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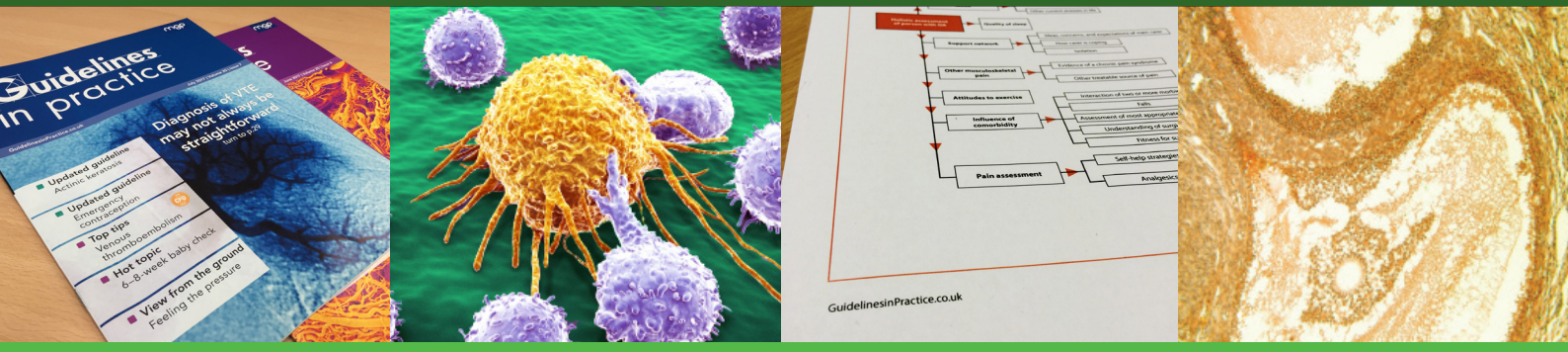
# Guidance Update

Gastrointestinal




# Switching from intravenous to subcutaneous infliximab biosimilar (Remsima®) in adult patients with inflammatory bowel disease: experience at an NHS trust

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# Switching from intravenous to subcutaneous infliximab biosimilar (Remsima®) in adult patients with inflammatory bowel disease: experience at an NHS trust

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## Introduction

Kettering General Hospital NHS Foundation Trust covers a population of 311,000 people across north Northamptonshire and south Leicestershire.[1] The Department of Digestive Diseases manages hundreds of patients each year with inflammatory bowel disease (IBD), including over 300 on biologic high cost therapies.

Inflammatory bowel disease is a debilitating condition for many patients, with more severe cases becoming increasingly common. Effective treatment can reverse the course/progressive nature of the disease, and can prevent significant surgery requirements and significant periods of ill health for patients.[2,3] Infliximab is a monoclonal antibody that has been successfully used at the trust for several years to treat some of the most unwell patients with IBD. A total of 95 patients with IBD were treated with intravenous (IV) infliximab at Kettering General Hospital during the past year. Of these, two patients were treated with a combination of Flixabi® and Inflectra®, and 89 patients received Inflectra (the US product name for Remsima®).

Biosimilar medicines are often used in place of original, or reference, biological products, such as monoclonal antibodies, once they are out of patent because they usually provide a more cost-effective alternative. While they are not identical to the original biological products, biosimilars are comparable in terms of their clinical efficacy, safety, and tolerability.[2,4] Some biosimilars are available in different preparations, with IV and subcutaneous (SC) versions each having their own advantages. Until earlier in 2020, infliximab was only available as an IV formulation, so the addition of SC infliximab provides another welcome treatment option for patients with IBD.

Kettering General Hospital NHS Trust was the first centre to switch patients with IBD from an IV version of any biosimilar infliximab to an SC version (Remsima SC). The reasons for switching, how the switch was implemented, early experiences of the switch, and advice on how to achieve a successful switch are discussed below.

## Infliximab

Infliximab is a chimeric monoclonal antibody that inhibits the pro-inflammatory cytokine tumour necrosis factor (TNF)-alpha.[5] It has been used to treat IBD for several years because of its ability to reduce symptoms and induce intestinal mucosal healing in many patients.[5,6] Infliximab is recommended for treatment of moderately to severely active ulcerative colitis (UC) in adults or, as IV infliximab, for severely active UC in children aged 6 to 17 years, if they have not responded to, or are unable to tolerate or have contraindications to, conventional treatment.[2,7] It is recommended for treatment of adults or, as IV infliximab, for children aged 6 to 17 years with severe active Crohn's disease (CD), or adults with active fistulising CD whose disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy.[3,8] Patients who respond to treatment should continue with treatment, with assessment at least yearly, and an option to try a withdrawal from treatment once in stable clinical remission.[3,7–9]

Infliximab has been available as an IV treatment since its approval by the European Medicines Agency (EMA) in 1999.[4] The biosimilar Remsima IV was approved for use in Europe for treating CD and UC in 2013.[4,10] The first subcutaneous form of infliximab, Remsima SC, which gives patients an option to self-administer infliximab, was licensed by the EMA in 2019 for the treatment of rheumatoid arthritis.[11] Remsima SC has recently been granted a marketing authorisation by the EMA for five additional indications: CD, UC, ankylosing spondylitis, psoriatic arthritis, and psoriasis.[12]

Intravenous infliximab is administered by IV infusion, with a recommended dose of 5 mg/kg at weeks 0, 2, and 6, and then

**Table 1: Mean serum concentration of infliximab in patients with CD receiving SC infliximab was shown to be consistently higher than for patients who were given IV infliximab[12]**

| | | Remsima IV 5 mg/kg | Remsima SC 120 mg | Remsima SC 180 mg | Remsima SC 240 mg |
|---|---|---|---|---|---|
| **Pre-dose concentration (µg/mL)** | | | | | |
| Week 2 | N | 12 | 11 | 12 | 6 |
| | Mean ± SD | 24.67±8.29 | 21.95±4.80 | 22.53±9.50 | 15.66±10.23 |
| Week 6 | N | 12 | 11 | 12 | 6 |
| | Mean ± SD | 11.49±10.06 | 12.73±6.97 | 13.04±14.19 | 6.60±6.40 |
| Week 14 | N | 12 | 10 | 12 | 6 |
| | Mean ± SD | 2.98±3.60 | 14.09±6.27 | 17.51±12.46 | 22.88±19.46 |
| Week 22 | N | 11 | 9 | 11 | 6 |
| | Mean ± SD | 1.71±1.74 | 15.67±4.32 | 16.23±10.08 | 22.33±14.61 |
| Week 30 | N | 10 | 9 | 10 | 5 |
| | Mean ± SD | 1.22±1.45 | 15.83±3.84 | 20.97±13.54 | 29.00±15.51 |
| Week 38 | N | 10 | 9 | 9 | 5 |
| | Mean ± SD | 1.12±1.61 | 16.98±4.75 | 22.45±13.28 | 27.20±14.74 |
| Week 46 | N | 9 | 9 | 7 | 5 |
| | Mean ± SD | 1.90±2.51 | 12.95±6.25 | 22.40±15.72 | 26.04±14.44 |
| Week 54 | N | 8 | 9 | 7 | 5 |
| | Mean ± SD | 1.55±1.92 | 15.40±7.44 | 20.89±10.42 | 26.00±18.53 |

every 8 weeks.[7,9] Remsima SC is prescribed for adults ≥18 years of age at a single dose, irrespective of patient body mass index, of 120 mg infliximab solution for injection in either a pre-filled syringe or pen to be administered every 2 weeks.[5] In addition to removing the need for patients to attend hospital regularly for IV infusion, having a simpler single dosing option, irrespective of BMI, means that in some patients there may be cost savings for commissioners compared with the IV formulation.

## Reasons for switching to SC infliximab biosimilar

Although transition to Remsima SC was already underway, the main driver for the switch to SC infliximab at Kettering was the COVID-19 pandemic, and a fear that hospital resources might quickly become overwhelmed with critically ill patients with COVID-19. The pandemic was predicted to peak in April 2020. The decision to implement the switch was reached in mid-March, and the approval documentation was ready by the end of March 2020. In addition to relieving pressure on hospital resources, giving patients with IBD who were being treated with IV infliximab the option of switching to an SC version would reduce the number of patients needing to attend the hospital for infusions and would reduce their risk of contracting COVID-19.

The pharmacy team at the trust had experience of using SC infliximab to treat rheumatoid arthritis and suggested that it might be a helpful option for gastroenterology at this time. Recent trial data had shown that the efficacy and safety of SC infliximab in treating CD and UC were comparable with IV infliximab.[13,14] A phase I open-label randomised controlled trial in patients with moderate to severe CD indicated that the mean serum concentration of infliximab achieved for patients with SC infliximab was consistently higher than for patients who were given IV infliximab (see Table 1, above).[12,13] This could be a result of the more frequent administration of SC infliximab, which is given fortnightly. While the treatment had not been licensed for IBD in March 2020, the extended licence was due to be approved by the EMA in a few months' time.[10]

Discussions with senior gastroenterology colleagues at Kettering and at other trusts were reassuring because they all agreed that the data meant they would have no concerns switching patients to SC infliximab. Box 1 (see p. 4) summarises the advantages of SC infliximab compared with IV infliximab, both for patients and hospital trusts.

## Planning the switch

The experience of using SC infliximab in rheumatology helped the pharmacy team with planning and implementing the switch. Because the SC preparation had not yet been licensed for use in gastroenterology at that time, the homecare lead pharmacist liaised with other stakeholders, including members of the gastroenterology department, the chief pharmacist, members of the contracts team, and the local clinical commissioning group (CCG) to work out the best way to proceed. A quality assurance technician, who is experienced with the use of off-label and unlicensed medicines

**Box 1: Benefits of using SC infliximab compared with IV infliximab**

**Benefits for patients:**

- significant time savings without regular hospital visits for IV infusions
- greater autonomy, making work, study, and travel easier
- access to help and advice via a helpline
- medicine provided at home on a 3-monthly basis
- being able to stay at home and away from hospital during the COVID-19 pandemic.

**Benefits for hospital trusts:**

- reductions in staff time:
  - the fixed dose of infliximab SC means pharmacists do not have to calculate and make up individual doses of IV infliximab, which needs to be undertaken in aseptic units (this also frees up resources for other purposes)
  - IBD nurses do not have to cannulate patients or administer IV infusions
- increased capacity of infusion chairs for other patients
- reduced traffic around the hospital
- increased car parking capacity at the hospital.

in chemotherapy, was able to advise about the process needed to use an off-label medicine.

The authors of this article produced a document detailing the need to expedite use of SC infliximab during the pandemic, which included data relating to its efficacy and safety, and a budget impact model. A risk assessment was carried out and was signed off by the trust's medical director. The risk assessment completed included aspects such as the risk of:

- non-compliance with an SC therapy
- misadministration in the patient's home setting
- a lack of response
- a failure of the supply chain resulting from demand in use of SC infliximab due to the COVID-19 pandemic
- unsustainable budget impact with implications for continued use.

## Blueteq

Blueteq software has been a requirement in the trust for CCG-commissioned medicines since 2015, with implementation of the extended version for management of high cost drug use and individual funding requests being rolled out across different departments over the 5 years since then. The software is used to send requests for new medicines to the appropriate commissioner and is a useful tool to audit medicine usage. It also ensures appropriate use of high cost medicines as recommended by NICE or any locally made agreements between commissioners. Having the system in place has enabled a more collaborative approach between the hospital and the CCG, and a greater understanding among the clinical team about the information commissioners need when it comes to requesting high cost drugs.

## Identifying suitable patients for the switch

The switch was to be available for patients with CD or UC who were stable on IV infliximab regardless of previous biosimilar usage, and not for those experiencing periods of flare. It was important to assess patients individually and the decision about whether to offer a switch to SC infliximab was based on each patient's health status. Suitable patients who were keen to switch to SC infliximab were counselled so that they understood what the treatment involved and were able to give fully informed consent to treatment.

## Implementing the switch

The switch began with administration of the first doses of Remsima SC on 30 March 2020, and patients with CD or UC, who were eligible for treatment with SC infliximab, were offered the opportunity to switch to the SC treatment when they attended the hospital for their regular IV infusion appointment. If they were agreeable, they were counselled by the IBD nurses, who gained their consent to treatment, and demonstrated how to administer SC infliximab correctly so that they would be able to use the treatment safely at home.

Homecare was not an option for patients with IBD at the beginning of the pandemic, when capacity was reserved for chemotherapy and other treatments, therefore the patient packs and coolboxes that patients needed were stored in the pharmacy and provided to IBD nurses along with patient training materials to give to patients when they attended. Regular communication between members of the pharmacy team and the gastroenterology department was important to ensure optimal procurement of SC infliximab. This meant that enough stock would be available for patients when attending the hospital but without any wastage.

Patients who wished to use SC infliximab were given 3 months' supply along with a sharps bin to dispose of their needles safely. Before their next 3-month supply was due, the pharmacy department assisted the gastroenterology nurses to complete the paperwork that would transfer patients to the homecare service, which would then take over the supply of their medicine.

Two-weekly follow-up appointments by phone with the homecare lead pharmacist were offered to patients if they had any questions about their medicines. They also had access to an IBD helpline (run by Kettering General Hospital IBD nurses) for support. Unless they had any problems, patients would then continue using SC infliximab until their usual annual review.

## Switch outcomes

### Patient response

The first six patients with CD or UC were switched at the end of March 2020, with more patients also being transferred to SC infliximab when they came for their IV infusion appointment. A total of 30 patients have been switched so far, which is approximately 30% of the IBD patients receiving infliximab at the hospital. Patients on IV infliximab biosimilar continue to be considered on a case by case basis.

Some patients initially had concerns about whether SC infliximab would be as effective as IV treatment, but were satisfied when the efficacy data was discussed with them. However, generally, patients were happy to be able to self-treat and understood the reasons behind the switch. Not having to attend the hospital for IV treatment during the height of the COVID-19 pandemic was an obvious advantage. The case study in Box 2 (to the right) gives one patient's account of switching to SC infliximab.

### Efficacy and tolerability

Detailed results for the patient cohort at the trust are not yet available, but a full picture of switch outcomes will be available in summer 2021. However, the emerging results indicate that SC infliximab appears to be effective for use in stable patients with CD or UC who were previously treated with IV infliximab, without any major adverse effects. Initial drug therapeutic monitoring results look promising: early trends suggest that drug levels are maintained and possibly increased, though this needs to be further evaluated over time, and there has not been a significant drop-off in patients' response to infliximab or increase in antibody formation above what would normally be expected with IV infliximab.

The only adverse effects reported so far are mild local skin reactions experienced by two patients, who have subsequently switched back to the IV formulation as a result of this.

### Hospital outcomes

The switch was achieved quickly, from the decision first being made to switch on 26 March 2020 to the first patients being switched to SC infliximab on 30 March 2020. The gastroenterology treatment area at Kettering General Hospital was (and remains) under pressure due to the number of gastroenterology patients requiring treatment, and switching patients from IV to SC infliximab has been beneficial in freeing up capacity for other patients.

As a result of the switch, gastroenterologists at Royal Liverpool and Broadgreen University Hospitals NHS Trust approached Dr Verma in April 2020 to find out more about how the switch was managed. The authors of this article provided information and documentation to help staff at Liverpool effectively switch patients with IBD who were being treated in their NHS trust to SC infliximab. This collaboration between teams in different NHS trusts has enabled a significant number of patients with IBD to benefit from self-treating with SC infliximab and the teams will continue to share efficacy and safety data to ensure the best possible outcome for patients.

**Box 2: Case study**

J, aged 18, was one of the first (and youngest) patients to switch to SC infliximab. His Crohn's disease was stable, maintained on IV Infliximab for >12 months after a difficult disease course through his mid-teens. When SC infliximab was discussed, he was keen to switch as it gave him more freedom immediately, reduced his concerns about contracting COVID-19 after being advised to practice strict social distancing to reduce his risk, and would allow him to continue taking infliximab with ease when he started at university. J previously had concerns about how he would manage to return to Kettering General Hospital for infusions without disrupting his future university studies and had discussed with his consultant whether his medication would need to be changed or his care transferred to another IBD team based in the same city as the university he would eventually be attending.

On outpatient follow up a few weeks after switching, J expressed his delight that he had not noticed any difference in his condition on switching (remaining well) and that he could continue with taking infliximab and stay under the care of the same consultant when he went to university. J had found the switch to home SC treatment straightforward and it had not caused him any issues.

## Addressing potential barriers to switching

Because of the increased risk to patients attending hospital and the need to free up hospital resources during the COVID-19 pandemic, switching needed to be implemented rapidly, which could potentially have been a barrier. However, planning and implementing the switch was achieved without too many difficulties. Ensuring also that good communication was maintained with colleagues and patients alike meant that everyone was well informed and confident about the switch.

A potential future barrier is that the trust is in a block contract until April 2021, which means that drugs are now paid for within the block. The finance director will therefore be responsible for assessing the cost implications of different medicines. It is hoped that any cost worries will be offset by looking at the budget impact of SC infliximab holistically, in terms of IBD patients self-treating at home and reducing the use of hospital resources. Additional wider benefits from the availability of an SC formulation as an alternative to an existing IV formulation are applicable to the whole health economy, and are often not

**Box 3: Advice for a successful switch from IV infliximab to SC infliximab biosimilar**

- Involve all stakeholders, including commissioners, in discussions about the switch at the earliest opportunity
- Build a good relationship with your CCG pharmacists if you do not already have one
- Approach staff in trusts that have already succeeded in switching for advice and to view their documentation
- Get organised—carry out a risk assessment, provide safety and efficacy evidence for SC infliximab, outline the holistic cost benefits of switching, including reductions in workload and freeing up of infusion chairs, and train staff who will be involved in carrying out the switch
- Prepare patients for the switch and explain the changes involved
- Communicate with the pharmacy team and homecare team to set up new procedures
- Set up a system to record patients' blood results and any adverse effects to enable easy monitoring of the outcomes of switching.

obvious. The availability of an SC formulation means that patients are more likely to be treated at home (aligning to the *NHS 10-Year plan: Providing care closer to Home*[15]), VAT savings are released, and capacity is released within IV suites, improving NHS efficiency and making better use of restricted resources.

Box 3 (above) summarises the key points to consider for a successful switch to SC infliximab.

## Future plans

Subcutaneous infliximab provides another route for administration, with the added bonus that patients can self-treat at home, and is a welcome addition to the trust's treatment armoury for IBD.

Further work will be undertaken to assess whether SC infliximab can be offered as an option for treating ankylosing spondylitis, psoriatic arthritis, and psoriasis, the other conditions covered by the recent EMA marketing authorisation;[12] for example, infliximab is normally reserved for very severe cases of psoriasis, but the SC formulation might be beneficial earlier in the treatment pathway.

Changes in commissioning intentions following the release of the *Revised arrangements for NHS contracting and payment during the COVID-19 pandemic*[16] will have an impact on future drug procurement, and it is difficult to make predictions for future applications of SC infliximab in Kettering General Hospital NHS Foundation Trust. It is fair to state, however, that based on the benefits described in Box 1 (see p.4), and the heritage/experience we have for infliximab as a treatment option, we would consider adding this formulation alongside IV infliximab in the pathway, possibly for earlier use.

## Conclusion

Infliximab is one of the the oldest biological agents yet is still used extensively due to its efficacy, especially in some of the patients with a high burden of disease. The SC formulation allows us to offer an effective treatment with the convenience of homecare, and it offers another welcome treatment option for patients with IBD.

The switch to SC infliximab at Kettering has been successful because, in addition to the benefits described above of switching to SC infliximab, it has enabled a proportion of patients with IBD to avoid attending hospital for IV infusions during the COVID-19 pandemic. Many patients were afraid to come to the hospital because of worries about catching COVID-19 and the switch to SC infliximab provided a timely solution for concerned patients with IBD. With the necessary systems in place, patients with IBD now have the opportunity to administer infliximab at home where possible, reducing their need to attend hospital appointments, as well as reducing the burden on hospital resources.

The success of the switch was a result of exceptional collaborative decision making by a large number of stakeholders, which was made easier by long established relationships between staff at the trust and the CCG. This meant they were rapidly able to put together a budget impact model and risk assessment, which were signed off without challenge in order to keep patients safe and at home. Members of the clinical team are proud of how well they worked together to deliver a new service for patients at a time of potential crisis.

Initial results of the switch look promising, with SC infliximab appearing to be effective in patients with CD or UC, with few cases of adverse reactions reported, and with positive drug therapeutic monitoring results. Patients who have switched to the SC formulation benefit from not needing to attend hospital and the hospital benefits by increasing capacity in the IV infusion unit and by freeing up time for IBD nurses and pharmacists.

A collaboration with staff in Liverpool means that many more IBD patients have been able to switch to SC infliximab and data sharing between trusts will continue to provide more information about the safety and efficacy of this treatment.

## Conflicts of interest

The authors have received honoraria from Celltrion and other pharmaceutical companies. Dr Verma has also received sponsorship for travel to conferences.

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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 administration 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** 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. **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, hydrocortisone 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 demyelinating 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/myocardial 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 Váci út 1-3. WestEnd Office Building B Torony. Hungary

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)