Novel treatment option Remsima® SC (infliximab) for Crohn's disease (CD) and Ulcerative Colitis (UC)

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Remsima® SC is currently indicated for:[1]

Rheumatoid arthritis (RA)

Remsima®, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the 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. In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated.

Crohn's disease (CD)

Remsima® is indicated for 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 (UC)

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.

Ankylosing spondylitis (AS)

Remsima® is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.

Psoriatic arthritis (PsA)

Remsima® is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Remsima® should be administered in combination with methotrexate or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated. Infliximab has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.

Psoriasis (PsO)

Remsima® is indicated for 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 ciclosporin, methotrexate or psoralen ultra-violet A (PUVA).

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Remsima® overview

Remsima® (infliximab) was the first biosimilar monoclonal antibody (mAb) to be approved by the EMA in 2013 and the FDA in 2016.[2,3] Since then, Remsima® has had a great impact on lives of the patients with autoimmune diseases, such as rheumatoid arthritis (RA), Crohn's disease (CD), ulcerative colitis (UC), ankylosing spondylitis (AS), psoriatic arthritis (PsA) and plaque psoriasis (PsO). Celltrion strived to offer biologic treatments in more accessible and affordable means. As a result, more patients were able to receive biologic treatments in the earlier course of their disease.[1]

Building on our commitment to improving population health, Celltrion Healthcare has launched a subcutaneous (SC) Remsima®. Remsima® SC is the first and only SC formulation of infliximab offering patients the proven benefits of infliximab in a more convenient form.

Now available in dual formulation offering patients rapid response and convenient care.[1]

IV: Rapid Response **SC:** Convenient Care

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North Tees and Hartlepool NHS Foundation Trust

The North Tees and Hartlepool Hospitals care for ~400 patients with inflammatory bowel disease (IBD) within the trust catchment area, of which ~180 have Crohn's disease (CD) and ~220 ulcerative colitis (UC).

Prior to the COVID pandemic, the decision to include Remsima® SC into treatment pathways had still yet to be discussed by the Trust's IBD team – it was considered to be low priority as subcutaneous adalimumab was available and this option, which is supported by a homecare delivery service, was working well. However, with the onset of COVID, the team wanted to free-up resources, increase space for social distancing, and reduce the need for patients to come into hospital – especially those at high-risk of COVID. Therefore, the decision to offer Remsima® SC was expedited. Consultant Gastroenterologist, Dr Roisin Bevan, and Directorate Pharmacist, Leung Yu Wu discussed the Trust's experience of switching to Remsima® SC, the benefits provided and insights gained.

Overview of the IBD service

The core multi-disciplinary team includes a medical team of consultants, registrars and IBD nurses who meet weekly to discuss difficult cases or patients escalating treatment. This is supplemented with a fortnightly surgical-medical meeting which also includes radiologists, colorectal surgeons, and pathologists to discuss more advanced patients.

Across the Trust there are several consultant-led and IBD nurse-led clinics a week. Typically, consultant and IBD nurse clinics are run concurrently allowing consultants to provide input into the IBD nurse-led clinic if needed.

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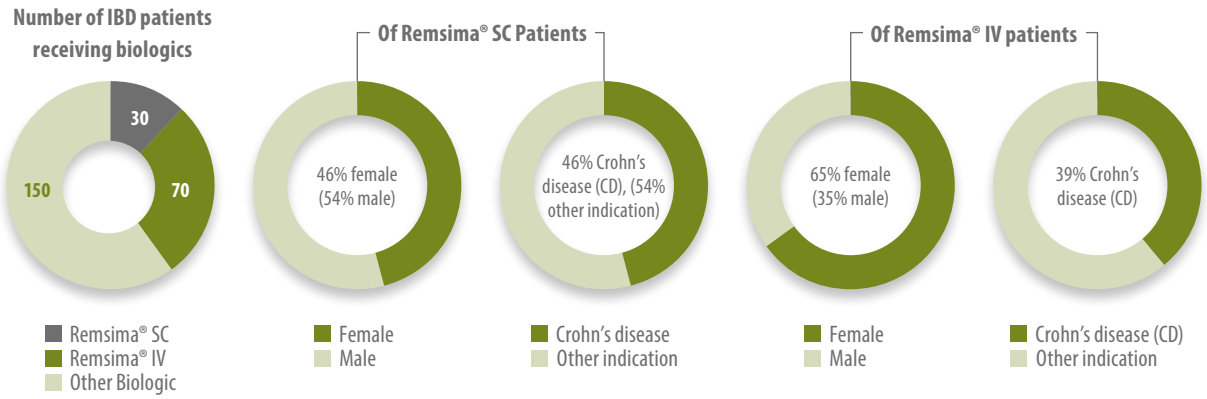
Treatment pathways

Remsima® is included in treatment pathways for both CD and UC. Once the decision has been made to escalate a patient to a biologic therapy, they are offered the choice of either Remsima® or subcutaneous adalimumab. Following the decision to add Remsima® SC to the formulary, patients now have the choice of IV or SC administration.

Remsima® IV may also be used as a rescue therapy for those patients admitted as an emergency with a flare and who do not respond to IV steroids. Patients may then remain on Remsima® once discharged.

Currently ~250 patients with CD or UC are receiving a biologic, of which ~70 are on Remsima® IV (5 mg/kg at weeks 0, 2, and 6, and then every 8 weeks) and ~30 on Remsima® SC (120 mg every two weeks).[1] Following the switch to Remsima® SC, only one patient has switched back to Remsima® IV due to a disease flare, as protocol recommend an infusion in acute situations.



Treatment decision: Remsima® vs adalimumab

The choice between Remsima® or adalimumab, as part of treatment escalation, is the patient's decision (following discussion with the consultant or IBD nurse). It is currently too early to see any trends or patterns in patient decisions. However, patients like the reassurance that Remsima® provides of being able to switch between IV and SC administration, without having to change drug.

Previously if patients were on Remsima® IV and wanted to change to a SC formulation they would have needed to change drug, which is a more complex process. Elective switching from infliximab IV to adalimumab SC has been associated with loss of tolerance and loss of response in CD.[4] Furthermore, NICE COVID-19 rapid guidelines recommend that patients with gastrointestinal conditions, who are receiving drugs that affect their immune response, continue with existing treatment to minimise the risk of flare-ups.[5] Now patients receiving infliximab IV can switch between formulations with minimal disruption.

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Treatment decision: Remsima® IV vs SC

The decision to switch a patient from Remsima® IV to SC is very straightforward and is ultimately the patient's choice. Even at the height of the COVID pandemic, patients still had the choice to continue with IV infusions or switch to SC.

As it is a change in administration route, not drug, the switch does not need to be discussed by the multi-disciplinary team. Provided that the patient is clinically stable (not transitioning between therapies, not flaring or a candidate for surgery) and there are no concerns around patient compliance or their ability to use the injection-pen, the option to switch to SC would be discussed at their next infusion appointment.

The switching process

Switching is a simple process that is coordinated by the IBD nurse who ensures the correct timing of the first SC administration and organises the prescription with the pharmacist and homecare delivery service.

Typically, the patient comes into hospital for the first SC administration and is trained by the IBD nurse on using the injection-pen. However, as the numbers of patients switching to Remsima® SC grows, this initial support and training will be provided by the homecare service. Training is straight forward – positive feedback has been received across all patient groups, with younger patients getting on especially well with the device. Should the patient have any difficulties or questions when they start administering at home, they have access to the IBD nurse helpline.

In terms of monitoring, patients continue with routine bloods which they get done either at the hospital or at their GP surgery, and have regular follow-ups with IBD nurses via telephone clinics.

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Patient reaction

Patients' reaction to the option of Remsima® SC varies depending on their individual circumstances. Some patients want to remain on Remsima® IV because they like the reassurance of coming into hospital. However, in general, patients' reactions to switching from Remsima® IV to SC are positive and for some patients the availability of Remsima® SC was greatly anticipated. Patients, who are experts on their treatment and take a proactive approach to their disease management, were aware of Remsima® SC before it was available and called the hospital to enquire about it.

Patients keen to switch are usually young with busy, active lives for whom avoiding the need to come into hospital for IV infusions is perceived as a big advantage. As an example, a young man who had been on Remsima® IV for a while was recently offered to switch to Remsima® SC. The ability to administer the drug at home and get his bloods reviewed at his GP surgery was very appealing – he was in the process of changing jobs and didn't want to be losing half-a-day every 8 weeks for his infusion. He also hoped that the peaks and troughs in disease activity he experienced with the infusion, could be avoided with the more frequent SC administration schedule.

Benefits of offering Remsima® SC

Remsima® SC was a valuable treatment option during the COVID pandemic, particularly for the more vulnerable patients, and its uptake freed up critical clinical resource. Workload for IBD nurses increased dramatically in this period with an increase in flare rates and patient concerns.

The time and resources that was saved by patients switching to Remsima® SC allowed the IBD nurses to cope with this additional demand while continuing to provide an infusion service for those patients who chose to remain on Remsima® IV. Furthermore, during COVID it reduced the number of infusion chairs needed, allowing better social distancing.

Post-COVID, Remsima® SC continues to benefit both the clinic and patient:

Benefits to the clinic	Benefits to the patient
Saves IBD nurse admin and nursing time – increasing their capacity to provide better care for the more severe patients	Saves patients' time as they no longer have to travel to the hospital and there is no waiting or infusion time
Remsima® SC prescriptions are easier to check and manage compared with Remsima® IV – the SC formulation is available as a single dose and dosing does not need to be calculated based on body weight	Daily life is more manageable and convenient – patients can administer the SC dose anywhere
Dispensing time is reduced in the pharmacy	Patients can switch between IV and SC formulation without changing drug
Less fridge storage space needed in pharmacy	

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Learnings and advice

The experience with Remsima® SC during the COVID pandemic has been very positive – it has become an established treatment option and will continue to be offered to patients as we move out of the pandemic.

The process of switching Remsima® IV to SC is simple - having an advocate within the pharmacy department really helps with a smooth transition.

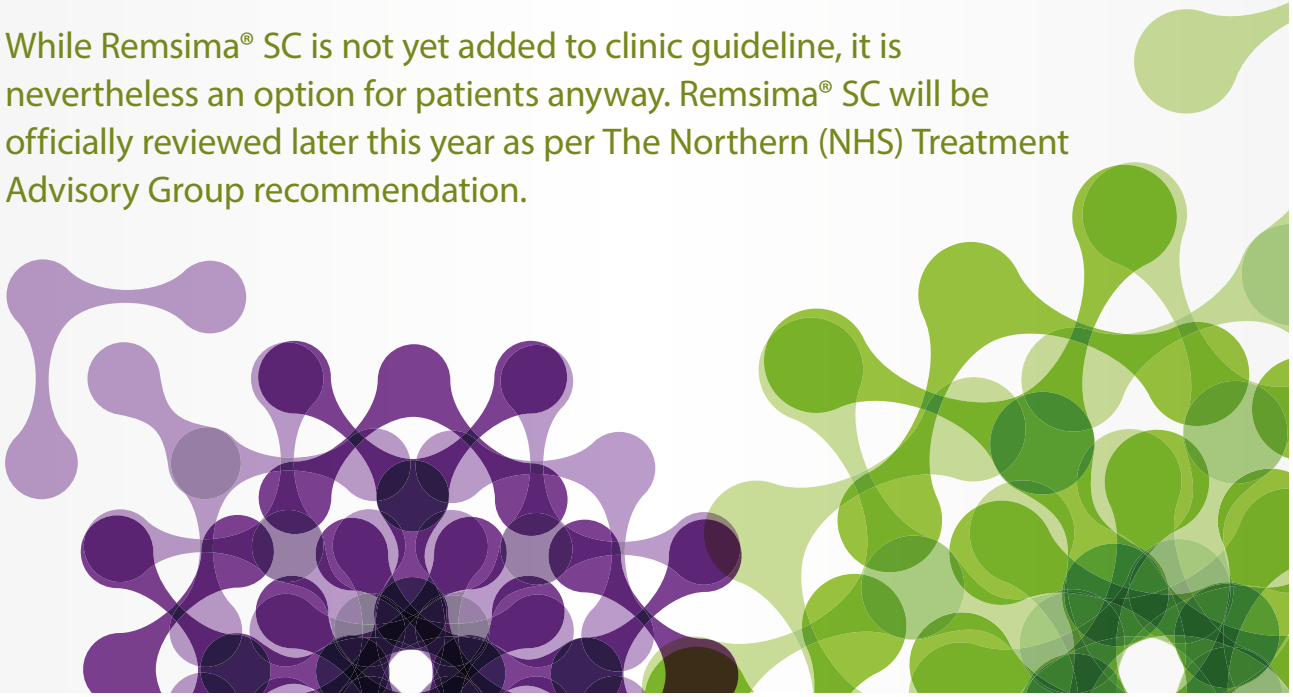
While there were potential concerns around compliance and injection site reactions with patient administration, these concerns have not materialised. IBD nurses monitor compliance through the repeat prescription rates and check for adverse events during follow-up appointments.

One of the keys to its success at North Tees and Hartlepool was not making the switch to SC mandatory and to respect patient choice. The switch was the patient's decision, and those who did switch were highly motivated and committed to the SC administration regimen, and therefore likely to be compliant. If the switch had been mandatory, the hospital would have had clinics to counsel patients through the switch to ensure that they were comfortable with the SC administration, in order to help improve compliance.

The switch has had little impact on overall budget, however, Remsima® SC provides considerable savings in terms of patient, nursing and administrative time.

North Tees and Hartlepool have an ongoing audit for disease activity score which is awaiting more data to support final conclusions.

While Remsima® SC is not yet added to clinic guideline, it is nevertheless an option for patients anyway. Remsima® SC will be officially reviewed later this year as per The Northern (NHS) Treatment Advisory Group recommendation.



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Professional Bodies and Organisations Guidance on Biosimilars

COVID-19 rapid guideline - gastrointestinal and liver conditions treated with drugs affecting the immune response (NICE Guideline NG 172):

"Treatment considerations - when deciding whether to start a new treatment with a drug that affects the immune response, discuss the risks and benefits with the patient or their parents or carers, and take into account the following in the context of COVID-19:

- Has the patient had COVID-19 vaccination?
- Is it essential to start this drug immediately?
- If treatment is needed, is there an alternative with a better risk profile?
- Is the required monitoring and review feasible?
- Can monitoring be done remotely or at a frequency that minimises the risk to the patient's safety and wellbeing?
- Is there a route of administration that could make hospital attendance or admission less likely?

For patients who are already taking drugs that affect the immune response, continue with existing courses of treatment to minimise the risk of a flare-up. Think about whether any changes are needed to minimise face-to-face contact during the COVID-19 pandemic, including - dosage, route of administration and mode of delivery."[5]

National Institute for Health and Care Excellence (NICE):

"Biosimilar medicines have the potential to offer the NHS considerable cost savings and widen the access to innovative medicines, therefore providing increased value for money."[6]

British Society of Gastroentrologists (BSG):

"There is sufficient data from observational studies to show that safety and clinical efficacy of CT-P13 are comparable to the originator drug, with similar immunogenicity [in IBD]."[7]

Remsima® SC (infliximab) provides an alternative treatment option for patients with RA, AS, CD, UC, PsA and PsO.[1,2]

Remsima® Infliximab

The availability of both an IV and a SC formulation of Remsima® translates into a treatment approach tailored to the individual needs of your patients.

With the Remsima® dual formulation strategy, you can choose the optimal treatment that works for your patients.

Remsima® SC offers comparable efficacy with stable potency to IV administration.[8-10]

References

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Prescribing information Remsima® SC (infliximab)

Remsima® 120 mg solution for injection in pre-filled syringe and pre-filled pen. Prescribing information. United Kingdom. Please read the Summary of Product Characteristics (SPC) before prescribing.

Presentation Each 1 mL single dose pre-filled syringe and in pre-filled pen contains 120 mg of infliximab for subcutaneous injection. **Indications Rheumatoid Arthritis (RA): Remsima**, in combination with methotrexate (MTX), is indicated for the reduction of signs and symptoms, as well as the improvement in physical function, in adult patients with active RA when the response to disease-modifying anti-rheumatic drugs (DMARDs), including MTX, has been inadequate; and in adult patients with severe, active and progressive RA not previously treated with MTX or other DMARDs. **Adult Crohn's Disease (CD): Remsima** is indicated for the treatment of moderately to severely active CD in adult patients who have not responded to a full and adequate course of, are intolerant of, or have medical contraindications to therapy with a corticosteroid and/or an immunosuppressant; and fistulising active CD 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 (UC): Remsima** is indicated for the treatment of moderately to severely active UC 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. **Ankylosing Spondylitis (AS): Remsima** is indicated for the treatment of severe, active AS, in adult patients who have responded inadequately to conventional therapy. **Psoriatic Arthritis (PsA): Remsima** is indicated for the treatment of active and progressive PsA, in adult patients when the response to previous DMARD drug therapy has been inadequate. Administration should be in combination with MTX or alone in patients who show intolerance to MTX or for whom MTX is contraindicated. In patients with polyarticular symmetrical subtypes of PsA a reduction in the rate of progression of peripheral joint damage has been shown, as measured by X-ray. **Psoriasis (PsO): Remsima** is indicated for the treatment of moderate to severe plaque PsO in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, MTX or PUVA. **Dosage and administration Remsima** should be initiated and supervised by physicians experienced in the diagnosis and treatment of RA, inflammatory bowel diseases, AS, PsA and PsO. Patients treated with **Remsima** should be given the package leaflet and the patient alert card. The following includes the recommended dosing regimens for each indication, however please see the SPC. **RA:** Treatment with **Remsima** administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 3 mg/kg given 2 weeks apart. The recommended dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. **Adult moderately to severely active CD:** 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. **Adult, fistulising, active CD: 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, no additional treatment with infliximab should be given**. UC:** 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. **AS**: 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. If a patient does not respond by 6 weeks, no additional treatment with infliximab should be given. **PsA:** 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. **PsO:** Treatment with **Remsima** administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administra- tion of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart. If a patient shows no response after 14 weeks (i.e. 2 intravenous infusions and 5 subcutaneous injections), no additional treatment with infliximab should be given. **Re-administration:** 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 (see section 4.8). 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 above given 4 weeks after the last administration of intravenous infliximab. **Switching to and from Remsima subcutane- ous 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. **Contraindications** Tuberculosis or other severe infections such as sepsis, abscesses and opportunistic infections; patients with moderate or severe heart failure (NYHA class III/IV); hypersensitivity to infliximab, other murine proteins or any of the excipients. **Precautions and warnings** Please check SPC before prescribing. **Systemic injection reaction/ localized injection site reaction/ hypersensitivity:** Infliximab has been associated with systemic injection reactions, anaphylactic shock and delayed hypersensitivity reactions. Acute reactions including anaphylactic reactions may develop during (within seconds) or within a few hours following administration of infliximab. For this reason, the 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, hydrocorti- sone and/or paracetamol to prevent mild and transient effects. Localised injection site reactions predominantly of mild to moderate in nature included the following reactions limited to injection site: erythema, pain, pruritus, swelling, induration, haematoma, oedema, bruising, coldness, irritation, paraesthesia, ulcer, urticaria, haemorrhage, rash and scab were reported to be associated with infliximab subcutaneous treatment. Most of these reactions may occur immediately or within 24 hours after subcutaneous injection. Most of these reactions resolved spontaneously without any treatment. Available data suggest an increased risk for delayed hypersensitivity with increasing infliximab free interval. Patients should be advised to seek immediate medical advice if they experience any delayed adverse reaction. If patients are re-treated after a prolonged period, they must be closely monitored for signs and symptoms of delayed hypersensitivity. **Infections:** Patients must be monitored closely for infections, including tuberculosis, before, during and up to 6 months after treatment with **Remsima**. Caution in patients with chronic infection or a history of recurrent infection. Patients should be advised of potential risk factors for infections. Suppression of TNFα may mask symptoms of infection such as fever. Tuberculosis, bacterial infections (including sepsis and pneumonia), invasive fungal, viral and other opportunistic infections, have been observed, some of which have been fatal. Infections were reported more frequently in paediatric populations than in adult populations. There have been reports of active tuberculosis in patients receiving infliximab. Before **Remsima** treatment, patients must be evaluated for active or latent tuberculosis and tests should be recorded on the Patient Alert Card. **Remsima** therapy must not be initiated if active tuberculosis is diagnosed. If latent tuberculosis is diagnosed, a physician with expertise in treatment of tuberculosis should be consulted and the benefit/risk of therapy should be considered. Treatment with anti-tuberculosis therapy must be initiated before initiation of **Remsima**. Patients should be advised to seek medical advice if symptoms of tuberculosis appear during or after treatment. An invasive fungal infection such as aspergillosis, candidiasis, pneumocystosis, histoplasmosis, coccidioidomycosis or blastomycosis should be suspected if a serious systemic illness develops. A physician with expertise in the diagnosis and treatment of invasive fungal infections should be consulted at an early stage. Patients with fistulising CD with acute suppurative fistulas must not initiate **Remsima** therapy until possible source of infection is excluded. **Hepatitis B (HBV) reactivation:** Reactivation of HBV has occurred in patients receiving infliximab who are chronic carriers. Some cases had a fatal outcome. Patients should be tested for HBV infection before initiating treatment and closely monitored for signs and symptoms of active HBV infection. **Hepatobiliary events:** Cases of jaundice and non- infectious hepatitis, some with features of autoimmune hepatitis, have been observed. Isolated cases of liver failure resulting in liver transplantation or death have occurred. **Remsima** should be discontinued if jaundice and/or ALT elevations ≥5 times the upper limit of normal develop. **Vaccinations/therapeutic infectious agents:** Patients should be brought up to date with all vaccinations prior to initiating therapy. Patients may receive concurrent vaccinations but the concurrent administration of live vaccines or therapeutic infectious agents is not recommended. In infants exposed in utero to infliximab, fatal outcome due to disseminated Bacillus CalmetteGuérin (BCG) infection has been reported following administration of BCG vaccine after birth. A six month minimum waiting period following birth is recommended before the administration of live vaccines to infants exposed in utero to infliximab. **Autoimmune processes:** If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with **Remsima** and is positive for antibodies against double-stranded DNA, treatment must be discontinued. **Neurological events:** Anti-TNF agents have been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of peripheral and CNS demyelinating disorders, including Guillain-Barré syndrome and multiple sclerosis. In patients with a history of demyelinat- ing disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation. Discontinuation of **Remsima** should be considered if these disorders develop. **Malignancies and lymphoproliferative disorders:** A risk of the development of lymphomas and other malignancies in patients (including children and adolescents) cannot be excluded. Caution in patients with history of malignancy, in patients with increased risk for malignancy due to heavy smoking, when considering continuing treatment in patients who develop a malignancy, in patients with PsO and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment. Possible increased risk of cervical cancer; periodic screening should continue in women treated with **Remsima**, including those over 60 years of age. Post-marketing cases of hepatosplenic T-cell lymphoma have been reported which is usually fatal. Most cases have occurred in patients with CD or UC treated concomitantly with AZA or 6-MP. Melanoma and Merkel cell carcinoma have been reported, periodic skin examination is recommended, particularly for patients with risk factors for skin cancer. Patients with UC at increased risk for, or with a prior history of dysplasia or colon carcinoma should be screened for dysplasia before therapy and at regular intervals throughout their disease course. Kaposi's sarcoma has been reported, a rare cancer related to infection with human herpes virus 8. **Heart failure:** Caution in patients with mild heart failure (NYHA class I/II) and discontinue in patients who develop new or worsening symptoms of heart failure. **Haematologic reactions:** Discontinuation should be considered in patients with confirmed significant haematologic abnormalities, including pancytopenia, leukopenia, neutropenia and thrombocytopenia. **Others:** Patients requiring surgery whilst on **Remsima** therapy should be closely monitored for infections. **Special populations:** Particular attention regarding the risk of infection should be paid when treating the elderly (>65 years). May have a minor influence on the ability to drive and use machinery. **Interactions** No interaction studies have been performed. Combination of **Remsima** with anakinra and abatacept as well as other biological therapeutics used to treat the same conditions as **Remsima**, is not recommended. **Fertility, pregnancy and lactation** 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 **Remsima** treatment. **Remsima** should only be used during pregnancy if clearly needed. Administration of **Remsima** is not recommended when breast-feeding. Cases of agranulocytosis in infants have been reported. Effects of infliximab on fertility and general reproductive function are unknown. **Undesirable effects** Frequencies are defined at very common (≥1/10), common (≥1/1000 to <1/100), not known (cannot be estimated from the available data). **Very common:** viral infection (e.g. influenza, herpes virus infection), headache, upper respiratory tract infection, sinusitis, abdominal pain, nausea, pain. **Common:** bacterial infections (e.g. sepsis, cellulitis, abscess), neutropenia, leukopenia, anaemia, lymphadenopathy, allergic respiratory symptom, depression, insomnia, vertigo, dizziness, hypoaesthesia, paresthesia, conjunctivitis, tachycardia, palpitation, hypotension, hypertension, ecchymosis, hot flush, flushing, lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnea, epistaxis, gastrointestinal haemorrhage, diarrhoea, dyspepsia, gastrointestinal reflux, constipation, hepatic function abnormal, transaminases increased, new onset or worsening psoriasis including pustular psoriasis (primarily palm and soles), urticarial, rash, pruritis, hyperhidrosis, dry skin, fungal dermatitis, eczema, alopecia, althralgia, myalgia, back pain, urinary tract infection, chest pain, fatigue, fever, injection site reaction, chills, oedema. **Not known:** vaccine breakthrough infection (after **in utero** exposure to infliximab, hepatosplenic T-cell lymphoma (primarily in adolescents and young adult males with Crohn's disease and ulcerative colitis), Merkel cell carcinoma, transient visual loss occurring during or within 2 hours of infusion, myocardial ischaemia/ myo- cardial infarction, liver failure, worsening of symptoms of dermatomyositis, Kaposi's sarcoma. **Serious, including fatal, adverse reactions have been reported**, including HBV reactivation, CHF (congestive heart failure), serious infections (including sepsis, opportunistic infections and TB), serum sickness (delayed hypersensitivity reactions), haematologic reactions, systemic lupus erythematosus/ lupus-like syndrome, demyelinating disorders, hepatobiliary events, lymphoma, HSTCL, leukaemia, Merkel cell carcinoma, melanoma, sarcoidosis/sarcoid-like reaction, and serious infusion reactions. **Other less common and rarely reported adverse reactions are listed in the SmPC.** Prescribers should consult the Summary of Product Characteristics for full prescribing information.

Special precautions for storage Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the medicinal product in its outer carton in order to protect from light. The medicinal product may be stored at temperatures up to a maximum of 25°C for a period of up to 28 days. The medicinal product must be discarded if not used within the 28-day period.

Legal category POM

Presentations and basic NHS costs: Remsima SC (infliximab) 120 mg solution for injection in pre-filled pen (pack size 2 is £755.32, £377.66 per unit)**;** Remsima SC (infliximab) 120 mg solution for injection in pre-filled syringe (pack size 2 is £755.32, £377.66 per unit)

Marketing Authorisation numbers EU/1/13/853/001

Marketing Authorisation holder

Celltrion Healthcare Hungary Kft 1062 Budapest

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For medical information enquiries, please contact UKmedical@celltrionhc.com

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Adverse events should be reported.
Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Celltrion Healthcare and its authorised commercialisation partners by calling +44 (0)1279 406759 (Diamond Pharma Services).

PI Code CTHC-UK-201(1)
Date of PI Preparation October 2020

CTHC-UK-422 May 2021. Developed and funded by **Celltrion Healthcare UK Ltd.**
The experiences, views and opinions of the HCPs are not necessarily those of Celltrion Healthcare UK Ltd.

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Prescribing information Remsima® IV (infliximab)

100 mg powder for concentrate for solution for infusion. Prescribing information. United Kingdom. Please read the Summary of Product Characteristics (SPC) before prescribing.

Presentation Type I vials, with rubber stoppers and aluminium seal with a flip-off button, containing a white powder. Each vial contains 100mg of infliximab. **Indications Rheumatoid Arthritis (RA): Remsima**, in combination with methotrexate (MTX), is indicated for the reduction of signs and symptoms, as well as the improvement in physical function, in adult patients with active RA when the response to disease-modify- ing anti-rheumatic drugs (DMARDs), including MTX, has been inadequate; and in adult patients with severe, active and progressive RA not previously treated with MTX or other DMARDs. In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated. **Adult Crohn's Disease (CD): Remsima** is indicated for the treatment of moderately to severely active CD in adult patients who have not responded to a full and adequate course of, are intolerant of, or have medical contraindications to therapy with a corticosteroid and/or an immunosuppressant; and fistulising active CD 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 (CD): Remsima** is indicated for the treatment of severe, active CD in children and adolescents aged 6 to 17 years who have not responded to conventional therapy including a corticoster- oid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindica- tions for such therapies. **Ulcerative Colitis (UC): Remsima** is indicated for the treatment of moderately to severely active UC 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 (UC): Remsima** is indicated for treatment of severely active UC, 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 (AS): Remsima** is indicated for the treatment of severe, active AS, in adult patients who have responded inadequately to conventional therapy. **Psoriatic Arthritis (PsA): Remsima** is indicated for the treatment of active and progressive PsA, in adult patients when the response to previous DMARD drug therapy has been inadequate. Administration should be in combination with MTX or alone in patients who show intolerance to MTX or for whom MTX is contraindicated. In patients with polyarticular symmetrical subtypes of PsA a reduction in the rate of progression of peripheral joint damage has been shown, as measured by X-ray. **Psoriasis (PsO): Remsima** is indicated for the treatment of moderate to severe plaque PsO in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, MTX or PUVA. **Dosage and administration Remsima** should be initiated and supervised by physicians experienced in the diagnosis and treatment of RA, inflammatory bowel diseases, AS, PsA and PsO. Administer intravenously over a 2-hour period by a healthcare professional qualified to detect any infusion-related issues and observe for at least 1-2 hours post-infusion for acute infusion-related reactions. Check product labels to ensure that the correct formulation of Remsima is being administered. Emergency equipment must be available. Patients treated with **Remsima** should be given the package leaflet and the patient alert card. **Shortened infusions across adult indications:** In selected adult patients who have tolerated at least 3 initial 2-hour infusions of **Remsima** (induction phase) and are receiving maintenance therapy, consider administering subsequent infusions over a period of not less than 1 hour. If an infusion reaction occurs in association with a shortened infusion, a slower infusion rate may be considered for future infusions if treatment is to be continued. Shortened infusions at doses >6 mg/kg have not been studied. The following includes the recommended dosing regimens for each indication, however please see the SPC for alternative strategies in RA and adult CD. **RA:** 3 mg/kg given as an intravenous (IV) infusion followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. **Remsima** must be given concomitantly with methotrexate. If there is no evidence of therapeutic benefit within the first 12 weeks or after dose adjustment, continued therapy should be reconsidered. **Adult moderately to severely active CD:** 5mg/kg given as an IV 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 should be given. **Adult, fistulising, active CD:** 5mg/kg IV infusion followed by additional 5mg/kg infusions at 2 and 6 weeks after first infusion. If a patient does not respond after 3 doses, no additional treatment should be given. **UC:** 5mg/kg given as an IV infusion followed by additional 5mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks. If there is no evidence of therapeutic benefit after 3 doses, continued therapy should be reconsidered. **AS**: 5mg/kg given as an IV infusion followed by additional 5mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks. If a patient does not respond after 2 doses, no additional treatment should be given. **PsA:** 5mg/kg given as an IV infusion followed by additional 5mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. **PsO:** 5mg/kg given as an IV infusion followed by additional 5mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks. If a patient shows no response after 4 doses, no additional treatment should be given. **Re-administration: Remsima** can be re-adminis- tered in RA and CD within 16 weeks following the last infusion. The safety and efficacy of re-administration after a **Remsima**-free interval of more than 16 weeks has not been established in either CD or RA. The safety and efficacy of re-administration in AS, other than every 6 to 8 weeks and in PsA and UC, other than every 8 weeks, has not been established. Re-administration with one single **Remsima** dose in PsO after an interval of 20 weeks suggests reduced efficacy and a higher incidence of mild to moderate infusion reactions when compared to the initial induction regimen. Limited experience from retreatment, using a re-induction regimen suggests a higher incidence of infusion reactions, some serious, when compared to 8 weekly maintenance treatment. In case maintenance therapy is interrupted in any indication, and there is a need to restart treatment, **Remsima** should be reinitiated as a single dose followed by the maintenance dose recommendations. **Paediatric population:** CD (6 to 17 years): 5 mg/kg given as an IV infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Data do not support further treatment of patients who do not respond within 10 weeks. **UC (6 to 17 years):** 5 mg/kg given as an IV infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Data do not support further treatment of patients who do not respond within 8 weeks. **Contraindications** Tuberculosis or other severe infections such as sepsis, abscesses and opportunistic infections; patients with moderate or severe heart failure (NYHA class III/IV); hypersensitivity to infliximab, other murine proteins or any of the excipients. **Precautions and warnings** To improve the traceability of biological medicinal products, the trade mark and the batch number of the administered product should be clearly recorded in the patient file. **Infusion reactions:** Acute infusion reactions including anaphylactic reactions may develop during (within seconds) or within a few hours following infusion. If these reactions occur, the infusion must be interrupted immediately. Emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway must be available. Antibodies to infliximab may develop and have been associated with increased frequency of infusion reactions. Symptomatic treatment should be given for serious reactions and further **Remsima** infusions must not be administered. Delayed hypersensitivity reactions have been reported. Data suggests an increased risk for delayed hypersensitivity with increasing **Remsima**-free intervals. **Infections:** Patients must be monitored closely for infections, including tuberculosis, before, during and up to 6 months after treatment with **Remsima**. Caution in patients with chronic infection or a history of recurrent infection. Patients should be advised of potential risk factors for infections. Suppression of TNFα may mask symptoms of infection such as fever. Tuberculosis, bacterial infections (including sepsis and pneumonia), invasive fungal, viral and other opportunistic infections, have been observed, some of which have been fatal. Infections were reported more frequently in paediatric populations than in adult populations. There have been reports of active tuberculosis in patients receiving infliximab. Before **Remsima** treatment, patients must be evaluated for active or latent tuberculosis and tests should be recorded on the Patient Alert Card. **Remsima** therapy must not be initiated if active tuberculosis is diagnosed. If latent tuberculosis is diagnosed, a physician with expertise in treatment of tuberculosis should be consulted and the benefit/risk of therapy should be considered. Treatment with anti-tuberculosis therapy must be initiated before initiation of **Remsima**. Patients should be advised to seek medical advice if symptoms of tuberculosis appear during or after treatment. An invasive fungal infection such as aspergillosis, candidiasis, pneumocystosis, histoplasmosis, coccidioidomycosis or blastomycosis should be suspected if a serious systemic illness develops. A physician with expertise in the diagnosis and treatment of invasive fungal infections should be consulted at an early stage. Patients with fistulising CD with acute suppurative fistulas must not initiate **Remsima** therapy until possible source of infection is excluded. **Hepatitis B (HBV) reactivation:** Reactivation of HBV has occurred in patients receiving infliximab who are chronic carriers. Some cases had a fatal outcome. Patients should be tested for HBV infection before initiating treatment and closely monitored for signs and symptoms of active HBV infection. **Hepatobiliary events:** Cases of jaundice and non- infectious hepatitis, some with features of autoimmune hepatitis, have been observed. Isolated cases of liver failure resulting in liver transplantation or death have occurred. **Remsima** should be discontinued if jaundice and/or ALT elevations ≥5 times the upper limit of normal develop. **Vaccinations/therapeutic infectious agents:** Patients should be brought up to date with all vaccinations prior to initiating therapy. Patients may receive concurrent vaccinations but the concurrent administration of live vaccines or therapeutic infectious agents is not recommended. In infants exposed in utero to infliximab, fatal outcome due to disseminated Bacillus CalmetteGuérin (BCG) infection has been reported following administration of BCG vaccine after birth. A six month minimum waiting period following birth is recommended before the administration of live vaccines to infants exposed in utero to infliximab. **Autoimmune processes:** If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with **Remsima** and is positive for antibodies against double-stranded DNA, treatment must be discontinued. **Neurological events:** Anti-TNF agents have been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of peripheral and CNS demyelinating disorders, including Guillain-Barré syndrome and multiple sclerosis. In patients with a history of demyelinat- ing disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation. Discontinuation of **Remsima** should be considered if these disorders develop. **Malignancies and lymphoproliferative disorders:** A risk of the development of lymphomas and other malignancies in patients (including children and adolescents) cannot be excluded. Caution in patients with history of malignancy, in patients with increased risk for malignancy due to heavy smoking, when considering continuing treatment in patients who develop a malignancy, in patients with PsO and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment. Possible increased risk of cervical cancer; periodic screening should continue in women treated with **Remsima**, including those over 60 years of age. Post-marketing cases of hepatosplenic T-cell lymphoma have been reported which is usually fatal. Most cases have occurred in patients with CD or UC treated concomitantly with AZA or 6-MP. Melanoma and Merkel cell carcinoma have been reported, periodic skin examination is recommended, particularly for patients with risk factors for skin cancer. Patients with UC at increased risk for, or with a prior history of dysplasia or colon carcinoma should be screened for dysplasia before therapy and at regular intervals throughout their disease course. Kaposi's sarcoma has been reported, a rare cancer related to infection with human herpes virus 8. **Heart failure:** Caution in patients with mild heart failure (NYHA class I/II) and discontinue in patients who develop new or worsening symptoms of heart failure. **Haematologic reactions:** Discontinuation should be considered in patients with confirmed significant haematologic abnormalities, including pancytopenia, leukopenia, neutropenia and thrombocytopenia. **Others:** Patients requiring surgery whilst on **Remsima** therapy should be closely monitored for infections. **Special populations:** Particular attention regarding the risk of infection should be paid when treating the elderly (>65 years). May have a minor influence on the ability to drive and use machinery. **Interactions** No interaction studies have been performed. 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Special precautions for storage Store in a refrigerator (2°C – 8°C). **Before reconstitution**: 5 years at 2°C – 8°C. Remsima may be stored at temperatures up to a maximum of 25°C for a single period of up to 6 months, but not exceeding the original expiry date. The new expiry date must be written on the carton. Upon removal from refrigerated storage, Remsima must not be returned to refrigerated storage. **After reconstitution and dilution:** Chemical and physical in use stability of the diluted solution has been demonstrated for up to 28 days at 2 °C to 8 °C and for an additional 24 hours at 25°C after removal from refrigeration. From a microbiological point of view, the infusion solution should be administered immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C, unless reconstitution/dilution has been taken place in controlled and validated aseptic conditions.

Legal category POM

Presentations and basic NHS costs 1 vial of 100 mg: £377.66

Marketing Authorisation numbers EU/1/13/853/001-005

Marketing Authorisation holder

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