Etanercept Biosimilar
(Benepali®)

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Summary

- Etanercept (Enbrel®) is a recombinant tumour necrosis factor (TNF) antagonist used in the treatment of several inflammatory autoimmune diseases. In February 2016, a biosimilar formulation of etanercept was launched in the UK under the brand name of Benepali®. Benepali is only licensed to be given as a 50 mg once-weekly dose, and therefore is not licensed for the paediatric indications of Enbrel (paediatric plaque psoriasis, juvenile idiopathic arthritis).

- In extensive product characterisation exercises all major physicochemical characteristics and biological activities of Benepali were shown to be comparable to those of the reference product Enbrel.

- In a Phase III, randomised, double-blind, study in 596 subjects with moderate to severe RA despite methotrexate therapy, the efficacy of Benepali was shown to be comparable to that of Enbrel in the primary outcome of ACR20 response at week 24. As the 95% CIs for the difference in ACR20 were contained within the predefined equivalence margin of ±15% the results are sufficient to demonstrate equivalent efficacy. The secondary efficacy outcomes at week 24 support the primary findings, and response rates were sustained to a similar degree in both treatment groups up to week 52.

- Overall, the type and incidence of treatment-emergent adverse events (TEAEs) observed in the pivotal study were similar between the two treatment groups and were in line with the well-characterised safety profile of Enbrel as outlined in the SPC. The majority of TEAEs were of mild to moderate severity, and no significant new safety signals were reported. There were no marked differences in the immunogenicity profile and the impact of auto-antibodies on efficacy and safety was comparable between treatment arms.

- Although clinical studies were only performed in patients with RA, efficacy and safety for other indications is assumed from the demonstration of equivalence to the reference product in accordance with regulatory procedures. Based on the totality of evidence, the EMA concluded that similarity has been convincingly demonstrated enabling extrapolation of Benepali approval to all other indications for which the reference product Enbrel® is approved, except the aforementioned paediatric indications.

- On 1st April 2016, a new CMU contract which will include the TNF inhibitors is due to start. The NHS list price of Benepali is £656 for 4 x 50 mg, which represents a discount of around 10% on the current list price of Enbrel.

- It is estimated that the 50mg presentations account for between 60 and 75% of the total current etanercept market. Based on a conservative estimate of a 70% switch to Benepali
Introduction and background

Etanercept is a recombinant human tumour necrosis factor (TNF) receptor fused to the Fc fragment of IgG1. TNF is a pro-inflammatory cytokine that plays an integral role in many inflammatory autoimmune diseases. Etanercept competitively inhibits the binding of TNF to cell surface receptors and thus renders TNF biologically inactive. It was first authorised in the EU in 2000 under the brand name of Enbrel® (Pfizer)¹ and is approved for the following indications:

- Rheumatoid arthritis
- Psoriatic arthritis
- Axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis)
- Plaque psoriasis (adults and paediatric)
- Juvenile idiopathic arthritis

The patent on Enbrel expired in Europe in August 2015, which has enabled manufacturers to produce biosimilar versions of the original drug. A biosimilar is a biological medicine that is developed to be highly similar to an existing licensed biological medicine (the ‘reference medicine’) in terms of quality characteristics, biological activity, safety, and efficacy. Biosimilars are not the same as generic medicines, which have simpler chemical structures and are considered to be identical to their reference medicines.²⁻⁴

Biosimilars are typically large, complex molecules manufactured using living organisms. Although the active substance of a biosimilar and its reference medicine are essentially the same biological substance, the characteristics of biologic drugs cannot be reproduced exactly due to their complex nature and production methods. Like the reference medicine, the biosimilar will have a degree of natural variability, and minor quality differences are expected to be observed between a biosimilar and its reference product. To gain approval in the EU, such variability and any differences between the biosimilar and its reference medicine must have been shown not to affect safety or effectiveness.²⁻⁴

In January 2016, the European Medicines Agency (EMA) approved a biosimilar formulation of etanercept manufactured by Biogen. The drug marketed under the brand name Benepali® was launched in the UK in February 2016. The marketing authorisation for Benepali only applies to the 50 mg etanercept dose, and therefore does not include the approved paediatric indications of Enbrel (paediatric plaque psoriasis, juvenile idiopathic arthritis).⁵

A second etanercept biosimilar currently known only as ‘GP2015’ was filed in the EU by Sandoz in December 2015 for all indications included in the Enbrel label. The results of the pivotal EGALITY study are expected to be published at EULAR in June 2016. Licensing is anticipated in Q1 2017, subject to regulatory approval. It is anticipated that the UK will be one of the first countries to launch.⁶

This document will review the comparability, efficacy, safety and cost of Benepali® with respect to the reference product Enbrel®.
Guidance and related advice

The National Institute for Health and Care Excellence (NICE) has updated its position and process for providing guidance and advice on biosimilar medicines within the NHS. These products will usually be considered in the context of a Multiple Technology Appraisal (MTA) in parallel with their reference products in the indication under consideration. NICE technology appraisals will use the name of the active drug substance, including reference products and brand named similar biological medicinal products in its documentation. In other circumstances, where it is considered a review of the evidence for similar biological medicinal product is necessary, NICE will consider producing an ‘Evidence summary new medicine’. Evidence summaries will use the brand names of the medicines because substitutability and interchangeability cannot be assumed. 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.4,7

NICE has not yet specifically addressed the role of Benepali in any of its Technology Appraisals or Clinical Guidelines. Benepali was not specifically taken into consideration as part of the recently issued guidance on TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (TA383, February 2016).8 However, the guidance recommends that the choice of treatment should be made after discussion between the clinician and the patient about the advantages and disadvantages of the treatments available. If more than one treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen. The recent NICE guidance on severe rheumatoid arthritis (TA375, January 2016), also recommends that patients should be started on the most cost-effective treatment option.9

NHS England has stated that “where NICE has already recommended the originator biological medicine, the same guidance will normally apply to a biosimilar of the originator”.2 However, it also states that “automatic substitution is not appropriate for biosimilar medicines and is not permitted at this time” and that “prescribers, of course, are always able to switch treatments for a given patient, provided it is safe to do so”. “Switching between a reference product and its biosimilar should be managed at the discretion of the individual prescriber in partnership with the patient, with appropriate monitoring in place”.2

The British Society for Rheumatology (BSR) issued a position statement on biosimilar medicines in February 2015.10 Although the BSR broadly supports the use of biosimilars in clinical rheumatology, it sets out some of the concerns on the use of biosimilars, and outlines measures on how to address these. It recommends that all biologics and biosimilars should be prescribed by brand name rather than by International Non-proprietary Name (INN); prescribing should be based on clinical reasons, and decisions made in partnership with the patients; substitution should only be with the consent of the prescribing clinician; all patients starting or switching to biosimilars should be registered with the BSR Biologic Register; raising awareness of biosimilars in patients and healthcare professionals; biosimilars should undergo robust technology appraisals; better information sharing across the care pathways; and that local tenders involving biosimilars seek to source a range of products.
The British Association of Dermatologists has issued a position statement on biosimilars.\textsuperscript{11} They state that, “patients who are responding to a particular product (reference or biosimilar) should not be switched to an alternative”.

**Non-clinical evidence**

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 EU regulatory process demands an extensive comparability exercise is performed through a stepwise process that begins with structural, physicochemical and biological analysis, non-clinical, then pharmacokinetic and pharmacodynamic studies, followed by clinical safety and efficacy trials.\textsuperscript{4,7,12}

In line with current European guidance on development of biosimilars, Biogen performed a comprehensive non-clinical comparability exercise testing the pharmacodynamic, pharmacokinetic and toxicological properties of Benepali in comparison with reference product Enbrel.\textsuperscript{13} The data demonstrated that all major physicochemical characteristics and biological activities of Benepali are comparable to those of Enbrel\textsuperscript{\textregistered}, except for some minor differences in Fc-related binding affinities, and antibody dependent cell-mediated cytotoxicity activity. However, these are not expected to translate into clinically relevant differences.

**Clinical evidence**

The clinical program demonstrating biosimilarity between Benepali and the reference product Enbrel consisted of a phase III efficacy and safety study in patients with active rheumatoid arthritis (SB4-G31-RA, NCT01895309), and a phase I pharmacokinetic study in healthy volunteers (SB4-G11-NHV, NCT01865552).

**Study SB4-G31-RA**\textsuperscript{13,14}

This Phase III, randomised, double-blind, parallel group, multicenter, study was designed to evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of Benepali compared to Enbrel in subjects with moderate to severe RA despite methotrexate (MTX) therapy.

The 52-week study recruited 596 male or female subjects aged 18 to 75 years who had been diagnosed as having RA according to American College of Rheumatology (ACR) criteria for ≥6 months, despite receiving MTX therapy for ≥6 months prior to randomisation. Participants were required to have moderate to severe active disease defined as ≥6 swollen and ≥6 tender joints, and either an ESR ≥28 mm/h or CRP ≥1.0 mg/dl. Non-steroidal anti-inflammatory drugs and oral glucocorticoids (equivalent to ≤10 mg prednisolone) and were permitted if received at a stable dose for ≥4 weeks prior to randomisation. Those previously treated with any biological including any TNF-α inhibitor were excluded.
Patients were randomised in a 1:1 ratio to receive either Benepali 50 mg (N=249) or Enbrel 50 mg (n=249) once-weekly for 52 weeks via self-administered subcutaneous injection. All patients had to take MTX (10-25 mg/week) and folic acid (5-10 mg/week) during the study. The primary endpoint was the proportion of patients achieving a clinical response according to ACR definition of a 20% improvement (ACR20) at week 24. Secondary endpoints included ACR50 and ACR70 at week 24, ACR20, ACR50 and ACR70 at week 52, mean change in Disease Activity Score based on a 28 joint count (DAS28) and European League Against Rheumatism (EULAR) response, both at weeks 24 and 52. Immunogenicity was measured in all patients, and PK analyses were performed on a subset of patients from pre-designated study sites.

The primary efficacy analysis for ACR20 response at week 24 was performed on the per-protocol set (PPS) which consisted of all subjects who completed the 24 week visit, received 80-120% of both the expected number of Benepali injections and expected sum of MTX doses, without major protocol deviations that affected the efficacy assessment. To declare equivalence between the two treatment groups, the 95% confidence interval (95% CI) for treatment difference had to be entirely contained within the predefined equivalence margin of ±15%. To explore the robustness of the results a sensitivity analysis was performed on the full analysis set (FAS) which included all patients who were randomised following the intention-to-treat (ITT) principle. This study is still ongoing, data up to 24 weeks has been fully published, and data up to 52 weeks have been reported in the European Public Assessment Report (EPAR) and in abstract form.

A total of 551 patients completed 24 weeks of treatment and 481 (80.7%) were included in the PPS analyses. The demographics and baseline characteristics were comparable between treatment groups. The data demonstrated comparable efficacy of Benepali and the originator product Enbrel in terms of the proportion of ACR20 responders at week 24. The 95% CIs for the difference in ACR20 response were completely contained within the predefined equivalence margins ±15% in both the PPS and FAS, providing robust evidence of equivalence (Table 1). The ACR20 time response curves of Benepali and Enbrel up to week 24 were estimated to be equivalent supporting the robustness of the primary efficacy analysis. The secondary efficacy endpoints in both the PPS and FAS also support the primary outcome, with the results being similar between treatment groups for all outcomes. Subgroup analyses of the primary outcome showed comparable results regardless of anti-drug antibody (ADA) status. Among subjects who tested negative for ADA an ACR20 response was achieved in 78.0% and 81.5% in the Benepali and Enbrel groups, respectively (treatment difference -3.57%; 95% CI -11.12%, 3.99%). The corresponding ACR20 response among subjects with a positive ADA result were 100% and 72.4%, respectively (22.14%; 95% CI -54.79%, 99.07%).

The 52-week results showed that after week-24, the ACR20 had effectively reached a plateau whereas there were further improvements in the higher response thresholds (ACR50 and ACR70), and DAS28 in both treatment groups (Table 2). The 95% CIs for the difference in ACR20/50/70 response rates were, with the exception of ACR70 (only in the in the PPS set), contained completely within the predefined equivalence margins ±15% for both analysis sets after 52 weeks.
Table 1. Summary of primary and secondary efficacy at week 24.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Benepali</th>
<th>Enbrel</th>
<th>Treatment difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 *</td>
<td>78.1%</td>
<td>80.3%</td>
<td>-2.22%</td>
<td>-9.41%, 4.98%</td>
</tr>
<tr>
<td>ACR50</td>
<td>46.6%</td>
<td>42.3%</td>
<td>4.79%</td>
<td>-3.92%, 13.49%</td>
</tr>
<tr>
<td>ACR70</td>
<td>25.5%</td>
<td>22.6%</td>
<td>3.02%</td>
<td>-4.47%, 10.51%</td>
</tr>
</tbody>
</table>

Full analysis set

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Benepali</th>
<th>Enbrel</th>
<th>Treatment difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>73.8%</td>
<td>71.7%</td>
<td>1.92%</td>
<td>-5.24%, 9.07%</td>
</tr>
<tr>
<td>ACR50</td>
<td>43.0%</td>
<td>39.1%</td>
<td>4.02%</td>
<td>-3.74%, 11.78%</td>
</tr>
<tr>
<td>ACR70</td>
<td>23.2%</td>
<td>19.9%</td>
<td>3.35%</td>
<td>-3.10%, 9.81%</td>
</tr>
<tr>
<td>DAS28</td>
<td>2.57</td>
<td>2.50</td>
<td>0.7</td>
<td>-0.14, 0.28</td>
</tr>
<tr>
<td>EULAR</td>
<td>Good</td>
<td>55.1%</td>
<td>-3.4</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>32.1%</td>
<td>2.3</td>
<td>-</td>
</tr>
</tbody>
</table>

* Primary endpoint

Table 2. Summary of primary and secondary efficacy at week 52.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Benepali</th>
<th>Enbrel</th>
<th>Treatment difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>80.8%</td>
<td>81.5%</td>
<td>0.7%</td>
<td>-</td>
</tr>
<tr>
<td>ACR50</td>
<td>58.8%</td>
<td>53.2%</td>
<td>4.50%</td>
<td>-4.67%, 13.67%</td>
</tr>
<tr>
<td>ACR70</td>
<td>37.5%</td>
<td>31.0%</td>
<td>7.02%</td>
<td>-1.69%, 15.74%</td>
</tr>
</tbody>
</table>

Full analysis set

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Benepali</th>
<th>Enbrel</th>
<th>Treatment difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>70.2%</td>
<td>65.7%</td>
<td>4.48%</td>
<td>-2.90%, 11.87%</td>
</tr>
<tr>
<td>ACR50</td>
<td>47.8%</td>
<td>42.1%</td>
<td>5.48%</td>
<td>-2.32%, 13.29%</td>
</tr>
<tr>
<td>ACR70</td>
<td>30.4%</td>
<td>24.6%</td>
<td>5.90%</td>
<td>-1.12%, 12.93%</td>
</tr>
<tr>
<td>DAS28</td>
<td>2.91</td>
<td>2.80</td>
<td>0.1</td>
<td>-</td>
</tr>
</tbody>
</table>

The PK characteristics of Benepali and Enbrel were comparable in a subset of 79 subjects in study SB4-G31-RA (41 receiving Benepali and 38 Enbrel). The trough concentrations from week 0 to week 24, and the steady-state PK parameters at week 8 were comparable at each time-point.

Study SB4-G11-NHV 13,15

This was a randomised, single-blind, three-part, two-period, two-sequence, single-dose crossover study designed to compare the PK profile, safety, tolerability and immunogenicity of Benepali and Enbrel (EU and US sourced) in 138 healthy male subjects.

In each part, 46 subjects were randomised in a 1:1 manner to receive a single 50 mg subcutaneous dose of Benepali or Enbrel (Part A: Benepali or EU-Enbrel, Part B: Benepali or US-Enbrel, Part C: EU-Enbrel or US-Enbrel) in Period 1 followed by the
cross-over treatment in Period 2. Study treatments were separated by a 28 day washout period. PK assessment was performed 21 days after the treatment in each period. Immunogenicity was assessed at pre-dose and 28 days after the first treatment in Period 1. The primary PK parameters were area under the concentration-time curve from time zero to infinity ($\text{AUC}_{\text{inf}}$) and maximum concentration ($\text{C}_{\text{max}}$).

In part A of the study, in which Benepali was compared to EU-sourced Enbrel the primary PK endpoints ($\text{AUC}_{\text{inf}}$ and $\text{C}_{\text{max}}$) were well within the pre-defined equivalence margin of 80-125%, therefore Benepali was shown to be bioequivalent to Enbrel (Table 3). In addition, all secondary PK parameters were shown to be comparable between treatments.

### Table 3. Primary PK parameters Benepali vs. EU-sourced Enbrel

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistics</th>
<th>Benepali (n=45)</th>
<th>EU-Enbrel (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{\text{inf}}$ ($\mu$g·h/mL)</td>
<td>Mean</td>
<td>769.069</td>
<td>771.680</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>243.9039</td>
<td>226.2874</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>772.425</td>
<td>790.480</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>331.650</td>
<td>339.815</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>1278.994</td>
<td>1167.015</td>
</tr>
<tr>
<td></td>
<td>Ratio (90% CI)</td>
<td>0.990 (0.947; 1.036)</td>
<td></td>
</tr>
<tr>
<td>$\text{C}_{\text{max}}$ ($\mu$g/mL)</td>
<td>Mean</td>
<td>728.169</td>
<td>734.015</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>234.7621</td>
<td>220.2722</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>723.986</td>
<td>743.629</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>306.598</td>
<td>308.166</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>1210.968</td>
<td>1100.399</td>
</tr>
<tr>
<td></td>
<td>Ratio (90% CI)</td>
<td>1.0370.(985; 1.092)</td>
<td></td>
</tr>
</tbody>
</table>

**Enbrel 50mg weekly regimen vs. 25mg twice weekly regimen**

The original license for Enbrel was based on pivotal trials that evaluated a 25mg twice-weekly regimen and this was reflected in the license when first launched. A number of subsequent studies have demonstrated the comparable efficacy and safety of the 50 mg once-weekly and 25 mg-twice-weekly regimens in rheumatoid arthritis, ankylosing spondylitis and psoriasis.\textsuperscript{16-18} Consequently, Enbrel is now licensed to be used at either a 25mg twice weekly or 50mg once weekly regimen.\textsuperscript{1}
Safety

The size of the safety database and duration of exposure is appropriate for an assessment of the overall safety profile of Benepali in comparison to the reference product Enbrel. The safety data were derived from the phase III clinical study SB4-G31-RA in RA patients, and supported by data from the phase I clinical study SB4-G11-NHV in healthy volunteers. A pooled safety analysis was not considered appropriate due to the heterogeneity of the study populations and duration of treatment.

Study SB4-G31-RA 13,14

A total of 596 patients received either Benepali or Enbrel for up to 52 weeks. All 596 patients received at least one injection during the study phase and were included in the safety analyses. The mean duration of exposure was 339 and 324 days in the Benepali Enbrel treatment groups, respectively, of whom 94.6% and 88.6% completed 24 weeks treatment, and 70.9% and 74.7% completed 52 weeks.

Overall, the type and incidence of treatment-emergent adverse events (TEAEs) was generally similar between the two treatment groups and were in line with the well-characterised safety profile of Enbrel as outlined in the Summary of Product Characteristics. The majority of TEAEs were of mild to moderate severity, and no significant new safety signals, which had not been observed previously with Enbrel, were reported.

The proportion of patients reporting at least on TEAE was comparable between the Benepali and Enbrel treatment groups (58.5% and 60.3%, respectively). The most frequently reported TEAEs in both treatment groups were upper respiratory tract infection (8.0% vs. 5.4%), alanine aminotransferase increased (6.0% vs. 5.7%) and nasopharyngitis (5.0 vs. 5.4%). The TEAEs considered to be casually related to the study drug are presented in Table 4. Fewer patients in the Benepali group reported at least one Injection site reactions compared with patients in the Enbrel group (0.3% vs. 5.7% up to week 24, and 0.7% vs. 5.7% up to week 52, respectively). However, the numbers involved were small, and a thorough review of all available data suggest that the observed difference were not clinically significant.

Serious adverse events were slightly less frequent in the Enbrel group than in the Benepali group. However, only one SAE was considered treatment related in the Bengali group versus six treatment-related SAEs in the Enbrel group. Two deaths were reported during the study in the Benepali group. In both cases, the events were not considered to be related to treatment. Serious infections were equally distributed, with no cases of active tuberculosis reported.

Immunogenicity

Benepali showed a favourable immunogenicity profile compared to Enbrel. In the Benepali treated group three (1.0%) of patients tested positive for ADAs at least once in the study, compared to 39 (13.1%) in the Enbrel group, one of which also tested positive for neutralising antibodies. There were no clinically significant differences in the incidence of TAEAs according to ADA status, and there did not appear to be any correlation between ADA status and administration site reactions. The ADA formation did not appear to result in a difference in efficacy.
Table 4. Summary of TEAEs by severity and causality (Study SB4-G31-RA).

<table>
<thead>
<tr>
<th></th>
<th>Benepali (n=299)</th>
<th>Enbrel (n=297)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>175 (58.5%)</td>
<td>179 (60.3%)</td>
</tr>
<tr>
<td><strong>TEAE Severity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>78 (26.1%)</td>
<td>91 (30.6%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>83 (27.8%)</td>
<td>77 (25.9%)</td>
</tr>
<tr>
<td>Severe</td>
<td>14 (4.7%)</td>
<td>11 (3.7%)</td>
</tr>
<tr>
<td><strong>TEAE - causally related</strong> (≥2% patients in any group)</td>
<td>88 (29.4%)</td>
<td>109 (36.7%)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>12 (4.0%)</td>
<td>11 (3.7%)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>6 (2.0%)</td>
<td>33 (11.1%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>6 (2.0%)</td>
<td>4 (1.3%)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>6 (2.0%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>AST increased</td>
<td>4 (1.3%)</td>
<td>6 (2.0%)</td>
</tr>
<tr>
<td>Erythema</td>
<td>2 (0.7%)</td>
<td>6 (2.0%)</td>
</tr>
<tr>
<td>Injection site rash</td>
<td>2 (0.7%)</td>
<td>6 (2.0%)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>1 (0.3%)</td>
<td>8 (2.7%)</td>
</tr>
<tr>
<td><strong>Serious Adverse Events</strong></td>
<td>18 (6.0%)</td>
<td>15 (5.1%)</td>
</tr>
</tbody>
</table>

**Study SB4-G11-NHV**\(^{13,15}\)

In part A of the study, in which Benepali was compared to EU-sourced Enbrel the proportion of subjects who experienced TEAEs was comparable (39.1% vs. 34.8%, respectively), overall, the most frequent TEAEs reported were nasopharyngitis, headache, and injection site reaction. The majority of TEAEs reported were mild or moderate in severity and transient. There were no SAEs or deaths reported during the study.

**Pharmacovigilance and Risk Management Plan**

All known risks associated with etanercept (Enbrel) treatment have been included in the Benepali Summary of Product Characteristics.\(^{1,5}\) The identified safety concerns include risk of infection (tuberculosis, bacterial infections, including sepsis and pneumonia, invasive fungal, viral, and other opportunistic infections), congestive heart failure, malignancies and lymphoproliferative disorders. The manufacturers have produced educational materials for healthcare professionals and information for patients, including Patient Alert cards addressing these risks.\(^{13}\)

In order to facilitate the safe introduction of etanercept biosimilars to the NHS, brand name prescribing, identification, recording and traceability needs to be in place. Brand name prescribing is vital if products are to be identified appropriately at the points of dispensing and/or administration. In addition, for each patient, a traceable
record of the brand, batch number, and other vital details of the product used should be made.\textsuperscript{2,19,20}

Robust postmarketing pharmacovigilance is essential to ensure that the biosimilars are both safe and effective in the treatment of each of the indications for which it has been approved. As with all new medicines, the safety of Benepali is subject to continuous monitoring after authorisation. In order that all suspected adverse drug reactions are assigned to the correct product, care must be taken to report the brand name rather than the non-proprietary name when reporting ADRs for biosimilars.\textsuperscript{2,19,20}

In addition to routine pharmacovigilance activities, a Risk Management Plan as outlined in the EPAR includes several post-authorisation studies and registries that will provide further long-term efficacy and safety profile of Benepali.\textsuperscript{13} The pivotal SB4-G31-RA study will be continued for another 48 weeks of open label treatment in which patients originally randomised to receive Enbrel will be switched to Benepali. Serious infections, including tuberculosis will be closely monitored on a longer-term and in larger patient cohorts through the use of several prospective registries in different patient populations. Rare ADRs, such as malignancies and lymphoproliferative disorders, will also be closely monitored as part of these registries.

**Extrapolation of efficacy and safety**

Extrapolation is an established scientific and regulatory principle that has been exercised for many years. If biosimilarity has been demonstrated in one indication, the EMA considers that extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification. Extrapolation should be considered in the light of the totality of data, i.e. quality, non-clinical and clinical data. It is expected that the safety and efficacy can be extrapolated when biosimilar comparability has been demonstrated by thorough physico-chemical and structural analyses as well as by in vitro functional tests complemented with clinical data (efficacy and safety and/or PK/PD data) in one therapeutic indication.\textsuperscript{2,12,13,21,22}

The efficacy of Benepali was shown to be similar to that of Enbrel in the primary endpoint (ACR20, week 24) and the other secondary endpoints in a model of acceptable sensitivity (moderate to severe RA in combination with MTX in Study SB4-G31-RA). Therefore these results are sufficient to demonstrate equivalence in efficacy between the proposed biosimilar Benepali and the reference product Enbrel.

Extrapolation of the pharmacokinetic, efficacy and safety data generated in the two clinical trials in healthy volunteers and RA to the other authorised indications of Enbrel is sufficiently justified.\textsuperscript{13}

As the PK of etanercept has been shown to be comparable in patients with RA, ankylosing spondylitis (AS), psoriasis, and healthy subjects, the PK results obtained with Benepali, demonstrating its biosimilarity with the reference product Enbrel in healthy subjects can be reasonably extrapolated to the approved therapeutic indications of Enbrel.\textsuperscript{13}
With regards to the efficacy, it is well established that an uncontrolled inflammatory process is common to all therapeutic indications of Enbrel. These indications share a common mechanism of action, i.e. the competitive inhibition of TNF-α binding and blockade of the ensuing inflammatory processes. 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.\textsuperscript{13}

**Dosage and administration**

Benepali is only available as a single-use pre-filled syringe and as a pre-filled pen each case containing 50 mg etanercept per mL to be administered via subcutaneous injection.\textsuperscript{5} In contrast, Enbrel is available in various presentations (10mg, 25mg, 50mg; syringe or pre-filled pens).\textsuperscript{1}

As the marketing authorisation for Benepali only applies to the 50 mg etanercept dose, it is only licensed for adults aged 18 years and over, whereas Enbrel is also approved for paediatric plaque psoriasis and juvenile idiopathic arthritis.\textsuperscript{1,5}

The maintenance dosage also differs between Benepali and Enbrel. Benepali is only licensed for 50 mg once-weekly administration, whereas Enbrel can be given at a dose of either 25mg twice-weekly, or 50mg once-weekly in adults.\textsuperscript{1,5}

The administration devices differ in that the Benepali pre-filled pen is an auto-injector device whereas the Enbrel pen requires the patient to press a button to administer the dose. Unlike the Enbrel pen, the needle sheath for the Benepali pen is latex free. In both cases the medicines must be stores in the refrigerator (2\textdegree{}C to 8\textdegree{}C) and brought to room temperature before administration.\textsuperscript{1,5}

As with Enbrel, the Benepali device is provided with suitable educational material for healthcare professionals and patients to support their use.\textsuperscript{1,5} The manufacturer of Benepali will also provide needle-free demonstration devices to facilitate training of patients in the safe use of the pre-filled syringe and device.\textsuperscript{23}

The UKMI has published an in-use product safety assessment report which advises on strategies to minimise the risks associated with the introduction of Benepali to the market.\textsuperscript{26}
Cost analysis

These data are confidential to the NHS and commercially sensitive, and should not be disclosed to third parties outside of NTAG.

Etanercept is a specified high-cost medicine and represents a significant expenditure for the NHS. Enbrel has an NHS list price of £357.50 and £715.00 for the 4 x 25mg, and 4 x 50mg doses, respectively. Benepali as a biosimilar should be available at significantly lower cost than the reference product Enbrel. As such, Benepali has the potential to considerably reduce treatment costs, expand market competition and increase patient accessibility.

On 1\(^{st}\) April 2016, a new Commercial Medicines Unit (CMU) contract which will include the TNF inhibitors is due to start. Under the CMU contract the price of some products is likely to differ substantially from list prices due to nationally or locally negotiated procurement discounts. The NHS list price of Benepali is £656 for 4 x 50mg, which represents a discount of around 10% on the current list price of Enbrel.\(^{24}\)

NHS England supports 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. Automatic substitution is not appropriate for biological medicines, including biosimilar medicines and is not permitted at this time. Prescribers, of course, are always able to switch treatments for a given patient, provided it is safe to do so. Switching between a reference product and its biosimilar should be managed at the discretion of the individual prescriber in partnership with the patient, with appropriate monitoring in place.\(^{2}\)

Benepali is only licensed as a 50mg once-weekly dose for adults. Therefore, it cannot directly replace all current prescribing of Enbrel. However, it is estimated that the 50mg presentations account for between 60 and 75% of the total current etanercept market.\(^{23}\) Based on a conservative estimate of a 70% switch to Benepali
Points to consider

A biosimilar formulation of etanercept was launched in the UK in February 2016 under the brand name of Benepali. It is only licensed to be given as a 50 mg once-weekly dose, and therefore it is not licensed for the paediatric indications of Enbrel (paediatric plaque psoriasis and juvenile idiopathic arthritis).

To gain approval in the EU, biosimilar medicines must demonstrate that they are as safe and as effective as the reference medicine, and have the same quality characteristics. In an extensive comparability exercise it was shown that all major physicochemical characteristics and biological activities of Benepali are comparable to those of Enbrel.

In a Phase III study (n=596) in subjects with moderate to severe RA despite MTX therapy, Benepali was shown to have equivalent efficacy to that of Enbrel in the primary outcome of ACR20 response at week 24. Secondary efficacy outcomes at week 24 support the primary findings, and response rates were sustained to a similar degree in both treatment groups up to week 52.

Overall, the type and incidence of treatment-emergent adverse events were generally similar between the two treatment groups and were in line with the well-characterised safety profile of Enbrel. The majority of adverse events were mild to moderate in severity with no significant new safety signals reported. There were no marked differences in the immunogenicity profile and the impact of auto-antibodies on efficacy and safety was comparable.

Although clinical studies were only performed in patients with RA, the efficacy and safety of Benepali for other indications is assumed from the demonstration of equivalence to Enbrel in accordance with regulatory procedures. Based on the totality of evidence, the EMA concluded that similarity has been convincingly demonstrated enabling extrapolation of Benepali approval to all other indications for which the reference product Enbrel® is approved, except the aforementioned paediatric indications.

The NHS list price of Benepali is £656 for 4 x 50 mg, representing a discount of ~10% on the current list price of Enbrel. It is estimated that the 50mg presentations account for between 60% and 75% of the total etanercept market. Based on a conservative estimate of a 70% switch to Benepali, automatic substitution is not appropriate for biosimilars and is not permitted at this time. However, prescribers are able to switch treatments for a given patient, provided it is safe to do so. Switching between a reference product and its biosimilar should be managed in partnership with the patient, with appropriate monitoring in place.
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References