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Answers to commonly asked questions about biosimilar versions of etanercept

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The first biosimilar version of etanercept (Benepali®) was approved for use in Europe in November 2015 and is due to be launched in the UK in February 2016. It is licensed for use in adults with rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis and plaque psoriasis. This briefing sheet is intended to support prescribers by providing answers to commonly asked questions about the introduction of this medicine.

What is a biosimilar medicine?

A biosimilar medicine is a biological medicine that is highly similar to a medicine that has already been authorised to be marketed in the EU (the biological reference medicine) with respect to quality, safety and efficacy. Information on biosimilar medicines and the background to their licensing and clinical use are discussed in an open access article from the Drug & Therapeutics Bulletin entitled; "What are biosimilars and are they important?" (1).

A comprehensive guide to biosimilars is also available from NHS England; this is intended to provide an update for stakeholders about their developing role in the NHS and can be used locally to inform finance and procurement discussions (2).

What brands of biosimilar etanercept will be available for use?

A biosimilar version of etanercept (Benepali®; Biogen) is licensed in the UK and will be launched in February (3,4). Benepali® is presented in single-use pre-filled syringes and pre-filled pens, in each case containing 50 mg etanercept per mL to be administered by subcutaneous (SC) injection.(4,5).

Are there any differences in the licensed indications and doses between biosimilar etanercept and the reference product?

In common with Enbrel®, Benepali® is licensed for the treatment of rheumatoid arthritis in adults, psoriatic arthritis in adults, axial spondyloarthritis in adults and plaque psoriasis in adults (5, 6). However unlike Enbrel®, Benepali® is not licensed for use in Juvenile Idiopathic Arthritis or in paediatric plaque psoriasis as it is only currently available as a 50mg presentation (5)

Also Benepali® is only licensed to be given as a 50mg once weekly dose whereas Enbrel® is also licensed to be given at a dose of 25mg twice weekly in adults (5,6).

How should etanercept be prescribed?

The Medicines and Healthcare Products Regulatory Agency (MHRA) recommends that it is good practice to prescribe biological products by brand name to ensure that substitution of a biosimilar product does not occur when the medicine is dispensed by the pharmacist (7).

The use of brand names in all stages of the medicines supply chain for etanercept will be essential to allow differentiation between the two forms, which is vital for post-launch pharmacovigilance and to ensure patient safety (avoidance of inadvertent switching).

Pharmacists should challenge any prescriptions for etanercept that refer to its generic rather than trade name, to ensure that the product dispensed is the correct one intended for the patient.

Are there any differences in administration devices for the available brands of etanercept?

Like Enbrel®, Benepali® is available as a 50mg in 1ml solution for injection in a pre-filled syringe (clear glass with stainless steel needle, rubber needle cover and plastic plunger) and as a pre-filled pen containing a pre-filled syringe as described above. The administration devices differ in that the pen used to administer Benepali® is an auto-injector and the needle sheath is latex free.(3).

In both cases the medicine must be stored in the refrigerator and warmed up to room temperature before administration.

The manufacturer of Benepali® will provide educational material for healthcare professionals and patients including needle-free demonstration devices to facilitate training of patients in the safe use of the pre-filled syringe and device.(3)

UKMI has published an in-use risk assessment which advises on strategies to minimise the risks associated with the introduction of Benepali® to the market (8).

What objections are being raised about using biosimilar versions of etanercept?

No specific concerns related to the introduction of a biosimilar version of etanercept were identified from a search of the literature.

Previous concerns voiced by clinicians about biosimilars in general relate to theoretical concerns about their pharmaceutical quality, safety, and their interchangeability with the reference product. They also include doubts about clinical efficacy and safety in extrapolated indications for which no formal clinical studies have been performed with the biosimilar (9).

What evidence is required for the approval of biosimilars in the EU?

The regulatory requirements for the approval of a biosimilar are considerably greater than those for a generic drug. For the latter, it is usually sufficient to demonstrate pharmaceutical equivalence (identical amounts of the same active ingredient in the same dose form) and bioequivalence to the reference medicine. However for a biosimilar, a much more comprehensive analysis is required, due to the complexity of these products and their manufacturing processes (2).

A legal pathway for the development of biosimilars (the ‘biosimilar pathway’) was established in the EU in 2005 and several biosimilars (e.g. somatropins; filgrastims; epoetins) have been licensed since this time (1). The guiding principle of the development of biosimilars is not to establish patient benefit per se (which has already been shown for the reference product), but to demonstrate high similarity to the reference product so that the experience gained with its use can be extrapolated to the biosimilar version (1).

The biosimilar development pathway involves an extensive comparability exercise, which is a head-to-head comparison of the biosimilar with the reference product in order to ensure a close resemblance in terms of physical chemistry, biological characteristics, safety and efficacy (1, 10). It is not expected that the biosimilar will be identical to the reference drug; the purpose of the comparability exercise is to show that the degree of variability is not significant. The development pathway follows a stepwise approach, with demonstration of: (10,11,12)

- Quality comparability (with regard to the molecular structure and functionality)
- Non-clinical comparability (comparative non-clinical studies)
- Clinical comparability (comparative clinical studies)

The extent of the non-clinical and clinical studies required to confirm biosimilarity will depend on the nature and the complexity of the reference product (10,11,12). The purpose of clinical data is to provide complementary information; for example the clinical relevance of any observed differences, and data on immunogenicity.

What evidence exists to support the use of a biosimilar version of etanercept?

A comprehensive comparability exercise was performed for the biosimilar with the reference product (Enbrel®). The initial stage consisted of numerous physiochemical tests and studies comparing biological activity, and the biosimilar was deemed to be comparable to the reference product from a quality perspective (12).

The non-clinical exercise consisted of studies evaluating their similarity in terms of pharmacology, pharmacokinetics and toxicology and again Benepali® was considered to be comparable to the reference product (12).

In addition to the overarching biosimilars guideline, the EMA has also produced a number of class-specific guidelines, including one on the development of monoclonal antibodies (10). This states that the most sensitive model and study conditions (pharmacodynamic or clinical) should be used in a homogeneous patient population. In cases where comparative pharmacodynamic studies are claimed to be most suitable to provide the pivotal evidence for similar efficacy, applicants will have to choose clinically relevant markers, justify these markers, and also provide sufficient reassurance of clinical safety, particularly immunogenicity. To demonstrate similarity between Benepali® and Enbrel® the manufacturers chose to demonstrate equivalence in a population of patients with moderate to severe RA using the ACR-20 response as a marker of disease response and this was accepted as valid by the EMA (13).

An equivalence study was conducted in which 596 patients with moderate-severe RA despite taking methotrexate were randomised to receive either Enbrel® (n=-297) or Benepali® n=299) (13). Equivalence was defined as being no more than a 15% difference in response rate within the lower and upper limits of the 95% confidence interval in favour of either drug – this figure was chosen as it represents half the estimated minimum response rate of etanercept compared with placebo.. After 6 months it was shown that 78.1% of patients that received Benepali® achieved an ACR20 response compared with 80.3% in the Enbrel® group. This equates to a 2.2% absolute difference in response rates with a confidence interval extending from 9.4% in favour of Enbrel® to 5.0% in favour of Benepali® As both figures are less than 15% this was accepted by the EMA as providing sufficient evidence that Benepali® is neither significantly better than, or inferior to Enbrel®.

The 12 month results of this study have been presented at conference and it was reported that in the 505 per-protocol patients that completed 52 weeks treatment the ACR20 response rate at Week 52 was 80.8% in the Benepali® group vs. 81.5% Enbrel® Group demonstrating that the response rates are also sustained to a similar degree in both groups (14). It was also reported that the safety profile in both groups was generally comparable

with 58.5% and 60.3% of patients randomised to Benepali® and Enbrel® respectively reporting at least one treatment emergent adverse event with 6% vs. 5.1% respectively classified as serious. However it is noted that Benepali® was associated with less injection reactions (3.7% vs. 17.5%) and lower levels of emerging antidrug antibody (1% vs. 13.2%).

Therefore there is evidence to demonstrate that Benepali® is similarly effective to, and as well tolerated as, Enbrel®. At the time of writing that evidence remains unpublished and is only available in regulatory documents and as conference abstracts

What is the evidence that a 50mg weekly regimen is as effective as a 25mg twice weekly regimen.

When Enbrel® was originally licensed the pivotal trials used a 25mg twice weekly regimen to demonstrate safety and efficacy and this was reflected in the license when first launched. However a number of studies have subsequently been published showing that a 50mg once weekly regimen is similarly effective to a 25mg twice weekly regimen in rheumatoid arthritis, ankylosing spondylitis and psoriasis (15,16,17). Enbrel® is now licensed to be used at either a 25mg twice weekly or 50mg once weekly regimen.

It is thought that there is currently between two and three times more 50mg etanercept prescribed than 25mg i.e. the 50mg presentations account for between 60 and 75% of the total etanercept market.(personal communication)

Why does the EMA feel it is justified to extrapolate the evidence for Benepali® derived from use in RA patients to also license for use in psoriatic arthritis, axial spondyloarthritis adults and plaque psoriasis

Extrapolation is the regulatory and scientific process of granting a clinical indication to a medicine without its own clinical efficacy and safety data to support that indication (1,2). This is an already established scientific and regulatory principle that has been exercised for many years; it has however recently become the focus of heightened interest following the introduction of biosimilars.

If biosimilarity has been demonstrated in one indication, the EMA considers that extrapolation of efficacy and safety data to all other indications of the reference product may be acceptable with appropriate scientific justifications (10,11,12). Although concerns have been expressed about this, the Working Party on Similar Biologic Medicinal Products of the EMA stress that extrapolation will only be approved on the basis of sound scientific justification, and only when the following requirements have been fulfilled (11):

- Similarity with the reference product must be convincingly demonstrated based on the totality of evidence from the comparability exercise
- If the mechanism of action involved in the extrapolated indication(s) is different or unknown, additional convincing data must be available for further reassurance that the biosimilar and the reference product
- The safety profile of the biosimilar must have been properly characterised and unacceptable immunogenicity excluded

In this case the EMA state that it is well established that an uncontrolled inflammatory process is common to all therapeutic indications of Enbrel and that these indications share a common mechanism of action, i.e. the competitive inhibition of TNF-α binding and blockade of the ensuing inflammatory processes (12). Therefore, and in line with the EMA guidelines on the similar biological medicinal products, the efficacy results obtained with Benepali®, demonstrating equivalence of Benepali® and Enbrel® in RA patients can be reasonably extrapolated to the other approved therapeutic indications of Enbrel®.

If the clinical studies were conducted in adults, what evidence is there to support use of the biosimilar in children?

Unlike Enbrel®, Benepali® is **not** licensed for use in children because the manufacturer is not launching a 25mg presentation of etanercept. As a condition of licensing the manufacturer is obliged to produce a patient alert card highlighting that the product is not to be used in children (4).

Will there be any independent guidance available to help inform clinical practice?

NICE has recently clarified its position with regards to the evaluation of biosimilars. These products will usually be considered in the context of a Multiple Technology Appraisal in parallel with their reference products in the indication under consideration. In other circumstances, where it is considered a review of the evidence for a similar biological medicinal product is necessary, NICE will consider producing an 'Evidence summary new medicine'. Evidence summaries do not make recommendations hence the decision regarding the choice of biosimilar or originator biologic for an individual patient rests with the responsible clinician in consultation with the patient (17).

NICE has not yet specifically addressed the role of Benepali® in any of its Technology Appraisals or Clinical Guidelines and it was not specifically taken into consideration as part of the recently issued guidance on the role of TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (18).

In the NHS England document entitled "What is a biosimilar medicine", it is stated that, "where NICE has already recommended the originator biological medicine the same guidance will normally apply to a biosimilar of the originator" (2) Although it is also stated that, "The decision to prescribe a biological medicine for an individual patient, whether an originator or biosimilar medicine, rests with the responsible clinician in consultation with the patient" and that "at the time of dispensing a biosimilar medicine should not automatically be substituted for the originator by the pharmacist".

The British Society for Rheumatology issued a position statement on biosimilars in February 2015 (19). The statement consists of 9 recommendations and is supportive of biosimilars being used in treatment naïve patients but state that until further data are available to support safe switching, strong safeguards are required to ensure that patients who have responded well to existing medicine are not switched for non-clinical reasons. This statement is now over 12 months old and was written when biosimilar versions of infliximab were just coming to market and there was very little clinical experience to draw upon. It is unclear if the Society intends to update it in light of the clinical experience gained over the last 12 months. The British Society of Gastroenterology has recently revised their guidance on the use of biosimilar infliximab and now state that switching patients to the biosimilar version may be appropriate to reduce costs to the overall service (20)

The British Association of Dermatologists has also issued a position statement (undated) which provides recommendations on the use of biosimilars (21). They state that, "patients who are responding to a particular product (reference or biosimilar) should not be switched to an alternative".

All three Associations state that all patients started on, or switched to a biosimilar medicine should be registered with the appropriate disease register so that data can be routinely captured that will ultimately enable patients and clinicians to make informed choices about these medicines. (19,20,21)

Are there any potential advantages to using a biosimilar version of etanercept?

As biosimilars will likely be available at lower costs than the originator, they have the potential to reduce treatment costs, expand market competition and increase patient accessibility. The cost savings of developing biosimilars compared with their originators is not likely to be as large as those that are achieved by generic drugs compared with their originator products. Nevertheless, the chronic nature of their use in many people can lead to significant absolute cost savings. This will of course be contingent upon their acceptance in the marketplace (1,2).

NHS England state that they support the appropriate use of biosimilars which will drive greater competition to release cost efficiencies to support the treatment of an increasing number of patients and the uptake of new and innovative medicines (2)

It is not yet clear what the list price of Benepali® will be but based on current expenditure on Enbrel® it is estimated that a 70% switch to a biosimilar version marketed at 70% of the price of Enbrel® would reduce overall expenditure on this medicine by over £43m in England which equates to about £87,000 per 100,000 population.

Will the biosimilar version of etanercept be available via homecare delivery schemes?

Yes the manufacturer of Benepali® has arranged for supplies to be made available through the same Homecare delivery companies that provide Enbrel® . So for those patients that receive their etanercept supplies in this way this aspect of service delivery is not affected.

What safeguards will be in place to ensure that post-marketing safety is being monitored?

Every biosimilar medicine authorised in the EU will have a risk management plan (RMP) in place and information on this is included in the European Public Assessment Report. Based on similarity being demonstrated with the reference product, the biosimilar can also refer to the safety experience gained with the reference product (12).

The EMA has requested that the manufacturer of Benepali® submits its first periodic update safety report within 6 months of marketing authorisation (4). The EMA has also noted that the non-inferiority study discussed above will be continued for another 48 weeks and patients originally randomised to receive Enbrel® will be switched to Benepali® and continue to be monitored in terms of safety (including serious and/or opportunistic infections, cancers, heart failure, and injection-site reactions). Also clinicians will be encouraged to register patients treated with Benepali® on the British Society for Rheumatology Biologics Register-rheumatoid arthritis (BSRBR-RA) so that long-term safety can be monitored. An interim report from this register is expected in late 2016. Similarly dermatologists will be encouraged to register patients with the British Association of Dermatologists Biologic Interventions Register (BADBIR) and again an interim report is expected in late 2016.

Also as a condition of marketing the manufacturers of Benepali® must provide educational materials to all healthcare professionals involved in the prescription of the product which includes:

- A teaching guide to facilitate training of the patients in the safe use of the pre-filled pen/prefilled syringes•
- A needle-free demonstration device•
- Material to remind healthcare professionals that Benepali® is not for paediatric use•
- Instructional materials to share with patients

Also the manufacturers of Benepali® must provide a Patient Alert card which highlights the following for patients

- The risk of opportunistic infections and tuberculosis (TB)
- The risk of Congestive Heart Failure (CHF).
- That Benepali® is not for use in children

What other biosimilar medicines are expected over the next few years?

Biosimilar versions of the following medicines are currently in development and are expected to be available in the UK over the next few years: trastuzumab (Herceptin®); rituximab (MabThera®); adalimumab (Humira®); bevacizumab (Avastin®) and pegfilgrastim (Neulasta®)

What information is available for patients?

Benepali® – an EPAR summary for the public
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/004007/WC500200381.pdf

Patient Information Leaflet- Benepali® 50mg solution in a pre-filled pen
http://www.medicines.org.uk/emc/medicine/31505

Patient Information Leaflet- Benepali® 50mg solution in a pre-filled syringe
http://www.medicines.org.uk/emc/medicine/31506

A Q&A on biosimilar medicines is available from the EMA
http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf

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