Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Jonathan G Fox

infliximab, 100mg, powder for concentrate for solution for infusion (Remsima®) SMC No. (1006/14)

Celltrion Healthcare Hungary Kft.

07 November 2014 *(Issued 06 March 2015)*

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

infliximab (Remsima®) is accepted for restricted use within NHS Scotland.

Indication under review: Rheumatoid arthritis: in combination with methotrexate, for the reduction of signs and symptoms as well as improvement in physical function in:

- adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate has been inadequate;
- adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.

Infliximab (Remsima®) is also indicated in the following conditions: adult and paediatric Crohn's disease and ulcerative colitis; adult psoriatic arthritis, psoriasis and ankylosing spondylitis.[1]

SMC restriction: Infliximab (Remsima®) is accepted for use in line with the current SMC and Healthcare Improvement Scotland advice for the reference product infliximab [Remicade®].

A phase III, randomised, double-blind, parallel-group study demonstrated similar efficacy and safety of biosimilar infliximab with originator infliximab in patients with rheumatoid arthritis.

Infliximab (Remsima®) is a biosimilar product to a reference product (infliximab [Remicade®]).

The British National Formulary advises that it is good practice to prescribe biologic medicinal products by brand name.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

Rheumatoid arthritis

In combination with methotrexate, for the reduction of signs and symptoms as well as the improvement in physical function in[1]:

- adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate;
- adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.

Adult Crohn's disease

- Treatment of moderately to severely active Crohn's disease in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contra-indications for such therapies.
- Treatment of fistulising, active Crohn's disease in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

Paediatric Crohn's disease

- Treatment of severe, active Crohn's disease in children and adolescents aged 6 to 17 years who have not responded to conventional therapy including a corticosteroid, and immunomodulator and primary nutrition therapy; or who are intolerant to or have contra-indications for such therapies. Infliximab has been studied only in combination with conventional immunosuppressive therapy.

Ulcerative colitis

- Treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Paediatric ulcerative colitis

- Treatment of severely active ulcerative colitis in children and adolescents aged 6 to 17 years who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.

Ankylosing spondylitis

- Treatment of severe, active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.

Psoriatic arthritis

- Treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Infliximab should be administered:

- in combination with methotrexate; or
- alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated.

Psoriasis

- Treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen ultra-violet A (PUVA).

Dosing Information

Adults(≥18 years)[1]

Rheumatoid arthritis

3mg/kg given as an intravenous infusion followed by additional 3mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Infliximab must be given concomitantly with methotrexate.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Step-wise dose increase by approximately 1.5mg/kg up to a maximum of 7.5mg/kg every 8 weeks or administration of 3mg/kg as often as every 4 weeks may be considered in patients who have not achieved adequate response within 12 weeks or loses response after this period. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment or after dose adjustment.

Moderately to severely active Crohn's disease

5mg/kg given as an intravenous infusion followed by an additional 5mg/kg infusion 2 weeks after the first infusion. If a patient does not respond after 2 doses, no additional treatment with infliximab should be given. Available data do not support further infliximab treatment, in patients not responding within 6 weeks of the initial infusion.
In responding patients, the alternative strategies for continued treatment are:

- Maintenance: Additional infusion of 5mg/kg at 6 weeks after the initial dose, followed by infusions every 8 weeks or
- Re-administration of 5mg/kg if signs and symptoms of the disease recur

Limited data in patients who initially responded to 5 mg/kg but who lost response indicate that some patients may regain response with dose escalation. Continued therapy should be carefully reconsidered in patients who show no evidence of benefit after dose adjustment.

Fistulising, active Crohn's disease

5mg/kg given as an intravenous infusion followed by an additional 5mg/kg infusion 2 and 6 weeks after the first infusion. If a patient does not respond after 3 doses, no additional treatment with infliximab should be given.
In responding patients, the alternative strategies for continued treatment are:

- Maintenance: Additional infusions of 5mg/kg every 8 weeks or
- Re-administration: Infusion of 5mg/kg if signs and symptoms of the disease recur followed by infusions of 5mg/kg every 8 weeks.

Limited data in patients who initially responded to 5 mg/kg but who lost response indicate that some patients may regain response with dose escalation. Continued therapy should be

carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment.

Ulcerative colitis
5mg/kg given as an intravenous infusion followed by an additional 5mg/kg infusion 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Available data suggest that the clinical response is usually achieved within 14 weeks of treatment, i.e. three doses. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Ankylosing spondylitis
5mg/kg given as an intravenous infusion followed by an additional 5mg/kg infusion 2 and 6 weeks after the first infusion, then every 6 to 8 weeks. If a patient does not respond by 6 weeks (i.e. after 2 doses), no additional treatment with infliximab should be given.

Psoriatic arthritis
5mg/kg given as an intravenous infusion followed by an additional 5mg/kg infusion 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Psoriasis
5mg/kg given as an intravenous infusion followed by an additional 5mg/kg infusion 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. If a patient shows no response after 14 weeks (i.e. after 4 doses), no additional treatment with infliximab should be given.

***Paediatric population*[1]**

Crohn's disease (6 to 17 years)
5mg/kg given as an intravenous infusion followed by additional 5mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data do not support further infliximab treatment in children and adolescents not responding within the first 10 weeks of treatment.

Some patients may require a shorter dosing interval to maintain clinical benefit, while for others a longer dosing interval may be sufficient. Patients who have had their dose interval shortened to less than 8 weeks may be at greater risk for adverse reactions. Continued therapy with a shortened interval should carefully be considered in those patients who show no evidence of additional therapeutic benefit after a change in dosing interval. The safety and efficacy of infliximab have not been studied in children with Crohn's disease below the age of 6 years.

Ulcerative colitis (6 to 17 years)
5mg/kg given as an intravenous infusion followed by additional 5mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data do not support further infliximab treatment in paediatric patients not responding within the first 8 weeks of treatment. The safety and efficacy of infliximab have not been studied in children with ulcerative colitis below the age of 6 years.

Treatment should be initiated and supervised by qualified physicians experienced in diagnosis and treatment of rheumatoid arthritis, inflammatory bowel diseases, ankylosing spondylitis, psoriatic arthritis or psoriasis. Infusions should be administered by qualified healthcare

professionals trained to detect any infusion-related issues.

Product availability date

25 February 2015

Summary of evidence on comparative efficacy

Infliximab is a chimeric human-murine monoclonal antibody that binds to and inhibits the activity of tumour necrosis factor-α (TNF-α). Inhibition of TNF-α is beneficial in several inflammatory autoimmune diseases. Infliximab (Remsima®) is a biosimilar medicine to a reference medicinal product, infliximab (Remicade®). It is licensed for the same indications as the reference product and is anticipated to become available in the UK in February 2015, when the patent for the reference product expires.

Evidence to support efficacy was from a phase III randomised, double-blind, parallel-group study (PLANETRA[2,4]) to investigate the efficacy and safety of biosimilar infliximab (CT-P13) compared with originator infliximab in patients with rheumatoid arthritis (RA). Patients aged 18 to 75 years with active RA (according to the American College of Rheumatology [ACR] 1987 criteria) for at least one year were eligible. Patients had to have ≥6 swollen and ≥6 tender joints and at least two of the following: morning stiffness lasting ≥45 minutes; serum C-reactive protein >2.0mg/dL and erythrocyte sedimentation rate >28mm/h despite methotrexate therapy for ≥3 months at a stable dose of 12.5 to 25mg per week for ≥4 weeks before screening. Oral corticosteroids (equivalent to ≤10mg daily prednisolone) and non-steroidal anti-inflammatory drugs (NSAIDs) were permitted if they had been taken at a stable dose for at least four weeks before screening. Patients were randomised equally to receive a two-hour intravenous infusion of 3mg/kg of CT-P13 (n=302) or originator infliximab (n=304) at weeks 0, 2, 6 and every 8 weeks up to week 54. Methotrexate (12.5 to 25mg orally or parenterally once weekly) and folic acid (≥5mg orally once weekly) were co-administered. Rescue therapy with tramadol and/or paracetamol was permitted. The primary endpoint was the proportion of patients achieving an ACR 20% improvement (ACR20) at week 30, assessed in both the intention-to-treat (ITT) and per protocol (PP) populations. This was achieved in 61% (184/302) and 59% (178/248) of patients in the CT-P13 and originator infliximab groups respectively in the ITT population, with an estimated treatment difference of 2% (95% confidence interval (CI): -6% to 10%). The corresponding results in the PP population were 73% (182/248) and 70% (175/251), with an estimated treatment difference of 4% (95% CI: -4% to 12%). Since the 95% CI of the treatment difference was within -15% to 15%, equivalent efficacy was concluded. Secondary outcomes included ACR20 response at week 14, and ACR50 and ACR70 responses at weeks 14 and 30 in the PP population; equivalence between the treatment groups was demonstrated in all of these outcomes. In the ITT population, the ACR50 and ACR70 responses were similar between treatment groups.

Patients who completed 54 weeks of the PLANETRA study could enter a 12-month open-label extension study. A total of 302 patients entered the extension study, of whom 158 continued on CT-P13 ('maintenance group') and 144 patients switched from originator infliximab to CT-P13 ('switch group'). ACR20/50/70 response rates were comparable between the maintenance group and switch groups at weeks 78 and 102.[3]

A phase I, randomised, double-blind, parallel-group study (PLANETAS[5]) compared the pharmacokinetics (PK), safety and efficacy of CT-P13 with originator infliximab in 250 patients with ankylosing spondylitis (AS). The study showed PK equivalence at steady state (area under the concentration-time curve [AUC] and observed maximum serum concentration [$C_{max,ss}$]) between the two treatments, and efficacy was similar between the groups for all outcomes assessed (including the 20% and 40% improvement response according to Assessment in Ankylosing Spondylitis International Working group criteria [ASAS20/ASAS40]).[4,5]

Summary of evidence on comparative safety

In the PLANETRA study, the proportions of treatment-emergent adverse events (TEAEs; 60% [181/301] for CT-P13 versus 61% [183/301] for originator infliximab), TEAEs considered related to study treatment (35% [106/301] versus 36% [108/301]) and serious TEAEs (10% [30/301] versus 7.0% [21/301]) were similar between the treatment groups.[2,4]

The most commonly reported TEAEs considered related to study treatment were similar in both groups: latent tuberculosis (4.3% [13/301] for CT-P13 versus 4.7% [14/301] for originator infliximab); increased alanine aminotransferase (4.0% [12/301] versus 3.7% [11/301]); increased aspartate aminotransferase (2.7% [8/301] versus 2.7% [8/301]); urinary tract infection (1.3% [4/301] versus 2.3% [7/301]); flare in RA activity (2.3% [7/301] versus 1.3% [4/301]; upper respiratory tract infection (1.3% [4/301] versus 1.3% [4/301]; hypertension (1.7% [5/301] versus 1% [3/301]).[2,]

Infusion-related reactions were reported in 6.6% (20/301) and 8.3% (25/301) of patients for CT-P13 and originator infliximab.[2,]

The European Medicines Agency concluded that the size of the safety database and extent of exposure was appropriate to evaluate the safety profile of CT-P13, and that the safety profile observed in the clinical studies was similar between CT-P13 and originator infliximab.[4]

Patients must be monitored closely for infections, including tuberculosis, before, during and after treatment with infliximab.[1]

Summary of clinical effectiveness issues

Infliximab (Remsima®) is a biosimilar medicine to a reference medicinal product (infliximab [Remicade®]) and is licensed for the same indications. The submitting company has asked SMC to consider infliximab (Remsima®) in all licensed indications; however, not all licensed indications for infliximab (Remicade®) have been accepted as cost-effective for use within NHS Scotland, after either SMC assessment or recommendations from the National Institute of Health and Care Excellence (NICE) Multiple Technology Appraisals subsequently endorsed by Healthcare Improvement Scotland. Infliximab (Remicade®) has been accepted for use in rheumatoid arthritis, Crohn's disease, psoriasis and psoriatic arthritis). It has been not recommended for use in ankylosing spondylitis and in ulcerative colitis in adults.

Previous advice on infliximab (Remicade®) is available on the SMC web-site.

A phase III, randomised, double-blind, parallel-group study (PLANETRA) demonstrated similar efficacy and safety of biosimilar infliximab (CT-P13) with originator infliximab in patients with RA. The primary outcome was ACR20 response, which is a validated outcome in RA. In an open-label extension study, ACR20/50/70 responses were maintained up to week 102. There are no efficacy data for infliximab (Remsima®) in many of the other licensed indications, as efficacy for these is assumed based on the demonstration of equivalence to the reference product in accordance with regulatory procedures.

Infliximab (Remsima®) has the same formulation and strength as originator infliximab (Remicade®). The British National Formulary advises that it is good practice to prescribe biologic medicinal products by brand name.

Summary of comparative health economic evidence

The company submitted a cost minimisation analysis comparing infliximab (Remsima®) with the reference product infliximab (Remicade®) in a number of indications as outlined above. The time horizon is 1 year.

The clinical data to support comparable efficacy were taken from the phase III study (PLANETRA) described above. As infliximab (Remsima®) is a biosimilar medicine, the conclusion of clinical equivalence based on this study is assumed to extrapolate to the other indications for the reference product. The doses were based on the doses recommended in the Summary of Product Characteristics. As comparable efficacy is assumed, only drug acquisition costs were included.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

The following information reflects the views of the specified Patient Interest Groups.

- Submissions were received from Crohn's and Colitis UK (CCUK), and the National Rheumatoid Arthritis Society (NRAS), which are both registered charities.

- Both CCUK and NRAS have received funding from several pharmaceutical companies in the past two years.

- Inflammatory bowel disease (IBD) and ulcerative colitis are lifelong conditions that most commonly first present in the teens and twenties. The unpredictable frequent and urgent need for the toilet, together with loss of sleep, pain and continual or profound fatigue, can severely affect self-esteem and social functioning, including educational attainment and work competence.

- Rheumatoid arthritis (RA) is a chronic, progressive and disabling autoimmune disease, which chiefly impacts upon joints but can also affect other organs such as the heart, eyes and lungs. RA can cause severe disability and seriously affects a person's ability to carry out everyday living activities. RA can also take a toll on the self-esteem and confidence of some individuals.

- CCUK believes that the new medicines may provide improved quality of life for people with IBD including their ability to access and retain work, socialise, have and maintain relationships and continue with education, for example.

- People with RA are concerned about the development of joint deformities, loss of function, work disability and the possible socio-economic effects of the RA. The potential toxicity of long-term treatment with disease modifying agents is also a concern. NRAS believe the new medicines will offer additional patient choice and cautiously welcomes their introduction.

- Both CCUK and NRAS are concerned that prescribing of infliximab biosimilars is done on clinical grounds with the consent of the patient and not simply for cost minimisation reasons.

Additional information: guidelines and protocols

- Scottish Intercollegiate Guidelines Network (SIGN) Guideline 123. Management of early rheumatoid arthritis (February 2011)
- SIGN Guideline 121. Diagnosis and management of psoriasis and psoriatic arthritis (October 2010)
- National Institute for Health and Care Excellence (NICE) technology appraisal guidance 130. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (October 2007).
- NICE technology appraisal guidance 143. Adalimumab, etanercept and infliximab for ankylosing spondylitis (May 2008).
- NICE technology appraisal guidance 187. Infliximab (review) and adalimumab for the treatment of Crohn's disease (May 2010).
- NICE technology appraisal guidance 130. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (October 2007)
- NICE technology appraisal guidance 195. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (August 2010).
- NICE technology appraisal guidance 199. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (August 2010).

Additional information: comparators

Infliximab (Remicade®). Other biosimilars may become available.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Infliximab (Remicade®)	3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.	£10,071 in the first year; £7553 to £8812 (6 to 7 doses) in subsequent years.

Cost for Remicade® from eMIMS on 01/09/14. Assumes a patient weight of 70kg and no vial sharing.

*Other data were also assessed but remain commercially confidential.**

Additional information: budget impact

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission.

Summary of Product Characteristics, Remsima® 100mg powder for concentrate for solution for infusion, European Medicines Agency.www.ema.europa.eu/ema/, accessed 13/08/14.

1. Yoo DH, Hrycaj P, Miranda P et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann. Rheum. Dis. 2013; 72: 1613 to 20.
2. Yoo DH, Prodanovic N, Jaworski J et al. Efficacy and safety of CT-P13 (infliximab biosimilar) over two years in patients with rheumatoid arthritis: comparison between continued CT-P13 and switching from infliximab to CT-P13. Late breaking abstract presented at the American College f Rheumatology/Association of Rheumatology Health Professionals Annual Meeting; 2013 October 23 to 25, San Diego, USA.
3. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP) assessment report Remsima® (infliximab), EMA/CHMP/589317/2013, 27 June 2013.
4. Park W, Hrycaj P, Jeka S et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann. Rheum. Dis 2013; 0: 1 -8.

This assessment is based on data submitted by the applicant company up to and including 17 October 2014.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.