensed indications (table 1). As the price of the Remicade® will increase as usage of the biosimilars increases, it assumes the lowest CMU contract price for Inflectra®▼ (£208.63) and Remsima®▼ (£220.20), and the full list price of Remicade® (£419.62). The results are presented based on cost savings per patient per year. As the pharmaceutical form, strength (100 mg infliximab per vial), and the dosing regimen for each licensed indication are identical for both the biosimilars and Remicade®, only the drug acquisition costs are considered. The illustrated cost savings represent treating infliximab-naive patients only. However, individual Trusts may consider a managed therapeutic switch between products.

**These data are confidential to the NHS and commercially sensitive. Local CCGs should contact NTAG if more detail is required.**
# Table 1. Estimated cost savings from the use of Inflectra®▼ and Remsima®▼ instead of Remicade® in all licensed indications.

<table>
<thead>
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<th>Indication</th>
<th>Dose Regimen</th>
<th>Inflectra®▼</th>
<th>Remsima®▼</th>
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<td><em>Cost savings vs. Remicade in year one (per patient)</em></td>
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<td><em>Cost savings in subsequent years (per patient)</em></td>
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<td>Adults</td>
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<td>Rheumatoid arthritis</td>
<td>3 mg/kg at 0, 2, and 6 weeks, then every 8 weeks. (8 doses in year 1 and 6.5 thereafter)</td>
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<td>Psoriatic arthritis</td>
<td>5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks. (8 doses in year 1 and 6.5 thereafter)</td>
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<td>5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks. (8 doses in year 1 and 6.5 thereafter)</td>
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<td></td>
<td></td>
<td>£3,376</td>
<td>£2,742</td>
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<tr>
<td>Crohn's disease</td>
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Based on a 70 kg adult and 40 kg paediatric patients, and that vial wastage occurs.

It assumes the lowest CMU contract price for Inflectra®▼ (£208.63) and Remsima®▼ (£220.20), and the full list price of Remicade® (£419.62).
Points to consider

A biosimilar formulation of infliximab was launched under two different brand names: Inflectra®▼ (Hospira), and Remsima®▼ (Napp). Despite two separate marketing authorisations, Inflectra®▼ and Remsima®▼ are essentially the same biosimilar product (CT-P13), and are both manufactured by Celltrion. The licensed therapeutic indications, dosing regimen, pharmaceutical form, strength and composition for both biosimilar products are identical to those of the originator infliximab (Remicade®).

To gain approval in the EU, biosimilar medicines must demonstrate that they are as safe and as effective as the reference medicine, and have the same quality characteristics. In an extensive comparability exercise it was shown that all major physicochemical characteristics and biological activities of CT-P13 are comparable to those of Remicade®.

The clinical trial program demonstrating biosimilarity between CT-P13 and Remicade® consisted of a phase III efficacy and safety study in patients with active rheumatoid arthritis (PLANETRA), and a phase I pharmacokinetic (PK) study in patients with ankylosing spondylitis (PLANETAS). Both studies showed that up to 54 weeks there were no clinically meaningful differences in the efficacy, safety or pharmacokinetic profile between CT-P13 and Remicade®. Preliminary data from 48-week open-label extensions showed that patients who switched from Remicade® to CT-P13, efficacy was sustained, and comparable to those maintained on CT-P13.

The type and incidence of treatment-emergent adverse events observed in the clinical studies was generally similar between the two treatment groups, and were in line with the well-characterised safety profile of Remicade®. A higher number of serious infections, including active TB were observed in the rheumatoid arthritis study, but the numbers involved are small and a thorough review of all available data by the EMA suggests that the observed difference was most likely due to chance. There were no marked differences in the immunogenicity profile and the impact of antibodies on efficacy and safety was comparable between treatment arms.

Although clinical studies were only performed in patients with RA and AS, efficacy and safety for other indications is assumed from the demonstration of equivalence to the reference product in accordance with regulatory procedures. Based on the totality of evidence, the EMA concluded that similarity has been convincingly demonstrated enabling extrapolation of CT-P13 approval to all other indications for which the reference product Remicade® is approved, including ulcerative colitis, Crohn’s disease, psoriatic arthritis and psoriasis.

A new CMU contract covers all three infliximab products in the NTAG area. Under the CMU contract the negotiated price for Remicade® (MSD) ranges from band A: £419.62 (list price) to £335.70, depending on usage. The price for Remsima®▼ (Napp) ranges from £266.08 to £220.20, depending on usage. Inflectra®▼ (Hospira) has a flat price of £208.63 for any usage. Based on the CMU contract price, the biosimilars would be cost saving in all indications compared with Remicade® at its current price. The exact level of cost savings depends on the price difference, together with the number of patients treated with each product and any differences in dosing and scheduling for the licensed indications.
Author’s declaration: The author has no relevant interests to declare.

References

27. NHS Dictionary of Medicines and Devices (DM+D). April 2015