New Medicine Assessment

INFLIXIMAB (SUBCUTANEOUS)

Recommendation: RED for the following indications:

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 contraindications for such therapies.

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.

Use of infliximab (subcutaneous) should be reserved for those whom attending a clinical setting to receive infliximab (intravenous) proves to be a barrier to receiving treatment.

The patient and/or carer must receive proper training in subcutaneous injection technique if their specialist determines that it is appropriate to self-inject and with medical follow- up as necessary. Suitability of the patient for subcutaneous home use should be assessed and patients should be advised to inform their healthcare professional if they experience symptoms of an allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions

Summary of supporting evidence:

- The currently provided descriptive clinical efficacy data from a small, randomized, open label, mainly PK-study supports that Remsima SC 120mg is clinically non-inferior to Remsima IV 5mg/kg also in CD and UC patients.
- The safety profiles for SC and IV were in general comparable. The only new unfavourable effect identified after SC dosing were injections site reactions. Also, immunogenicity seemed comparable between SC and IV formulations.
- There are many limitations to the main study, including its small size, the primary outcome was pharmacokinetic, it was open label, the study was not powered to detect differences in the secondary efficacy and safety outcomes, no comparative statistical analyses were conducted for the clinical effectiveness outcomes, a 240mg dose was used in some study patients despite this not being part of the licensing, and colonoscopy was not performed on all patients
- There are several patient groups in which Remsima SC has not been studied, including those with renal or hepatic impairment, those with fistulating Crohn’s disease (despite its licensing in these patients), patients with a BMI>35, people switching to Remsima SC from Remsima IV at administration frequencies higher than every 8 weeks, people switching from other infliximab products to Remsima SC, and patients switching from IV to SC infliximab who are already established on IV infliximab, because all participants in the study were biologic-naive.
- Remsima SC is suitable for home administration by the patient or carer, in certain circumstances after appropriate training. This could improve access to treatment for some patients but may also reduce the frequency of interaction of the patient with HCPs, which may reduce the assessment of efficacy and or side effects. This is of particular note due to the increased frequency of injection site reactions in those given the SC formulation.

- Longer-term safety of Remsima SC beyond 54 weeks is unknown, but this should be considered against the average length of a course of treatment in practice.
- The higher C_{trough} levels achieved with the proposed Remsima SC posology is a long-term a safety concern because of the potential of infliximab to cause serious side effects.
- Awaiting results from a post-approval observational safety study requested by the EMA.
- Subcutaneous infliximab is currently in phase 3 trials in the US and awaits FDA approval. The FDA required the company to submit its application as a new drug, rather than as a line extension.

Details of Review

Name of medicine (generic & brand name)**:**

Infliximab (Remsima)

Strength(s) and form(s):

Remsima (infliximab) 120 mg solution for injection in pre-filled pen

Remsima (infliximab) 120 mg solution for injection in pre-filled syringe

Dose and administration:[1,2]

Remsima 120 mg solution for injection in a pre-filled pen or a pre-filled syringe is administered by subcutaneous injection only.

For subsequent injections and after proper training in subcutaneous injection technique, patients may self-inject with Remsima if their physician determines that it is appropriate and with medical follow- up as necessary.

For the two initial intravenous infusions, patients may be pre-treated with, e.g., an antihistamine, hydrocortisone and/or paracetamol and infusion rate may be slowed in order to decrease the risk of infusion-related reactions especially if infusion-related reactions have occurred previously. The physician should ensure appropriate follow-up of patients for any systemic injection reaction and localised injection site reaction after the initial subcutaneous injection is administered.

Moderately to severely active Crohn's disease

Treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart. The recommended dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. If a patient does not respond after 2 doses of intravenous infusions, 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.

Fistulising, active Crohn's disease

Remsima 120 mg given as a subcutaneous injection 4 weeks after the last administration of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart. The recommended dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. If a patient does not respond after 6 doses (i.e. 2 intravenous infusions and 4 subcutaneous injections), no additional treatment with infliximab should be given.

In Crohn's disease, experience with re-administration if signs and symptoms of disease recur is limited and comparative data on the benefit/risk of the alternative strategies for continued treatment are lacking.

Ulcerative colitis

Treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart. The recommended dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks.

Available data suggest that the clinical response is usually achieved within 14 weeks of treatment, i.e. 2 intravenous infusions and 4 subcutaneous injections. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Re-administration across indications

In case maintenance therapy is interrupted, and there is a need to restart treatment, use of a re-induction regimen of intravenous infliximab is not recommended. In this situation, infliximab should be re-initiated as a single dose of intravenous infliximab followed by the maintenance dose recommendations of subcutaneous infliximab described in the SPC given 4 weeks after the last administration of intravenous infliximab.

Switching to Remsima subcutaneous formulation across indications

When switching from the maintenance therapy of infliximab intravenous formulation to the subcutaneous formulation of Remsima, the subcutaneous formulation may be administered 8 weeks after the last administration of the intravenous infusions of infliximab.

There is insufficient information regarding the switching of patients who received the intravenous infusions of infliximab higher than 3 mg/kg for rheumatoid arthritis or 5 mg/kg for Crohn's disease every 8 weeks to the subcutaneous formulation of Remsima.

BNF therapeutic class / mode of action:

Tumor necrosis factor alpha (tnf-a) inhibitors.

Infliximab is a chimeric human-murine IgG1 monoclonal antibody produced in murine hybridoma cells by recombinant DNA technology.[1,2]

Infliximab binds with high affinity to both soluble and transmembrane forms of TNFα but not to lymphotoxin α (TNFβ).[1,2]

Licensed indication(s):[1,2]

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 contraindications 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).

Ulcerative colitis

Remsima is indicated for 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.

Rheumatoid arthritis

See SPC for detailed indication specifications.

Ankylosing spondylitis

See SPC for detailed indication specifications.

Psoriatic arthritis

See SPC for detailed indication specifications.

Psoriasis

See SPC for detailed indication specifications.

Proposed use (if different from, or in addition to, licensed indication above):

As per licensed indications for Crohn's disease and ulcerative colitis.

Course and cost:

Remsima 120mg/1ml solution for injection pre-filled pens = £755.32 (pack size = 2)

Remsima 120mg/1ml solution for injection pre-filled syringes = £755.32 (pack size = 2)

Moderately to severely active Crohn's disease, fistulising active Crohn's disease and ulcerative colitis

Maintenance 120mg every 2 weeks = Annual cost approx. £9819.16 (dependent on length of course which may be <1 year)

Infliximab is a high cost drug and is excluded from the scope of the national tariff of Payment by Results.

Prices as per BNF May 2022[3]

Current standard of care/comparator therapies:

LSCMMG Crohn's Disease Recommended Biologic Commissioning Pathway[4]

NB. This guideline expired Oct 2020

Infliximab IV is currently a first line treatment option for patients with severe active Crohns disease who have had an inadequate response with, lost response to, or intolerant to either conventional therapy or a TNF-alpha inhibitor or have medical contraindications to such therapies.

Adalimumab is also a first line option in these patients.

Ustekinumab IV/SC and Vedolizumab IV are first-line options if a TNF-alpha inhibitor isn't suitable or hasn't worked well enough.

*LSCMMG Ulcerative Colitis Recommended Biologic Commissioning Pathway*4

NB. This guideline expired Oct 2020

Infliximab IV is currently a first line treatment option for patients who have moderately to severely active ulcerative colitis whose disease has responded inadequately to conventional therapy, or who cannot tolerate, or have medical contraindications for these are eligible for treatment with a biologic.

Adalimumab SC, golimumab SC and vedolizumab IV are also first line treatment options in these patients.

NICE Crohn's disease management[5]

Steroids or aminosalicylates are used to induce remission initially.

Add-on treatment is then an option if clinically indicated. E.g. azathioprine, mercaptopurine, methotrexate.

Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy.

Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed to determine whether ongoing treatment is still clinically appropriate.

Treatment with infliximab or adalimumab can either be as monotherapy or in combination with an immunosuppressant.

Ustekinumab and vedolizumab are also options.

NICE Ulcerative colitis management[6]

Steroids or aminosalicylates are used to induce remission initially.

For moderately to severely active ulcerative colitis options include infliximab, adalimumab, golimumab, vedolizumab and tofacitinib.

Infliximab is recommended as an option for the treatment of acute exacerbations of severely active ulcerative colitis only in patients in whom ciclosporin is contraindicated or clinically inappropriate, based on a careful assessment of the risks and benefits of treatment in the individual patient.

Relevant NICE guidance:

Remsima (infliximab biosimilar) for subcutaneous injection for managing Crohn's disease and ulcerative colitis ES35 (2021)

Crohn's disease: Management NG129 (2019)

Ulcerative colitis: Management NG130 (2019)

Infliximab and adalimumab for the treatment of Crohn's disease TA187 (2010)

Infliximab for acute exacerbations of ulcerative colitis TA163 (2008)

Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy TA329 (2015)

Inflammatory bowel disease QS81 (2015)

Background and context

Crohn's disease is a chronic, relapsing-remitting, non-infectious inflammatory disease of the gastrointestinal tract. The inflammation involves discrete parts of the gastrointestinal tract, anywhere from the mouth to the anus and the full thickness of the intestinal wall is inflamed. The anti-tumour necrosis factor (TNF)-alpha monoclonal antibody agents infliximab and adalimumab are effective at inducing remission in people with severe active disease which has not responded to conventional therapy, or where conventional therapy is not tolerated; for treating perianal disease; and for maintaining remission.[7]

Ulcerative colitis is a chronic, relapsing-remitting, non-infectious inflammatory disease of the gastrointestinal tract. It is characterised by diffuse, continuous, superficial inflammation of the large bowel limited to the intestinal mucosa, and usually affects the rectum with a variable length of the colon involved proximally. The anti-TNF-alpha monoclonal antibody agents intravenous infliximab and subcutaneous adalimumab and golimumab are effective at inducing remission in people with severe active disease which has not responded to conventional therapy, or where conventional therapy is not tolerated. These drugs are also effective at maintaining remission.[8]

Remsima for subcutaneous injection is a biosimilar monoclonal antibody of infliximab that inhibits the activity of tumour necrosis factor (TNF)-alpha. It received a marketing authorisation for managing rheumatoid arthritis in December 2019 and received a license extension for Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and psoriasis in July 2020.[9]

Subcutaneous infliximab has not currently been RAG rated for any indications by LSCMMG.

Summary of evidence

Summary of efficacy data in proposed use:

European Medicines Agency: Extension of indication variation assessment report (2020)[10]

The development of this formulation focused on whether a subcutaneous formulation of infliximab may differ from IV infliximab in both efficacy and safety because of the different pharmacokinetic profile, with lower peak concentrations, higher C_{trough} values and a more even concentration time curve. In addition, differences in exposure and intrinsic immunogenicity of the subcutaneous administration route could alter the immunogenic response. The potential consequences of flat dosing were also of special interest, in particular for individuals that belong to the extremes with regards to body weight.

It was commented that if non-inferior efficacy could be demonstrated in the Rheumatoid Arthritis (RA) setting and PK data from an IBD population would show similar exposure and C_{trough} levels between SC and IV formulations, full extrapolation to other indications should be possible. It was further commented that the safety database should be sufficiently large to provide for a meaningful comparison of safety and immunogenicity; one year of comparative assessment of immunogenicity was considered critical to assess the benefit/risk of the proposed SC formulation given the high level of anti-drug antibody with Remsima IV and the known much higher immunogenicity of the SC route. It was clarified that an indirect comparison to historical IV immunogenicity data could be acceptable.

- In the line extension application (EMEA/H/C/002576/X/0062), non-inferior efficacy and safety was shown for Remsima SC 120mg (2 weekly) compared to Remsima IV 3mg/kg in RA patients.
- For Remsima SC dosing the mean AUC-values and C_{trough} levels were constantly and in long-term higher compared to Remsima IV.
- The number of patients (157) exposed to long term treatment with Remsima SC was limited

and some uncertainty remained regarding the effect of higher C_{trough} levels of infliximab on the potential risk of some rare adverse events. Moreover, data on safety and immunogenicity among patients without the use of concomitant immunosuppressive medication (CIM) was lacking.

Schreiber et al[11]

*The proposed extension to the indications is supported by the results from this study, referred to in the EMA document as CT-P13 1.6.*10

Study CT-P13 1.6 was an open-label, randomized, multicenter, parallel group, phase I study designed to evaluate PK, efficacy, PD, and safety between infliximab (Remsima) SC and infliximab (Remsima) IV in patients with active Crohn's disease (CD) or active ulcerative colitis (UC) up to Week 54.

The open label design is considered acceptable by the EMA as the primary endpoint (C_{trough}) is not expected to be subject to bias due to lack of blinding.

A total of 195 patients from 62 study centres in 16 countries were screened and 136 patients from 50 study centres in 15 countries were enrolled in this study.

The study consisted of 2 parts. Part 1 was designed to find the optimal dose of infliximab (Remsima) SC whereas Part 2 was designed to demonstrate that infliximab (Remsima) SC was non-inferior to infliximab (Remsima) IV, in terms of PK.

In the induction phase, all enrolled patients received two loading doses of 5mg/kg infliximab (Remsima) IV infusion at Weeks 0 and 2. Patients who received two full doses and for whom there were no safety concerns were randomly assigned to receive either infliximab (Remsima) SC or infliximab (Remsima) IV. The duration of Study CT-P13 1.6 Part 2 was up to 62 weeks, which included screening (up to 6 weeks) and the last dose at 54 weeks, plus the following 2 weeks off-dose period, prior to the end of study visit.

For CD patients, the patient had to have been treated for active CD, but had not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or was intolerant to or had medical contraindications for such therapies. Efficacy was assessed in CD patients by CDAI score and endoscopic response. CD patients with severe disease activity or fistulating CD were not included in the study. Such patients are expected to have a high inflammatory burden and possibly an accelerated drug clearance.

For UC patients, the patient had to have been treated for active UC, but not responded despite conventional therapy including corticosteroids alone or in combination with 6-mercaptopurine (6-MP) or azathioprine (AZA) and medications containing 5-aminosalicylates (5-ASA), or who was intolerant to or had medical contraindications for such therapies. Assessment of efficacy in UC patients using Mayo score is in line with the EMA Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis.

Patients with a BMI>35 were excluded from this study and have not been included in any of the other clinical studies in the development of Remsima SC. Thus, drug exposure and efficacy among the heaviest patients is based on simulations.

The primary objective to demonstrate non-inferiority of C_{trough} at week 22 with Remsima SC compared to Remsima IV in CD and UC patients was agreed by CHMP through scientific advice.

The currently provided descriptive clinical efficacy data from a small, randomized, open label, mainly PK-study supports that Remsima SC 120mg is clinically non-inferior to Remsima IV 5mg/kg also in CD and UC patients.

NICE evidence summary (2021)9

In practice Remsima (subcutaneous) is most likely to be used in people:

• who are already established on intravenous infliximab

• with stable disease but who have difficulty attending hospital appointments

• for whom the risk of attending hospital for intravenous infusions outweighs the benefits.

It may also be beneficial for people who are starting on infliximab who have not used a biologic before, or who are switching from a biologic with a different mechanism of action from the TNF-alpha inhibitors.

The study used in the license extension study for the EPAR was small, and the primary outcome was pharmacokinetic. Therefore, the study was not powered to detect differences in the secondary efficacy and safety outcomes. No comparative statistical analyses were conducted for the clinical effectiveness outcomes.

Another limitation of this study is that people weighing 80kg or more received 240mg of Remsima (subcutaneous) and people under 80kg on 120mg could have their dose increased to 240mg. This differs from the licensed dose for the subcutaneous formulation, which is 120mg for all weights without dose escalation. Therefore, these findings may not be generalisable to all people receiving the licensed dose of 120mg. The study was open label and as such subject to potential bias. Some components of the outcome scores used are subjective, therefore are subject to bias in an open-label trial in which clinician and patient outcome reporting could be influenced by the treatment received.

Colonoscopy was not performed on all participants. Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) was only assessed in people who had confirmed mucosal abnormalities at their previous assessment. Therefore, only improvements are likely to be seen and any disease progression in people without abnormalities at previous assessment could be missed. The EPAR stated that, on request, the company provided convincing evidence that this approach did not produce skewed results, but this evidence was not included in the EPAR.

Another limitation is that there are currently no data on the efficacy or safety of switching from intravenous to subcutaneous infliximab in people who are already established on intravenous infliximab, because all participants in the study were biologic-naive. There are also no long-term outcomes comparing Remsima (subcutaneous) with Remsima (intravenous) after 30 weeks. Although, participants in the study were followed-up for 54 weeks, participants in the Remsima (intravenous) group were switched to Remsima (subcutaneous) at week 30.

Summary of safety data:

European Medicines Agency: Extension of indication variation assessment report (2020)10

In all, safety data for Remsima SC have been collected in four clinical studies:

- Study CT-P13 1.5: Phase I, open-label, dose-escalating, single-dose study in which 38 healthy subjects were treated with IV or SC infliximab
- Study CT-P13 1.9: Phase I, open-label, single-dose PK and safety study in which 215 healthy subjects were treated with infliximab SC via auto-injector or SC via pre-filled syringe
- Study CT-P13 3.5 Parts 1 and 2: Phase I/III, double-blind, randomised, multi-dose, parallel group study in which 391 patients with RA were treated with IV or SC infliximab
- Study CT-P13 1.6 Parts 1 and 2: Phase I, open-label, randomised, multi-dose, parallel-group study in which 175 patients with active Crohn's disease or active ulcerative colitis were treated with IV or SC infliximab.

The safety profiles for SC and IV were in general comparable. The only new unfavourable effect identified after SC dosing were injections site reactions. Also, immunogenicity seemed comparable between SC and IV formulations.

There is still relatively limited safety data that would allow for a complete comparative safety assessment of Remsima SC with Remsima IV. However, the planned post-approval observational safety study to collect further safety data was considered acceptable.

Some uncertainties, also relevant for the extrapolation, of the Remsima SC safety data remain. They include:

- The higher C_{trough} levels achieved with the proposed Remsima SC posology is in long-term a safety concern.
    - Although the exposure could be estimated to be adequate and sufficient for the present extrapolation purposes, it is acknowledged that the overall patient exposure to the SC formulation is not extensive, even for the current extrapolation.
    - A total of 751 subjects (363 RA patients, 79 CD patients, 74 UC patients and 235 healthy subjects) have received at least one dose of Remsima SC and of them 249 have been treated for up to week 54, that is, for up to a year, and a further 277 patients for a shorter duration of time; among them 201 patients (155 RA, 24 CD and 22 UC patients) receiving the sought dose of 120 mg of CT-P13 SC for up to a year.
- Longer-term safety of Remsima SC beyond the 54 weeks remains yet unknown
- Scarcity of data on treatment with SC formulation in the absence of immunosuppressive comedication.

Caporali et al[12]

Systematic review comparing the safety and efficacy of infliximab IV, adalimumab or etanercept versus infliximab SC. The study identified 13 relevant RCTs that evaluated the efficacy and safety of infliximab IV, adalimumab, or etanercept and their respective biosimilars. Pooled data from these studies were compared with data from a pivotal study of infliximab SC in patients with rheumatoid arthritis.

Compared with IV infliximab, a numerical advantage was observed for infliximab SC for every safety outcome evaluated, including the proportions of participants experiencing AEs or infections, or discontinuing study treatment.

Summary of Product Characteristics

Contraindications

- Hypersensitivity to the active substance, to other murine proteins or to any of the excipients.
- Patients with tuberculosis or other severe infections such as sepsis, abscesses and

opportunistic infections.
- Patients with moderate or severe heart failure (NYHA class III/IV).

Special warnings and precautions for use

- Infliximab has been associated with systemic injection reactions, anaphylactic shock and delayed hypersensitivity reactions.
- Antibodies to infliximab may develop and have been associated with an increased frequency of infusion reactions when administered by intravenous infusion.
- Patients must be monitored closely for infections including tuberculosis before, during and after treatment with infliximab.
- Administration of infliximab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled.
- Patients with fistulising Crohn's disease with acute suppurative fistulas must not initiate infliximab therapy until a source for possible infection, specifically abscess, has been excluded.
- Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including infliximab, who are chronic carriers of this virus.
- With the current knowledge, a risk for the development of lymphomas or other malignancies in patients treated with a TNF-blocking agent cannot be excluded.
- All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course.
- All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias.

Undesirable effects

The safety profile of Remsima subcutaneous formulation from active rheumatoid arthritis (evaluated in 168 and 175 patients for the subcutaneous infliximab group and the intravenous infliximab group, respectively), active Crohn's disease (evaluated in 59 and 38 patients for the subcutaneous infliximab group and the intravenous infliximab group, respectively) and active ulcerative colitis patients (evaluated in 38 and 40 patients for the subcutaneous infliximab group and the intravenous infliximab group, respectively) was overall similar to the safety profile of the intravenous formulation.

Infections and infestations	
Very common:	Viral infection (e.g. influenza, herpes virus infection).
Common:	Bacterial infections (e.g. sepsis, cellulitis, abscess).
Uncommon:	Tuberculosis, fungal infections (e.g. candidiasis, onychomycosis).
Rare:	Meningitis, opportunistic infections (such as invasive fungal infections [pneumocystosis, histoplasmosis, aspergillosis, coccidioidomycosis, cryptococcosis, blastomycosis], bacterial infections [atypical mycobacterial, listeriosis, salmonellosis], and viral infections [cytomegalovirus]), parasitic infections, hepatitis B reactivation.
Not known:	Vaccine breakthrough infection (after *in utero* exposure to infliximab)*.
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare:	Lymphoma, non-Hodgkin's lymphoma, Hodgkin's disease, leukaemia, melanoma, cervical cancer.
Not known:	Hepatosplenic T-cell lymphoma (primarily in adolescents and young adult males with Crohn's disease and ulcerative colitis), Merkel cell carcinoma, Kaposi's sarcoma.

Blood and lymphatic system disorders	
Common:	Neutropenia, leukopenia, anaemia, lymphadenopathy.
Uncommon:	Thrombocytopenia, lymphopenia, lymphocytosis.
Rare:	Agranulocytosis (including infants exposed *in utero* to infliximab), thrombotic thrombocytopenic purpura, pancytopenia, haemolytic anaemia, idiopathic thrombocytopenic purpura.
Immune system disorders	
Common:	Allergic respiratory symptom.
Uncommon:	Anaphylactic reaction, lupus-like syndrome, serum sickness or serum sickness-like reaction.
Rare	Anaphylactic shock, vasculitis, sarcoid-like reaction
Psychiatric disorders	
Common:	Depression, insomnia.
Uncommon:	Amnesia, agitation, confusion, somnolence, nervousness.
Rare:	Apathy.
Nervous system disorders	
Very common:	Headache.
Common:	Vertigo, dizziness, hypoaesthesia, paraesthesia.
Uncommon:	Seizure, neuropathy.
Rare:	Transverse myelitis, central nervous system demyelinating disorders (multiple sclerosis-like disease and optic neuritis), peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy).
Not known:	Cerebrovascular accidents in close temporal association with infusion.
Eye disorders	
Common	Conjunctivitis
Uncommon	Keratitis, periorbital oedema, hordeolum
Rare	Endophthalmitis
Not known	Transient visual loss occurring during or within 2 hours of infusion
Cardiac disorders	
Common	Tachycardia, palpitation
Uncommon	Cardiac failure (new onset or worsening), arrhythmia, syncope, bradycardia
Rare	Cyanosis, pericardial effusion
Not known	Myocardial ischaemia/myocardial infarction
Vascular disorders	
Common	Hypotension, hypertension, ecchymosis, hot flush, flushing
Uncommon	Peripheral ischaemia, thrombophlebitis, haematoma
Rare	Circulatory failure, petechia, vasospasm
Respiratory, thoracic and mediastinal disorders	
Very common	Upper respiratory tract infection, sinusitis
Common	Lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, epistaxis
Uncommon	Pulmonary oedema, bronchospasm, pleurisy, pleural effusion
Rare	Interstitial lung disease (including rapidly progressive disease, lung fibrosis and pneumonitis)

Gastrointestinal disorders	
Very common:	Abdominal pain, nausea
Common:	Gastrointestinal haemorrhage, diarrhoea, dyspepsia, gastroesophageal reflux, constipation
Uncommon	Intestinal perforation, intestinal stenosis, diverticulitis, pancreatitis, cheilitis
Hepatobiliary disorders	
Common:	Hepatic function abnormal, transaminases increased.
Uncommon:	Hepatitis, hepatocellular damage, cholecystitis.
Rare:	Autoimmune hepatitis, jaundice.
Not known:	Liver failure.
Skin and subcutaneous tissue disorders	
Common:	New onset or worsening psoriasis including pustular psoriasis (primarily palm & soles), urticaria, rash, pruritus, hyperhidrosis, dry skin, fungal dermatitis, eczema, alopecia.
Uncommon:	Bullous eruption, seborrhoea, rosacea, skin papilloma, hyperkeratosis, abnormal skin pigmentation.
Rare:	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, furunculosis, linear IgA bullous dermatosis (LABD), acute generalised exanthematous pustulosis (AGEP), lichenoid reactions.
Not known:	Worsening of symptoms of dermatomyositis.
Musculoskeletal and connective tissue disorders	
Common:	Arthralgia, myalgia, back pain.
Renal and urinary disorders	
Common:	Urinary tract infection.
Uncommon:	Pyelonephritis.
Reproductive system and breast disorders	
Uncommon:	Vaginitis.
General disorders and administration site conditions	
Very common:	Infusion-related reaction, pain.
Common:	Chest pain, fatigue, fever, injection site reaction, chills, oedema.
Uncommon:	Impaired healing.
Rare:	Granulomatous lesion.
Investigations	
Uncommon:	Autoantibody positive.
Rare:	Complement factor abnormal.
* including bovine tuberculosis (disseminated BCG infection)	

Strengths and limitations of the evidence:

Strengths

- The currently provided descriptive clinical efficacy data from a small, randomized, open label, mainly PK-study supports that Remsima SC 120mg is clinically non-inferior to Remsima IV 5mg/kg also in CD and UC patients.
- The safety profiles for SC and IV were in general comparable. The only new unfavourable effect identified after SC dosing were injections site reactions. Also, immunogenicity seemed comparable between SC and IV formulations.

- Suitable for home administration by patient or carer, in certain circumstances after appropriate training.

Limitations

- The study used in the license extension study for the EPAR was small, and the primary outcome was pharmacokinetic. Therefore, the study was not powered to detect differences in the secondary efficacy and safety outcomes. No comparative statistical analyses were conducted for the clinical effectiveness outcomes.
- The pivotal study was open label and as such subject to potential bias. Some components of the outcome scores used are subjective, therefore are subject to bias in an open-label trial in which clinician and patient outcome reporting could be influenced by the treatment received.
- Awaiting results from a post-approval observational safety study.
- There are also no long-term outcomes comparing Remsima (subcutaneous) with Remsima (intravenous) after 30 weeks. Although, participants in the study were followed-up for 54 weeks, participants in the Remsima (intravenous) group were switched to Remsima (subcutaneous) at week 30.
- The higher C_{trough} levels achieved with the proposed Remsima SC posology is in long-term a safety concern. Longer-term safety of Remsima SC beyond the 54 weeks remains yet unknown.
- Information regarding switching patients from the subcutaneous formulation to the intravenous formulation of Remsima is not available.
- There is insufficient information regarding the switching of patients who received the intravenous infusions of infliximab higher than 5 mg/kg for Crohn's disease every 8 weeks to the subcutaneous formulation of Remsima.
- Another limitation is that there are currently no data on the efficacy or safety of switching from intravenous to subcutaneous infliximab in people who are already established on intravenous infliximab, because all participants in the study were biologic-naive.
- Scarcity of data on treatment with SC formulation in the absence of immunosuppressive comedication.
- Infliximab has not been studied in patients with renal or hepatic impairment.
- Patients with a BMI>35 were excluded from this study and have not been included in any of the other clinical studies in the development of Remsima SC. Thus, drug exposure and efficacy among the heaviest patients is based on simulations.
- In the pivotal study, people weighing 80kg or more received 240mg of Remsima (subcutaneous) and people under 80kg on 120mg could have their dose increased to 240mg. This differs from the licensed dose for the subcutaneous formulation, which is 120mg for all weights without dose escalation. Therefore these findings may not be generalisable to all people receiving the licensed dose of 120mg.
- Remsima is licensed for fistulating Crohn’s disease, but these patients were excluded from the pivotal study population.
- Colonoscopy was not performed on all participants.
- Subcutaneous infliximab is currently in phase 3 trials in the US and awaits FDA approval.

Summary of evidence on cost effectiveness:

None available.

Prescribing and risk management issues:

It is recommended that patients, if possible, be brought up to date with all vaccinations in

agreement with current vaccination guidelines prior to initiating Remsima therapy.

Women of childbearing potential should consider the use of adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last infliximab treatment.

Initial intravenous administrations should take place where emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway is immediately available. Patients may be pre-treated with e.g., an antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects.

For subsequent injections and after proper training in subcutaneous injection technique, patients may self-inject with Remsima if their physician determines that it is appropriate and with medical follow- up as necessary.

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous) is being administered to the patient, as prescribed.

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.[1]

Commissioning considerations:

Innovation, need and equity implications of the intervention:
The development of a SC formulation enables patients to be treated outside of a clinical setting and potentially allows self-administration of the medication. May improve access to treatment for some patient groups, including those who experience factors which limit their ability to attend a hospital setting.
Financial implications of the intervention:
Remsima 120mg/1ml solution for injection pre-filled pens = £755.32 (pack size = 2) Remsima 120mg/1ml solution for injection pre-filled syringes = £755.32 (pack size = 2) *Moderately to severely active Crohn's disease, fistulising active Crohn's disease and ulcerative colitis* Maintenance 120mg every 2 weeks = Annual cost approx. £9819.16 (Excluding the initial IV infusions and dependent on length of course which may be <1 year) Direct comparison with the cost of infliximab IV is complex as it is influenced by many variables including patient weight, choice of product, use of premedication, frequency of infusions and cost of administration. Current NHS indicative prices for a 100mg vial of infliximab range from £377- £419. Assuming the least expensive product is selected, the biologic cost of a single 5mg/kg infusion could range from £1131 - £1508 based on a body weight range of 50–80 kg. If a patient received 7 infusions/year this would be an annual estimated cost of £7917 - £10556. Infliximab is a high cost drug and is excluded from the scope of the national tariff of Payment by Results.
Service Impact Issues Identified:

The SC formulation has an increased frequency of administration which could impact the volume of prescriptions which need issuing and have potential logistical issues around delivery of the product to the patient.
Equality and Inclusion Issues Identified:
None identified.
Cross Border Issues Identified:
The **Pan Mersey APC** have infliximab 120mg SC injection in their formulary as RAG rating RED for Crohn's disease and active ulcerative colitis. The **Greater Manchester Medicines Management Group** (GMMMG) does not currently have subcutaneous infliximab in their GI formulary.
Legal Issues Identified:
None identified.
Media/ Public Interest:
None identified.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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