



## Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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### Switching to biosimilar infliximab in people with stable disease

A 52-week, Norwegian, double-blind randomised study (NOR-SWITCH) examined whether switching from originator infliximab to the infliximab biosimilar CT-P13 was safe and effective in 482 people on stable treatment with infliximab originator for a range of diseases. Switching to biosimilar CT-P13 was found to be non-inferior to continuing originator infliximab in terms of disease worsening. The frequency of adverse events was similar between groups. This study is consistent with NICE guidance on infliximab, which allows the use of the biosimilar for the same indication as originator infliximab. The NICE adoption resource on [introducing biosimilar versions of infliximab: Inflectra and Remsima](#) was produced to help manage the introduction of biosimilar medicines into care pathways safely and effectively.

#### Overview and current advice

The NHS England publication, [What is a biosimilar medicine?](#) states that a biosimilar medicine is a biological medicine which is highly similar to another biological medicine already licensed for use. It is a biological medicine which has been shown not to have any clinically meaningful differences from the reference originator biological medicine in terms of quality, safety and efficacy. Biosimilar medicines have the potential to offer the NHS considerable cost savings and widen the access to innovative medicines.

In the development of a biosimilar medicine, there is no requirement to demonstrate clinical benefit to patients per se, as this has been shown for the originator biological medicine. Instead, biosimilars undergo a comprehensive regulatory process which demands extensive comparability studies that demonstrate similarity to the reference biological medicine. 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](#). [NICE's position statement on evaluating biosimilar medicines](#) was published in January 2015.

In the UK, the [MHRA recommends](#) that all biological medicines, including biosimilar medicines, are prescribed by brand name so that products cannot be automatically substituted at the point of dispensing. The choice of whether a patient receives a biosimilar or reference biological medicine rests with the responsible clinician in consultation with the patient.

In September 2013, the EMA authorised a biosimilar version of infliximab (CT-P13) under 2 brand names: [Inflectra](#) and [Remsima](#). The pharmaceutical form, strength, therapeutic indications and dosing regimens of Inflectra and Remsima are the same as those of the reference medicine, [Remicade](#),

Infliximab is currently recommended as an option for people in 7 NICE technology appraisals:

- [Infliximab for acute exacerbations of ulcerative colitis \(TA163\)](#)
- [Infliximab and adalimumab for the treatment of Crohn's disease \(TA187\)](#)
- [Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy \(TA329\)](#)
- [Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor \(TA195\)](#)
- [Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed \(TA375\)](#)
- [Infliximab for the treatment of adults with psoriasis \(TA134\)](#)
- [Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis \(TA199\)](#)

The recommendations in these pieces of guidance also apply to biosimilar products of infliximab that have a marketing authorisation allowing the use of the biosimilar for the same indication.

A NICE key therapeutics topic on [biosimilar medicines](#) summarises the evidence-base for biosimilar medicines. NICE has also published an adoption resource [introducing biosimilar versions of infliximab: Inflectra and Remsima](#) to help manage the introduction of biosimilar medicines into care pathways safely and effectively. See also the NHS publication [Answers to commonly asked questions about biosimilar versions of infliximab](#) for more information.

## New evidence

The [NOR-SWITCH study](#), a 52-week, Norwegian [double-blind](#), non-inferiority trial was the first [randomised](#) study to examine whether switching from originator infliximab to biosimilar infliximab CT-P13 was safe and effective in all 6 indications for which infliximab is currently approved ([Jørgensen et al. 2017](#)). The investigators randomised 482 adults who had been on stable treatment with infliximab originator for at least 6 months for Crohn's disease (32.2%), ulcerative colitis (19.3%), spondyloarthritis (18.9%), rheumatoid arthritis (16.0%), psoriatic arthritis (6.2%), or chronic plaque psoriasis (7.4%). Participants were randomised to either continue originator infliximab (n=241) or a dose-for-dose switch to biosimilar CT-P13 (n=241). One person who was randomised to CT-P13 withdrew consent before treatment and was not included in the analyses. The mean duration of infliximab treatment before randomisation was 6.8 years and the mean age of participants was 48 years, 39% of whom were female.

The primary [outcome](#) was disease worsening during the 52-week follow-up, measured using disease-specific composite measures or a consensus about disease worsening between the investigator and patient leading to a major change in treatment. A non-inferiority limit of 15% was set (assuming a 30% disease worsening in each group).

At 52-weeks, disease worsening occurred in 53/202 (26%) of people in the originator infliximab group and 61/206 (30%) of people in the biosimilar CT-P13 group ([per-protocol](#) set, adjusted treatment difference -4.4%, 95% [confidence interval](#) [CI] -12.7 to 3.9). Since the 95% CIs were within the pre-defined limit of 15%, non-inferiority of biosimilar CT-P13 to originator infliximab was demonstrated. There was no statistically significant difference in remission rates, which occurred in approximately 61% of each group (secondary outcome). Changes in patient-reported outcomes, time to disease worsening, treatment discontinuations, disease state at baseline and changes in disease-specific composite measures were generally similar in both infliximab groups (in the per-protocol set and in the full analysis set). However, [statistically significant](#) differences in favour of biosimilar CT-P13 for two of

the endpoints (the Modified Health Assessment Questionnaire and SF-36 physical component summary score) were seen in the per-protocol set.

A similar frequency of adverse effects was also seen between the originator infliximab and biosimilar CT-P13 groups. Treatment-emergent adverse events were reported in 70% of people in the originator infliximab group and in 68% of the biosimilar CT-P13 group, serious adverse events in 10% and 9%, and adverse events leading to discontinuation in 4% and 3%, respectively. The incidence of anti-drug antibodies detected during the study (excluding people who had detectable antibodies at baseline) was similar across both treatment groups (7% for originator infliximab and 8% for biosimilar CT-P13 in the full analysis set).

## Commentary

### Commentary provided by NICE

Biosimilar medicines have the potential to offer the NHS considerable cost savings and widen the access to innovative medicines. This Norwegian study (NOR-SWITCH) shows that switching people with stable disease on originator infliximab to biosimilar CT-P13 is non-inferior to continuing originator infliximab in terms of disease worsening and does not seem to be associated with any adverse outcomes in a range of licensed conditions.

This is the first randomised controlled trial (RCT) designed to assess the efficacy and safety of switching people with stable disease from originator infliximab to biosimilar CT-P13. Previous studies that compared the 2 forms of infliximab have been conducted in people with ankylosing spondylitis ([PLANETAS](#)) or rheumatoid arthritis ([PLANETRA](#)) who have not previously received TNF inhibitors. The authors of the [NOR-SWITCH study](#) note that the extrapolation of indication has been debated in clinical communities, especially gastroenterology, because the mechanisms of action for infliximab might differ between indications. A previous NICE [Medicines Evidence Commentary](#) discusses a study that found a managed programme (at Southampton General Hospital) of switching all people with inflammatory bowel disease from originator infliximab (Remicade) to biosimilar infliximab (Inflectra) was highly acceptable to patients, clinicians, commissioners and other stakeholders. The NOR-SWITCH study is important because it is the first randomised study to investigate switching stable people in all 6 relevant disease groups (Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis and chronic plaque psoriasis).

A limitation of [NOR-SWITCH](#) is that it was not powered to demonstrate non-inferiority for each of the diagnoses separately. Results for disease worsening across the different diagnoses were heterogeneous. In addition, the study was not completely blinded because local personnel had to prepare the infusions. Also, the authors were unable to rule out whether people with stable disease and low disease burden were over-represented in the study cohort. In addition, the study would have been underpowered if a more stringent non-inferiority margin had been selected ([Jørgensen et al. 2017](#)).

This study is consistent with NICE guidance on infliximab, which allows the use of the biosimilar for the same indication as originator infliximab. The NHS England [Medicines Optimisation Dashboard](#) indicates that, in April 2017 (the most recent data available), use of biosimilar infliximab by hospital Trusts as a proportion of all infliximab varied considerably across England, although this has increased in the last year. Median use of biosimilar infliximab as a proportion of all infliximab was about 86% (interquartile range 72% to 94%). Biosimilar use was more than 95% in 21 hospital Trusts but 2 Trusts for which data were available used only originator infliximab.

The NICE adoption resource on [introducing biosimilar versions of infliximab: Inflectra and Remsima](#), was produced to help manage the introduction of biosimilar medicines into care pathways safely and

effectively. NHS organisations shared their learning and experiences of introducing biosimilar medicines and these are 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. See also the NICE key therapeutics topic on [biosimilar medicines](#) that summarises the evidence-base for biosimilar medicines.

## Study sponsorship

This study was funded by the Norwegian Ministry of Health and Care Services.

## References

Jørgensen K, Olsen I, Goll G et al. (2017) [Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab \(NOR-SWITCH\): a 52-week, randomised, double-blind, non-inferiority trial](#). Lancet 389: 2304–16 (see [correction](#))

### About this Medicines Evidence Commentary

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