

# Introducing biosimilar versions of infliximab: Inflectra and Remsima

<http://guidance.nice.org.uk/hta329>

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## 1 Introduction

This resource has been developed to provide practical information and advice on the use of biosimilar versions of infliximab (Inflectra and Remsima).

It is intended for use by both clinical and non-clinical staff considering the introduction of these biosimilar medicines into the NHS.

NICE's Adoption and Impact Programme worked with NHS organisations to share their learning and experiences of introducing biosimilar medicines. The information presented in this resource is intended for the sole purpose of supporting the NHS in decisions that are made around the introduction of biosimilars. It summarises the issues that are considered to be of significance to the NHS, but is not NICE guidance.

There are a number of considerations when introducing biosimilar versions of infliximab, some of which may be common to the introduction of other biosimilar medicines. The NHS staff involved in the production of this resource reported that the use of biosimilars can reduce costs, allowing more treatment with new medicines as long as the appropriate follow-up and monitoring systems are in place to manage risk and patient needs and expectations.

The learning gained from NHS organisations that have introduced biosimilars is presented as a series of examples of current practice. They are not presented as best practice but as real-life examples of how NHS sites have planned and managed the introduction of biosimilars.

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## 2 Background on biosimilar medicines

### ***NICE position statement on evaluating biosimilars***

A biosimilar medicine (or biosimilar) is a biological medicine that is developed to be highly similar to an existing biological medicine in physicochemical and biological terms. [NICE's position statement on evaluating biosimilar medicines](#) was published in January 2015. This states that biosimilars notified to the NICE topic selection process for referral to the Technology Appraisal programme will usually be considered in the context of a Multiple Technology Appraisal, in parallel with their reference products in the indication under consideration. The Department of Health has confirmed that a technology appraisal remit referred to NICE enables NICE to decide to apply the same remit, and the resulting guidance, to relevant licensed biosimilar products which subsequently appear on the market. In other circumstances, where it is considered a review of the evidence for a biosimilar medicine is necessary, NICE will consider producing an [evidence summary: new medicine](#).

Biosimilars have the potential to offer the NHS considerable cost savings, especially as biological medicines are often expensive and are often used to treat long-term conditions.

### ***Licensing and comparability***

Biosimilar medicines introduced into the UK market are authorised by the [European Medicines Agency](#) (EMA). The EMA has produced a document covering a series of [questions and answers on biosimilar medicines](#). Biological medicines such as monoclonal antibodies, growth hormone and insulin are produced in or derived from living systems. The size and complexity of biological medicines, as well as the way they are produced, may result in a degree of variability in molecules of the same active substance, particularly in different batches of the medicine. The EMA document explains that a biosimilar medicine is a biological medicine that is developed to be highly similar to an existing biological medicine (the reference medicine). Biosimilars are not the same as generic versions of non-biological medicines, which have simpler chemical structures and are considered to be identical to their reference medicines. The active substance of a biosimilar and its reference medicine is essentially the same biological substance but, just like the reference medicine, the biosimilar has a degree of natural variability and there may also be a degree of variability between the biosimilar and its reference medicine. Further information is available in a report for the European Community ([What you need to know about biosimilar medicinal products](#)).

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In the development of a biosimilar, there is no requirement to demonstrate clinical benefit to patients *per se* as this has been shown for the reference medicine. Instead, biosimilars undergo a comprehensive regulatory process which demands extensive comparability studies that demonstrate similarity to the reference medicine. The benefits and risks can then be inferred from the similarity of the biosimilar product to the reference product in terms of quality, efficacy and safety. Biosimilar medicines are usually licensed for all the indications in the licence of the originator biological medicine, but this requires appropriate scientific justification on the basis of demonstrated or extrapolated equivalence. They are generally used at the same dose and route of administration as the biological reference medicine and have the same contraindications and warnings. For more information see 'What evidence is required for the approval of biosimilars in the EU?' in the NHS publication [Answers to commonly asked questions about biosimilar versions of infliximab](#).

Any biological drug is likely to be modified several times during its production history and development, for example when there is a change in manufacturing process. In the case of Remicade, the infliximab reference medicine, there have been 40 listed changes made to the manufacturing process for the active substance or the final product since its original authorisation (1999–2011). After each such change, the same comparability exercise that is carried out for a biosimilar is carried out to ensure that the new biological drug is similar to the old one. For more information see 'Is Remicade still the same product as the one used in the original clinical trials?' in the NHS publication [Answers to commonly asked questions about biosimilar versions of infliximab](#).

## ***Brand name prescribing and pharmacovigilance***

In the UK, the MHRA recommends that all biological medicines, including biosimilar medicines, are prescribed by brand name ([Drug Safety Update 2008](#)). Because biosimilar and reference biological medicines that have the same international non-proprietary name (INN) are not presumed to be identical in the same way as generic non-biological medicines, brand name prescribing ensures that the intended product is received by the patient. It ensures that products cannot be automatically substituted at the pharmacy level. The choice of whether a patient receives a biosimilar or originator biological medicine rests with the responsible clinician in consultation with the patient.

As with all new medicines, biosimilars have a 'black triangle' in the first years after approval to make providers aware of the importance of pharmacovigilance ([Drug Safety Update 2009](#)).

Patient registers are used to monitor for emerging safety and efficacy issues with biological medicines, and the MHRA supports the recording of brand names and batch numbers for traceability when reporting suspected adverse drug reactions ([Drug Safety Update 2012](#)). The UKMI [in-use product safety assessment report for infliximab biosimilars](#) states that brand name prescribing is vital if products are to be identified appropriately at the points of dispensing and/or administration. As with all biological medicines, for each patient, a traceable record of the brand, batch number, and other vital details of the product used should be made. Reporting and monitoring of patients through clinical registries will enable collection of specific data on serious adverse events in both gastroenterology and rheumatology, and these mechanisms will act in addition to routine pharmacovigilance activities. Safe introduction and ongoing safe use of biosimilars requires both practitioner and manufacturer engagement with these processes.

## ***Background on infliximab***

Infliximab is a tumour necrosis factor alpha (TNF-alpha) inhibitor that is used to treat several autoimmune and inflammatory disorders. It is a monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNF-alpha. The originator biological medicine, [Remicade](#) was approved in Europe in 1999 and is licensed for treating adult rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and psoriasis, and adult and paediatric Crohn's disease and ulcerative colitis. The use of infliximab in these conditions has been covered by several pieces of NICE guidance (see [summary of relevant NICE recommendations section](#)).

In September 2013, the EMA authorised a biosimilar version of infliximab (CT-P13) under 2 brand names: [Inflectra](#) (Hospira UK) and [Remsima](#) (Celltrion Healthcare Hungary; marketed in the UK by Napp Pharmaceuticals). The pharmaceutical form, strength, therapeutic indications and dosing regimens of Inflectra and Remsima, and of the reference medicine, [Remicade](#), are the same. See the [summary of evidence for Inflectra and Remsima section](#) for more details.

[Inflectra](#) and [Remsima](#) were launched in the UK in February 2015.

## **3 Tips from the NHS for managing the introduction of biosimilar medicines**

- Identify clinical and pharmacy champions to take the lead in introducing biosimilars (see [project team](#)).

- Consult all stakeholders (including patients) to ensure confidence in using biosimilars (see [communication and collaborative working](#)).
- Provide information about:
  - the EMA licensing process for biosimilars
  - extrapolation and equivalence
  - the manufacturing process and intra-product manufacturing changes for both biological medicines and their biosimilars (see [licensing and comparability](#)).
- Identify the potential cost saving and re-investment opportunities and explore gain-share agreements (see [resource impact](#)).
- Seek formal approval at the local formulary committee once there is clinical consensus to include biosimilars on the formulary (see [insights from the NHS](#)).
- Collect baseline data and agree metrics to be collected during and after the introduction of biosimilars (see [measuring success](#)).
- Submit data to national audits and registries (see [measuring success](#)).
- Prescribing should be done by brand name to ensure that there is no unintended substitution of drugs at the pharmacy level (see [brand name prescribing and pharmacovigilance](#)).

## 4 Insights from the NHS: managing the introduction of biosimilar medicines

NICE worked with 2 NHS organisations to share their learning and experiences of planning for and managing the introduction of biosimilar medicines, in particular biosimilar versions of infliximab.

### ***University Hospital Southampton NHS Foundation Trust***

[University Hospital Southampton NHS Foundation Trust](#) provides services to around 1.9 million people living in Southampton and South Hampshire, as well as specialist services (including neurosciences, cardiac services and children's intensive care) to more than 3.7 million people in Southern England and the Channel Islands. The trust's gastroenterology team comprises 9

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consultants, 5 nurse specialists, 2 pharmacists, 2 specialist dietitians and 1.5 whole time equivalent administrators. There are 4 consultants with a defined interest in inflammatory bowel disease (IBD) who are part of a specialist adult IBD service. The team care for approximately 4000 patients with a wide range of complexity.

The consultant clinical lead for the IBD service saw an opportunity for the development of a gain-share agreement with the 2 main local clinical commissioning groups (CCGs) for the introduction of an infliximab biosimilar.

The trust had previously developed a gain-share agreement for the establishment of a dedicated IBD biologics service in 2012. This followed an audit done by the gastroenterology team of all 120 patients who were having biological medicines at the time. The audit results showed that patients were not being screened and assessed in accordance with NICE technology appraisal guidance on [infliximab \(review\) and adalimumab for the treatment of Crohn's disease](#).

Discussions were held with the 2 local CCGs to discuss how this could be improved and it was agreed that a gain-share agreement would be put in place to develop a coordinated nurse-led biologics service. This agreement enabled the trust to employ a full-time, band 7 specialist nurse to lead the service and oversee all patients, as well as being responsible for data collection and liaising with the infusion service and home care companies. The original agreement was for 3 years, with 350 specialist nurse follow-up appointments per year. As part of the agreement, the trust also updated its existing gastroenterology database; this resulted in a new patient management system for those having biologic medicines. The data from the system can be used to demonstrate the efficacy, safety and appropriate use of biological therapies in the trust to commissioners and is automatically uploaded to the [UK IBD biological therapy audit](#) and [UK IBD Registry](#). Data are collected prospectively at the point of care and the specialist nurse generates a twice-yearly report for the 2 CCGs on all patients having biologic medicines. The report documents the review of the effectiveness of treatments and positive decisions made about ongoing management in line with NICE guidance.

By January 2015, IBD in over 350 patients was being treated with a biologic, 150 of whom received infliximab as Remicade (originator brand of infliximab). Before the infliximab biosimilars Inflectra and Remsima launched, the consultant clinical lead for the IBD service proposed implementing a managed switching programme for all patients having Remicade to one of the infliximab biosimilars. It was recognised that the principles and science of biosimilars were not fully understood by clinicians and that it was important to discuss this as a team to ensure that everyone was fully briefed and in agreement. The clinical lead suggested that a new gain-share

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agreement could be developed to fund the additional staffing needed to implement and monitor a safe switch programme.

Having agreed to proceed with the gastroenterology team, the consultant clinical lead for the IBD service worked with a trust assistant director of finance to develop a business case for a 3-year service improvement programme. The trust then worked with the lead specialist pharmacists for commissioning in the 2 local CCGs to discuss the potential savings from safely switching from Remicade to a biosimilar version.

The CCGs agreed to the proposal and the gain-share agreement has enabled the trust to recruit another full-time band 7 IBD nurse specialist, a 0.5 wte band 3 administrator and 2 additional sessions of pharmacy support. The Department of Health Commercial Medicines Unit, working in close collaboration with the regional specialist procurement pharmacist, undertook a tendering exercise for an infliximab biosimilar, and as a result the trust now uses Inflectra.

The proposed switching programme was discussed in detail with the [IBD patient panel](#) as well as with people in clinic on an ad hoc basis. Many patients on the panel are on infliximab or other biological medicines and were able to offer insight from the patient perspective. Feedback suggested that for patients, it was ultimately a matter of trust in the clinicians providing the service and the re-assurance of no harm. Many were already aware of the high cost of their treatment, and before the publication of this NICE guidance some had fought hard for it to be approved by their primary care trust or CCG through individual funding requests. The patient panel agreed that the additional clinical monitoring and surveillance provisions included in the programme, including being seen by the IBD nurse specialist at all infusions, would satisfy their concerns. A major motivation for patients was seeing at least some of the cost savings being reinvested in improvements to their care.

The safe switch programme started in April 2015. Patients having Remicade were approached by the IBD specialist nurses at the time of their infusions and were given a [letter](#) (adapted from a [PrescQIPP](#) template) advising them that their medicine was being switched from Remicade to Inflectra and asking them to get in touch with the specialist nurse if they had any concerns. Copy letters were also sent to the GP. A nurse followed up with a phone call before the patient's next visit to ensure that they understood the process. Patients were also told that some people being taking Remicade may have adverse reactions and that there should be no difference with Inflectra.

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The team have identified good communication with patients as being vital to the successful implementation of its safe switch programme.

## Switching from Remicade to a biosimilar

All patients taking Remicade were asked to complete a [questionnaire](#) at each of the 2 infusions before their planned switch date. This included a patient-recorded outcome measure for IBD control, disease activity scoring and a questionnaire on side effects. As part of the evaluation, drug trough levels and antidrug antibodies were measured before and after the switch. It is expected that these data will show any changes between the originator biological medicine and the biosimilar with reasonable scientific rigour and confidence. The ongoing data collected are regularly reviewed by the team as part of a risk management strategy, given the uncertainties around using biosimilar infliximab in IBD. This ensures a longitudinal dataset spanning before and after switching.

Currently, the lead biologicals pharmacist prescribes by brand name to reduce any risk of interchangeability between Remicade and Inflectra. Once the service is more developed, this responsibility will pass to the specialist biologicals nurse prescriber who will continue to prescribe by brand name.

After 2 months, all 150 patients were switched from Remicade to the biosimilar Inflectra. They continue to be monitored and to date only 2 patients have requested a review of the switch on medical grounds. Understandably some patients with severe disease had more detailed discussions and reassurance before agreeing to the switch. These people have had a full assessment and review in line with local protocols and will be monitored on a case-by-case basis.

The team concluded that large cost savings can be achieved, not only through using biosimilar infliximab but also through more effective use of all biologic therapies in IBD, providing that there remains a focus on patient needs and investment in local IBD biologics services including staff (in this case IBD nurses, clerical support and pharmacists) and IT (such as the UK IBD registry patient management system). They reflected that none of this would have been possible without close collaboration and trust between clinicians, hospital management and CCGs, with all parties being appropriately incentivised to deliver high quality patient care and cost savings.

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## ***University College London Hospitals NHS Foundation Trust***

The University College Hospital gastrointestinal services division is organised into 5 service groups: hepatopancreatobiliary, colorectal, upper gastrointestinal cancer, obesity and endoscopy. The division comprises over 45 consultants and specialists working across these 5 groups. The colorectal service group offers a specialist IBD service offering multidisciplinary management of patients from their initial presentation of Crohn's or colitis through to complex surgery. The IBD service comprises 6 consultants and 2 specialist IBD nurses and has a caseload of over 3000 people with IBD. Of these, approximately 400 people are taking a biological drug with a split between infliximab (150) or adalimumab (250).

The medicines management team at the trust had successfully introduced biosimilars onto the formulary before (specifically biosimilar filgrastim, epoetin and human growth hormone) and so had experience of the challenges involved. Lessons learnt from their implementation were as follows:

- Common issues arise with the introduction of a biosimilar medicine in any speciality.
- Clinical and pharmacy champions need to be identified.
- Information needs to be provided about:
  - the EMA licensing process for biosimilars
  - extrapolation and equivalence
  - the manufacturing process and intra-product manufacturing changes for both biological medicines and their biosimilars
  - the potential cost-savings and re-investments that can be made
  - the importance of gain-share agreements.
- There needs to be clear starting and stopping criteria because it is always unknown how a new patient will respond to either the originator biological medicine or a biosimilar.
- Formal approval at the local formulary committee should be sought once there is clinical agreement.

- Patients need information if a switch is planned and reassurance around the monitoring of their condition during this process.

The medicines management team prepared to introduce infliximab biosimilars (Inflectra and Remsima) before they were available by building on its experience with other specialities. The team identified this as an opportunity for cost savings through a gain-share agreement. The lead pharmacists from the medicines management team approached the lead IBD gastroenterology and rheumatology clinicians in the trust to discuss an implementation programme based on previous experience. A meeting was held with the clinical staff involved in prescribing biological medicines in both specialties to plan a way forward.

Initially some clinicians were unaware of the intra-manufacturing changes which had already taken place with Remicade, and not all understood that the 2 biosimilars are in fact exactly the same product, being packaged and distributed by 2 different companies. Once all the potential issues were discussed, most clinicians were reassured about starting new patients on a biosimilar medicine. However, some still expressed concerns about switching gastroenterology patients from Remicade to a biosimilar, based on clinical data extrapolation from studies with rheumatology patients. Clinicians were concerned about patients relapsing, particularly when remission had often been difficult to achieve.

Agreement has now been reached for patients starting a new course of infliximab in the IBD service to be prescribed a biosimilar. This will be closely monitored and reviewed in 6 months. An interim tender arrangement is in place through a London procurement partnership agreement for use of the infliximab biosimilar, Remsima. This will be re-tendered later in 2015.

## 5 How to implement biosimilar medicines

The experiences of NHS trusts have been used to develop practical suggestions on how to best adopt biosimilar medicines.

### ***Project management***

It is the experience of the Adoption and Impact Programme that in order to gain maximum benefit, biosimilar medicines should be adopted using a project management approach.

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NICE has produced the [into practice guide](#) which includes a section on what organisations need to have in place to support the implementation of NICE guidance. These principles could be applied to managing the introduction of biosimilar medicines.

## Project team

The first step in this approach is to form a local project team who will work together to introduce biosimilar medicines and manage any changes in practice.

Individual NHS organisations will determine the membership of this team and how long the project will last. In order to introduce biosimilars in an effective and sustainable way, consider the following membership of the team:

- **Clinical champion(s):** a consultant clinician/physician in the relevant field. They should have the knowledge and understanding to be able to drive the project, answer any clinical queries and champion the project at a senior level.
- **Pharmacy lead:** this could be a specialist procurement pharmacist or a medicines management pharmacist who will be able to provide specialist expertise in the field of biosimilar medicines.
- **Management sponsor:** will be able to help assess the financial viability of the project, drive the formulation of a business case and help to demonstrate the cost savings achieved.
- **Commissioning lead(s):** will have responsibility for negotiating any gain-share agreements.
- **Other stakeholders or staff:** these may include nursing and other ward staff who will be valuable members of the project team as they will be involved in providing the service.

## Measuring success

In order to demonstrate the benefits of introducing biosimilar medicines it is important to take measurements before, during and after implementation.

University Hospital Southampton NHS Foundation Trust gastroenterology team has developed a clinical data collection template and a [patient questionnaire](#) to ensure a longitudinal dataset before and after switching. Other trusts may want to create similar templates suitable for local use.

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The Royal College of Physicians IBD audit – [biological therapy audit](#) aims to assess nationally:

- the appropriate use/prescribing of biological therapies (adalimumab and infliximab) in the treatment of IBD
- the efficacy of biological therapies in the treatment of IBD
- the safety of biological therapies in the treatment of IBD
- IBD patients' views on their quality of life at defined intervals throughout their use of biological therapies.

The [UK IBD Registry](#) collects anonymised IBD adult and paediatric patient data for prospective audit and research purposes.

## ***Communication and collaborative working***

Experience shared by NHS sites has indicated that when implementing biosimilar medicines, it is important that there is clear and wide communication between all stakeholders. This will include the clinical speciality staff involved, day case units, pharmacy, managers, general practice, commissioners and patients. The communication strategy for the project should be considered alongside any planned educational activities.

The specific communications may include information on the following:

- Background to the proposed switch from a biological medicine to a biosimilar medicine including which patients may and may not be eligible.
- The timetable for the proposed switch, including detailed steps.
- Details of risk assessment and control measures put in place to mitigate risks during the switch-over phase.
- The requirements and arrangements for clinical audit.
- Who to contact for further information and how to report problems.

In order to achieve the desired aims of the project, clear written and verbal communication may include:

- Letters to hospital consultants, departments, general practice and patients.
- Dissemination of information at directorate, departmental and team meetings.
- Electronic messages displayed when prescriptions are ordered.

## ***Resource impact***

Biosimilar medicines have the potential to offer the NHS considerable cost savings, especially as they are often used to treat long-term conditions. NICE has published a costing statement, [implementing the NICE guidance on infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy \(TA329\)](#), which includes biosimilar versions of infliximab. The statement highlights that, in the context of this guidance, using biosimilar infliximab may lead to drug cost savings for commissioners. The statement shows a cost saving of 10% per cycle by changing to a biosimilar version of infliximab. However, costs may vary locally depending on local contractual arrangements and it is reported that some centres have achieved much greater cost savings. CCGs will need to collaborate with provider trusts and regional procurement pharmacists on the local contractual arrangements.

The [NHS standard contract: a guide for clinical commissioners](#) (2013) describes gain-share agreements as a transformational approach which can be used to allow the provider and commissioner to work together collaboratively to identify savings and support the development of long-term strategic partnerships by facilitating new patterns of provision. The following considerations should apply:

- Need to use robust and transparent indicators to ensure behaviours are not distorted towards savings at the expense of clinical safety and quality.
- The length of time of the arrangements should be carefully considered, to avoid gain sharing cost reductions which could have been achieved without intervention.
- Requirements for QIPP (Quality, Innovation, Productivity and Prevention) and efficiency need to be taken account of when determining the gain share agreement.

[Principles for sharing the benefits associated with more efficient use of medicines not reimbursed through national prices](#) (2014) describes how NHS England will incentivise provider trusts to ensure maximum value for money from medicines excluded from the National Tariff and states that CCGs could adopt the same principles.

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## Business case

The implementation team should treat the development of a robust business case as an early priority in the life of the implementation project.

Local arrangements for developing and approving business plans will vary from trust to trust and each organisation is likely to have its own template and process in place.

NICE has produced advice on [building a business case](#) to provide clear information through the steps involved to help organisations with technology adoption. These principles could be applied to managing the introduction of biosimilar medicines.

## Other resources

When managing the introduction of biosimilar medicines, NHS trusts may find it useful to refer to the following resources:

- [What are biosimilars and are they important?](#) Drug and Therapeutics Bulletin 2013;51:57-60, doi:10.1136/dtb.2013.5.0181 2013; 51(5)
- European Commission (2013). [What you need to know about biosimilar medicinal products. Process on corporate responsibility in the field of pharmaceuticals access to medicines in Europe: a consensus information document](#)
- European Medicines Agency (2012). [Questions and answers on biosimilar medicines \(similar biological medicinal products\)](#)
- British Society of Gastroenterology. [IBD Section Statement on Biosimilar drugs](#)
- London and South East Regional Medicines Information Service. (2015) [Answers to commonly asked questions about biosimilar versions of infliximab](#)
- UK Medicines Information. (2015) [In-use product safety assessment report: Remsima and Inflectra \(infliximab biosimilars\)](#)
- PrescQIPP (2015) Webinars on biosimilars ([secondary care](#) and [primary care](#))

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## 6 Summary of NICE guidance on infliximab

NICE has issued guidance on the use of infliximab within the therapeutic areas for which it is licensed and this is summarised below (see the guidance for details). The Department of Health has confirmed that a technology appraisal remit referred to NICE enables NICE to decide to apply the same remit, and the resulting guidance, to relevant licensed biosimilar products which subsequently appear on the market.

### *Ulcerative colitis*

The NICE guideline on the [management of ulcerative colitis in adults, children and young people](#) makes recommendations for treating mild to moderate ulcerative colitis and acute severe ulcerative colitis.

For guidance on infliximab for treating subacute ulcerative colitis (all extents of disease), the guideline refers to the technology appraisal on [infliximab for subacute manifestations of ulcerative colitis](#), which has been superseded by the multiple technology appraisal on [infliximab, adalimumab and golimumab for the second line treatment of moderately to severely active ulcerative colitis after the failure of conventional therapy](#).

In the multiple technology appraisal, infliximab, adalimumab and golimumab are recommended as options in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies. The choice of treatment should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available. This should take into consideration therapeutic need and whether or not the patient is likely to adhere to treatment. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose). The multiple technology appraisal also recommends infliximab as an option for treating severely active ulcerative colitis in children and young people aged 6–17 years whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.

The Appraisal Committee for the multiple technology appraisal was aware that biosimilar versions of infliximab were licensed for the same indications as the reference product. The

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Committee noted that the European Medicines Agency was content that the pharmacokinetics, efficacy, safety, and immunogenicity profiles of the biosimilars were similar to those of the reference product, and they concluded that the recommendations for infliximab could apply both to the reference product and to its biosimilars.

For acute severe ulcerative colitis, infliximab is recommended as outlined in the NICE technology appraisal guidance on [infliximab for acute exacerbations of ulcerative colitis](#). Infliximab is an option for the treatment of acute exacerbations of severely active ulcerative colitis only in patients in whom ciclosporin is contraindicated or clinically inappropriate, based on a careful assessment of the risks and benefits of treatment in the individual patient, or in clinical trials.

## ***Crohn's disease***

The NICE guideline on the [management of Crohn's disease in adults, children and young people](#) recommends biological drugs as outlined in the NICE technology appraisal guidance on [infliximab and adalimumab for the treatment of Crohn's disease](#). In the technology appraisal guidance, infliximab and adalimumab are recommended as treatment options for adults with severe active Crohn's disease, and infliximab is recommended as a treatment option for adults with active fistulising Crohn's disease, if their disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy. Treatment should normally be started with the less expensive drug (taking into account drug administration costs, required dose and product price per dose). This may need to be varied for individual patients because of differences in the method of administration and treatment schedules. Infliximab is also recommended as a treatment option for people aged 6–17 years with severe active Crohn's disease whose disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy.

## ***Rheumatoid arthritis***

In the NICE guideline on [the management of rheumatoid arthritis in adults](#), biological drugs are recommended as outlined in NICE technology appraisal guidance, including the guidance on [adalimumab, etanercept and infliximab](#) for the treatment of rheumatoid arthritis. An update of this guidance is in progress as a multiple technology appraisal on [adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab for rheumatoid arthritis](#) (publication expected October 2015). The scope for this multiple technology appraisal includes all 3 infliximab products: Remicade, Inflectra and Remsima. The current technology appraisal

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guidance recommends adalimumab, etanercept and infliximab as options for the treatment of adults who have active disease and have undergone trials of 2 disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate (unless contraindicated). Treatment should normally be initiated with the least expensive drug (taking into account administration costs, required dose and product price per dose). This may need to be varied in individual cases due to differences in the mode of administration and treatment schedules.

NICE has also issued technology appraisal guidance on [adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor](#). This recommends rituximab in combination with methotrexate as an option for the treatment of adults in this clinical scenario. Adalimumab, etanercept, infliximab and abatacept, each in combination with methotrexate, are recommended as treatment options only for adults who cannot receive rituximab therapy because they have a contraindication to rituximab, or when rituximab is withdrawn because of an adverse event.

## ***Ankylosing spondylitis***

The NICE technology appraisal guidance on [adalimumab, etanercept and infliximab for ankylosing spondylitis](#) does not recommend infliximab for the treatment of ankylosing spondylitis because it is not cost-effective. Adalimumab and etanercept are recommended as treatment options for adults with severe active ankylosing spondylitis if they fulfil certain criteria, as is golimumab (in NICE technology appraisal guidance on [golimumab for the treatment of ankylosing spondylitis](#)). A review of both these technology appraisals is ongoing: [ankylosing spondylitis and axial spondyloarthritis \(non-radiographic\) – adalimumab, etanercept, infliximab and golimumab](#) (publication expected September 2015).

## ***Psoriatic arthritis***

The NICE technology appraisal guidance on [etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis](#) and [golimumab for the treatment of psoriatic arthritis](#) recommends all these drugs as options for the treatment of adults with active and progressive psoriatic arthritis when certain criteria are met.

Treatment should normally be started with the least expensive drug (taking into account drug administration costs, required dose and product price per dose). This may need to be varied for

individual patients because of differences in the method of administration and treatment schedules.

## ***Psoriasis***

In the NICE guideline on the [assessment and management of psoriasis](#), biological drugs are recommended as outlined in the NICE technology appraisal guidance on [adalimumab for the treatment of adults with psoriasis](#), [etanercept and efalizumab for the treatment of adults with psoriasis](#) (efalizumab was later withdrawn from the market), [infliximab for the treatment of adults with psoriasis](#) and [ustekinumab for the treatment of adults with moderate to severe psoriasis](#).

Infliximab is recommended as a treatment option for adults with plaque psoriasis only when certain criteria are met.

## 7 Summary of evidence for Inflectra and Remsima

Effectiveness	Safety
<ul style="list-style-type: none"> <li>• In 1 RCT in people with ankylosing spondylitis (n=250), CT-P13<sup>a</sup> was pharmacokinetically equivalent to Remicade<sup>b</sup> in terms of the AUC and C<sub>max</sub> at steady state (between weeks 22 and 30).</li> <li>• In 1 RCT in people with active rheumatoid arthritis despite methotrexate therapy (n=606), CT-P13<sup>a</sup> had equivalent efficacy to Remicade<sup>b</sup> based on the ACR20 response at week 30.</li> </ul>	<ul style="list-style-type: none"> <li>• Overall, the type and incidence of adverse events to CT-P13<sup>a</sup> and Remicade<sup>b</sup> reported in clinical trials appeared generally similar and in line with those expected for infliximab.</li> <li>• The summaries of product characteristics for <a href="#">Inflectra</a> and <a href="#">Remsima</a> include the same contraindications and warnings as for <a href="#">Remicade</a>. They are contraindicated in people with tuberculosis or other severe infections, and people with moderate or severe heart failure. Warnings include those relating to infusion reactions and hypersensitivity, infections, live vaccines, neurological events, malignancies and lymphoproliferative disorders, heart failure and haematologic reactions.</li> <li>• Inflectra and Remsima have a '<a href="#">black triangle</a>' for additional safety monitoring and patient registers should be used to monitor for any emerging safety issues.</li> </ul>

Patient factors	Resource implications
<ul style="list-style-type: none"> <li>• Pharmaceutical form, strength, therapeutic indications, and dosing regimens of Inflectra and Remsima are the same as for Remicade.</li> <li>• All biological medicines, including biosimilars should be prescribed by brand name and the trademark and batch number of the administered product should be recorded in the patient notes.</li> <li>• Intravenous administration.</li> </ul>	<ul style="list-style-type: none"> <li>• Costs for Inflectra, Remsima and Remicade may vary locally depending on local drug procurement arrangements.</li> </ul>
<p><sup>a</sup> CT-P13 is the infliximab biosimilar medicine marketed as Inflectra and Remsima</p> <p><sup>b</sup> Remicade is the infliximab biological reference medicine</p>	

## Product overview

### Licensed therapeutic indication

A biosimilar version of infliximab (CT-P13) is available under 2 brand names: Inflectra (Hospira UK Limited) and Remsima (Celltrion Healthcare Hungary Kft; marketed in the UK by Napp Pharmaceuticals Limited). The pharmaceutical form, strength, therapeutic indications, and dosing regimens of Inflectra and Remsima are the same as for each other and for the biological reference medicine, Remicade. Inflectra and Remsima are licensed for:

- Moderate to severe, active **ulcerative colitis in adults** who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies.
- Severely active **ulcerative colitis in children and young people** aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies.
- Moderate to severe, active **Crohn's disease in adults** who have not responded despite a full and adequate course of therapy with a corticosteroid or an immunosuppressant, or who are intolerant to or have medical contraindications for such therapies; fistulising active Crohn's disease in adults who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).
- Severe, active **Crohn's disease in children and young people** aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy, or who are intolerant to or have contraindications for such therapies.
- **Rheumatoid arthritis in adults** , in combination with methotrexate, to reduce signs and symptoms, and improve physical function in adults with active disease when the response to disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate, has been inadequate; or in adults with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.
- Severe, active **ankylosing spondylitis in adults** who have responded inadequately to conventional therapy.
- Active and progressive **psoriatic arthritis in adults** when the response to previous DMARD therapy has been inadequate.
- Moderate to severe plaque **psoriasis** in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.

Each Inflectra or Remsima vial contains 100 mg infliximab, which should be reconstituted with 10 mL of water for injections and given intravenously. The usual dose is 3 mg/kg, 5 mg/kg or up

to a maximum of 7.5 mg/kg given as an IV infusion depending on the indication. See [summaries of product characteristics](#) for details.

## **Evidence overview**

To support the European Medicines Agency authorisation of the infliximab biosimilar medicine CT-P13 ([Inflectra](#) and [Remsima](#)), the results of an extensive comparability exercise between CT-P13 and the biological reference medicine, [Remicade](#) were presented; this included quality, non-clinical and clinical data. The European public assessment reports (EPAR) for [Inflectra](#) and [Remsima](#) state that as part of the comparability exercise it was shown that all major physicochemical characteristics and biological activities of CT-P13 were comparable to those of Remicade.

The clinical data demonstrating the similarity between CT-P13 and Remicade consisted of 2 main randomised controlled trials (RCTs):

- A 30-week, multicentre, double-blind, parallel group pharmacokinetic (phase 1) RCT in 250 people with active ankylosing spondylitis, conducted in 46 centres in 10 countries in Europe, Asia and Latin America ([PLANETAS](#), Study CT-P13 1.1; ClinicalTrials.gov Identifier: [NCT01220518](#))<sup>[1]</sup>. People were randomised to 5 mg/kg CT-P13 or 5 mg/kg Remicade, both given as a 2-hour intravenous infusion at weeks 0, 2 and 6, and then every 8 weeks up to week 30.
- A 30-week, multicentre, double-blind, parallel group efficacy and safety (phase 3) RCT in 606 people with active rheumatoid arthritis despite treatment with methotrexate, conducted in 100 centres in 19 countries in Europe, Asia and Latin America and the Middle East ([PLANETRA](#), Study CT-P13 3.1; ClinicalTrials.gov identifier: [NCT01217086](#))<sup>[2]</sup>. People were randomised to 3 mg/kg CT-P13 or 3 mg/kg Remicade, both given as a 2-hour intravenous infusion at weeks 0, 2 and 6, and then every 8 weeks up to week 30. Weekly methotrexate (12.5 mg to 25 mg per week) and folic acid (at least 5 mg per week) were also given.

## **Pharmacokinetic equivalence and clinical effectiveness**

In [PLANETAS](#), CT-P13 was pharmacokinetically equivalent to Remicade in terms of the area under the concentration-time curve (AUC) and observed maximum serum concentration ( $C_{max}$ ) at steady state (between weeks 22 and 30) in the 222 or 223 patients for which data were available. Equivalence was demonstrated for both AUC (mean 104.5%; 90% confidence interval

[CI] 94.3 to 115.8%) and  $C_{max}$  (101.5%; 90% CI 94.7 to 108.9%), with the 90% CIs for the ratio of geometric means being within the reference range of 80% to 125%. The secondary efficacy endpoints, such as the proportion of people achieving Assessment in Ankylosing Spondylitis International Working Group criteria (ASAS20 or ASAS40) responses, were similar for CT-P13 and Remicade. However, the study was not powered to show therapeutic equivalence.

In [PLANETRA](#), CT-P13 had equivalent efficacy to Remicade based on the American College of Rheumatology (ACR20) response at week 30. The pre-specified criterion for equivalence was for the 95% CIs for the between-group difference to be within the range of -15% to 15%. In the intention-to-treat population, the proportion of people achieving an ACR20 response at week 30 was 60.9% with CT-P13 and 58.6% with Remicade (treatment difference 2%; 95% CI -6% to 10%, meeting the criterion for equivalence). In the per-protocol population, the proportions were 73.4% with CT-P13 and 69.7% with Remicade (treatment difference 4%; 95% CI -4% to 12%, again meeting the criterion for equivalence).

## Safety and tolerability

Most adverse events reported in the clinical trials PLANETAS and PLANETRA were mild-to-moderate in intensity. Serious adverse events were reported in 4.7% of the CT-P13 group and 6.6% of the Remicade group in PLANETAS and 10.0% of the CT-P13 group and 7.0% of the Remicade group in PLANETRA. These included neutropenia, infections, infusion-related reactions and tuberculosis. No deaths were reported during either study.

The EPAR for [Inflectra](#) and [Remsima](#) included a safety database of 339 patients treated with CT-P13 for up to 1 year. It reports that overall, the type and incidence of adverse events to CT-P13 and Remicade reported in clinical trials appeared generally similar and in line with those expected based on the [Remicade summary of product characteristics](#). The most common adverse drug reactions were infections, including tuberculosis (latent or active) and nasopharyngitis, increase in liver enzymes, infusion-related reactions, hypertension and headache. There were no marked differences in the immunogenicity profile of CT-P13 and Remicade up to 54 weeks and the impact of antibodies on efficacy and safety was comparable.

The main safety concern with CT-P13 raised in the EPAR related to a slightly higher incidence of serious adverse events with CT-P13 compared with Remicade in the rheumatoid arthritis trial. This was mainly due to an excess of infections (active tuberculosis and pneumonia) and vascular disorders in the CT-P13 group. Based on the totality of the evidence presented, it was concluded that the difference observed in the clinical programme was likely to be a chance finding.

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However, the risk of serious infections including tuberculosis and rare adverse reactions known to Remicade, such as malignancies and lymphoproliferative disorders, will be monitored with patient registries.

The summaries of product characteristics for Inflectra and Remsima include the same contraindications and warnings as for Remicade. All 3 summaries of product characteristics also state that in order to improve the traceability of biological medicinal products, the trademark and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

## Evidence strengths and limitations

In the development of a biosimilar product, there is no requirement to demonstrate benefit to the patient *per se* as this has been shown for the reference product. The benefits and risks are inferred from the similarity of the test product to the reference product in terms of quality, efficacy and safety. The purpose of an application to the European Medicines Agency to approve a biosimilar medicine is therefore to demonstrate similarity to the reference product (EPAR for [Inflectra](#) and [Remsima](#)).

The clinical trials PLANETAS and PLANETRA reported their primary endpoints at 30 weeks. Limited efficacy and safety data for the use of CT-P13 for up to 1 year are included in the EPAR, and 102 week data are now available in abstract form but are not yet fully published. PLANETAS and PLANETRA were conducted mainly in Eastern Europe and Latin America, with additional enrolment in Korea or Philippines. Few people from Western Europe were included.

There are currently no completed clinical trials of CT-P13 in people with Crohn's disease, ulcerative colitis, psoriatic arthritis or psoriasis. However, the EPAR states that extrapolation of clinical efficacy and safety data to other indications of the reference monoclonal antibody, not specifically studied during the clinical development of the biosimilar monoclonal antibody, is possible based on the overall evidence of comparability provided from the comparability exercise and with adequate justification. The EPAR states that there are preliminary clinical data for CT-P13 from a very small cohort of 15 people with Crohn's disease and 8 people with ulcerative colitis. People with inflammatory bowel disease have also been enrolled in a post-marketing surveillance study ([ClinicalTrials.gov identifier NCT02326155](https://clinicaltrials.gov/ct2/show/study/NCT02326155)) and a comparative trial of CT-P13 compared with Remicade in people with active Crohn's disease is ongoing ([ClinicalTrials.gov identifier: NCT02096861](https://clinicaltrials.gov/ct2/show/study/NCT02096861)).

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Recently, a Korean retrospective study in 32 people with Crohn's disease and 42 people with ulcerative colitis ([Jung et al. 2015](#))<sup>[3]</sup> and a Korean case series in 8 people with Crohn's disease and 9 people with ulcerative colitis ([Kang et al. 2015](#))<sup>[4]</sup> have been published.

A Norwegian RCT (the NOR-SWITCH study; [ClinicalTrials.gov identifier: NCT02148640](#)) is also ongoing to evaluate the safety and efficacy of switching from Remicade to CT-P13 compared with continued treatment with Remicade in people with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease and chronic plaque psoriasis.

There are no trials comparing CT-P13 with any other biological medicine other than Remicade.

## Cost and procurement

The cost of Inflectra, Remsima and Remicade may vary locally depending on local drug procurement arrangements.

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<sup>[1]</sup> Park W, Hrycaj P, Slawomir J et al. (2013) [A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study](#). *Annals of the Rheumatic Diseases* 72: 1605–12

<sup>[2]</sup> Yoo DH, Hrycaj P, Miranda et al. (2013) [A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study](#). *Annals of the Rheumatic Diseases* 72: 1613–20

<sup>[3]</sup> Jung YS, Park DI, Kim YH et al. (2015) [Efficacy and safety of CT-P13, a biosimilar of infliximab, in patients with inflammatory bowel disease: a retrospective multicenter study](#). *Journal of Gastroenterology and Hepatology* doi: 10.1111/jgh.12997

<sup>[4]</sup> Kang YS, Moon HH, Lee SE et al (2015) [Clinical experience of the use of CT-P13, a biosimilar to infliximab in patients with inflammatory bowel disease: a case series](#). *Digestive Diseases and Sciences* 60:951–6

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## 9 About this resource

The NICE Adoption and Impact Programme produces practical advice on adopting health technologies in the NHS in England. In this case, these principles have been applied to managing the introduction of biosimilar medicines.

NICE's Adoption and Impact Programme worked with NHS organisations to collect and share their experiences of managing the introduction of biosimilar medicines, in particular biosimilar versions of infliximab, with organisations that may want to use these in the future. The information gained from these NHS organisations and included in this resource is intended for the sole purpose of supporting the NHS in managing the introduction of biosimilar medicines.

This resource was developed using the NICE Adoption and Impact Programme process. It is an implementation tool and discusses and summarises the experiences reported by NHS sites who have previously considered using biosimilar medicines and shares the learning that took place.

Implementation of the use of biosimilar medicines is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement NICE guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this document should be interpreted in a way that would be inconsistent with compliance with those duties.

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