UK Medicines Information

IN-USE PRODUCT SAFETY ASSESSMENT REPORT
BENEPALI®▼ (ETANERCEPT BIOSIMILAR)

SUMMARY OF ASSESSMENT AND ITS FINDINGS

BACKGROUND

A UK marketing authorisation has been granted to an etanercept biosimilar (SB4, Benepali®, Biogen Idec Limited) and this review summarises practical in-use safety considerations associated with its introduction. Useful background summaries on biosimilar medicines, their science, and licensing are available elsewhere[1, 2].

DETAILS OF PRODUCT(S) ASSESSED

Benepali® is available as:
1. Pre-filled syringe 50mg
2. Pre-filled pen 50mg

The products were assessed using the validated UKMi product assessment tool[3] and compared with the originator Enbrel® 50mg pre-filled syringe and pen, Pfizer Ltd (a formal assessment of Enbrel® was not undertaken).
Assessments were carried out with reference to: high resolution images supplied by the manufacturers; summaries of product characteristics (SmPC) and packaging inserts; and the European Medicines Agency Public Assessment Reports (EPARs) for the products.
The images are reproduced below. The assessment process is summarised at the end of the report.

CONCLUSION FOLLOWING APPLICATION OF VALIDATED ASSESSMENT TOOL

Overall the presentation, physical characteristics, and accompanying information for both products are considered appropriate. However, some (largely inherent) risks will be associated with the introduction of biosimilar etanercept. These risks should be broadly manageable, but safe introduction will require specific implementation work. Potential risks are identified below; mitigating and other necessary actions are considered in the next section.

Differences between products

Benepali® is only licensed for adults aged 18 and over[4] whereas Enbrel® is licensed in children from the age of 2 years[5]. In addition, Benepali® is currently only available as a 50mg pre-filled pen or syringe as opposed to Enbrel® which comes in various presentations (10mg, 25mg, 50mg; syringe, vial or pre-filled pen).
Maintenance dosage regimens differ between the products. Benepali® is licensed for 50mg once weekly by subcutaneous injection whereas Enbrel® can be administered as either 25mg twice weekly or 50mg weekly as a maintenance dose in adults.
The MHRA have advised that, for all biosimilar products, the brand name should be used for prescribing and for the reporting of adverse events[6]. Patients should be maintained on one brand of biosimilar products and should not be switched between products without careful assessment.
From the assessment, the packaging and presentation between the two products is well differentiated and should enable rather than hinder differentiation.
Etanercept is used across a range of care settings, and there is hence potential for risk

associated with this.
The pre-filled pen devices will have some differences in appearance. No dummy devices of Benepali® were available for this assessment but the devices for both products look similar in size and design[7,8]. 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. The rubber needle sheath for the Enbrel® pen and syringe contains latex, whereas Benepali® is latex-free[7,8].
Disposal methods for the syringe and pen presentations will be the same for both products.

Similarities with Enbrel®
As with Enbrel®, Benepali® is provided with suitable patient and professional information to support their use. Both are provided with an insert containing a full PIL, as well as information on administration for professionals and for patients and patient alert cards[8,9]. Benepali® is licensed for the same range of adult indications as Enbrel®. Most known current risks associated with Enbrel® will apply to Benepali®. In 2014 the MHRA issued a warning of the potential for increased susceptibility to infectious diseases such as tuberculosis, and the increased risk of reactivation of latent tuberculosis with tumour necrosis factor inhibitors[10]. This warning is of relevance to both Enbrel® and Benepali®.

POTENTIAL NEXT STEPS AND MITIGATION ACTIONS
Potential next steps and mitigation actions can be considered in two respects: those of particular relevance to the NHS, and those of particular relevance to manufacturers.
Safe introduction of etanercept biosimilars to the NHS will need to consider a number of actions:

1. 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 presentation of the product used should be made. The MHRA recommend branded prescribing for biological products to ensure that automatic substitution does not occur when dispensing/ administering.
It is likely that the brand and batch number is currently recorded routinely for Enbrel®; additional recording of the brand should not therefore be onerous. However the manufacturers of both products could simplify the procedure by providing removable stickers on the products.
Local education and training for prescribers, pharmacists, pharmacy staff, nurses, and others may also be necessary to ensure brand name prescribing, identification, and recording occurs.

2. Other risk mitigations for Benepali® to be consistent with measures for Enbrel®

Other risk mitigation steps for Benepali® should be similar to those currently in place for Enbrel®. Appropriate processes will be required to assess patient suitability for treatment (particularly in relation to tuberculosis).
When considering the use of Benepali®, commissioners will need to consider whether it will be used in new patients only or whether existing patients will be switched from Enbrel® to Benepali®. Published data are not currently available on patients switched from Enbrel® to Benepali®- this is likely later in 2016.
Any plans to switch all patients to Benepali® should take into consideration the differences in licensing and formulation. For example, Benepali® is only licensed for adults. Patients under the age of 18 currently prescribed etanercept must remain on

Enbrel®. There may thus be a need for both brands of etanercept to be stocked and prescribed.
In addition, some patients may be receiving Enbrel® 25mg twice a week currently. These patients would need careful assessment as to their suitability of transferring to a 50mg once weekly dose and it may not be possible to switch these patients to Benepali®.

3. Training and patient-related material

The majority of etanercept is self-administered currently using the pen device or pre-filled syringes. This is likely to also be the case with Benepali® which is only available as a pre-filled pen or syringe. Patient factors therefore need to be considered carefully to ensure patients are clear how to use each device. Dummy devices for Benepali® were not available for this assessment but patient material, including line drawing of the devices, were assessed. The devices appear to be similar in design and the administration steps and processes are comparable except that Benepali® is an auto-injector device as opposed to Enbrel® which requires the patient to press a button to administer the dose. The manufacturers of Benepali® are providing one nurse visit for each patient who receives the product through a homecare provider and this visit will provide training on the new device if required. Ongoing telephone support is also available. If homecare providers are not used for the supply of Benepali®, any patient training on switching to the new device would need to be organised by the prescribing organisation.

Both products need to be stored in a fridge. Processes are likely to be in place currently to ensure the cold chain is not broken and these should be continued if Benepali® is used.

Both products will require safe disposal methods and patients will require sharps bins and instructions for safe disposal regardless of the product supplied.

4. Reporting and monitoring of patients through registries and pharmacovigilance

Clinical registries will enable collection of specific data on serious adverse events for Benepali® in both dermatology and rheumatology. These mechanisms will act in addition to routine pharmacovigilance activities as Benepali® will be subject to additional monitoring under intense MHRA regulatory surveillance. Safe introduction and ongoing safe use of Benepali® requires both practitioner and manufacturer engagement with these processes.

5. Safe use of both available products across care settings

The risks identified are not particular to any individual care setting; however, the mitigation strategies suggested will apply universally. The majority of Enbrel® is currently supplied through the homecare route and comparable governance arrangements may need to be reflected in contracts with homecare providers for Benepali®.
The manufacturer of Benepali® has put in place a package of care through specific homecare providers, including one home visit by a nurse and ongoing telephone helpline support. If the homecare route of supply is not used, patient training and ongoing support will need to be provided through alternative methods.
It is possible that if a commissioner switches to Benepali®, this may involve a transfer from one homecare provider to another. Steps should be taken to ensure that there is no disruption to supplies for individual patients. This would also be required if the supply of the drug were repatriated to an outpatient service- either in-house or outsourced.

PROCESS STATEMENT

This report was produced in January 2016 following application of the validated UKMi product safety assessment tool using photographic images from the manufacturers and actual products as described above. This report summarises the results of product assessments undertaken by:

- Trent Medicines Information Service (Leicester)
- Welsh Medicines Information Service (Cardiff).

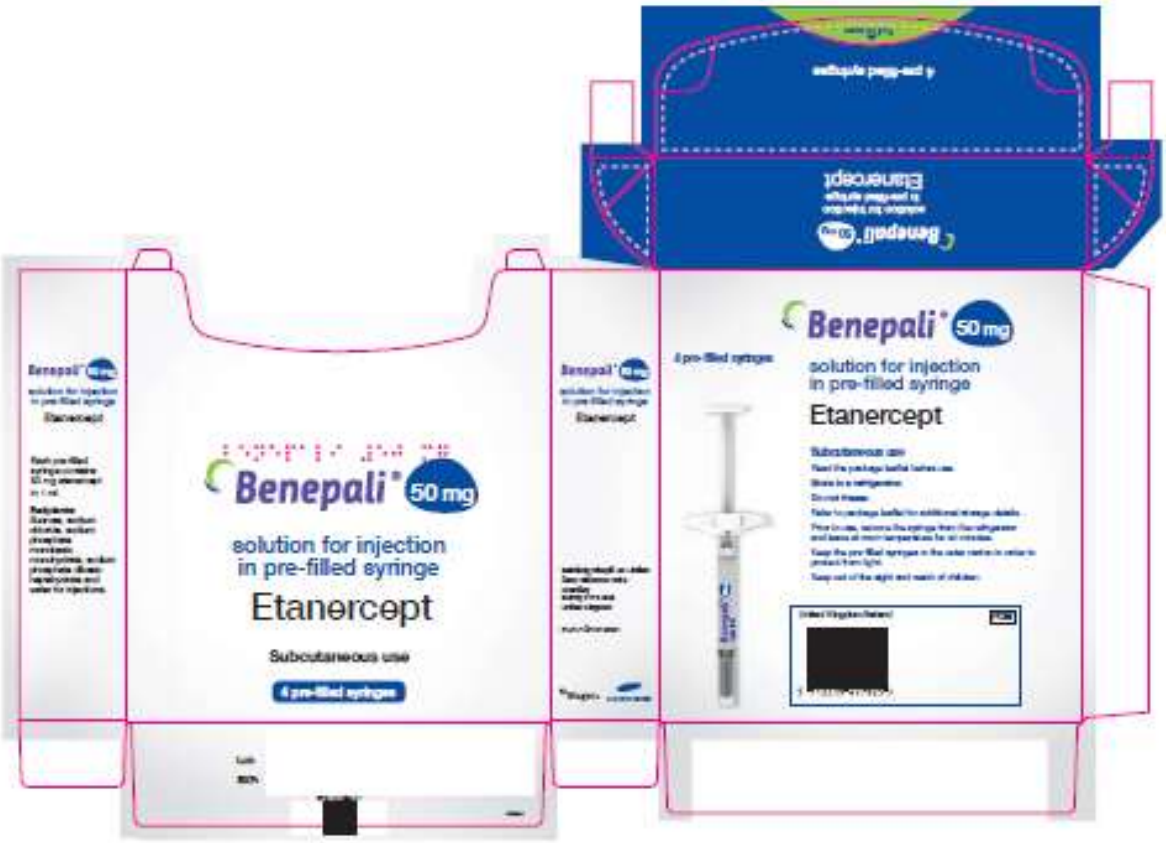
We are also grateful for the input of clinical specialists and SPS colleagues in procurement in completing this piece of work. Contact vanessa.chapman@uhl-tr.nhs.uk for comments.

References

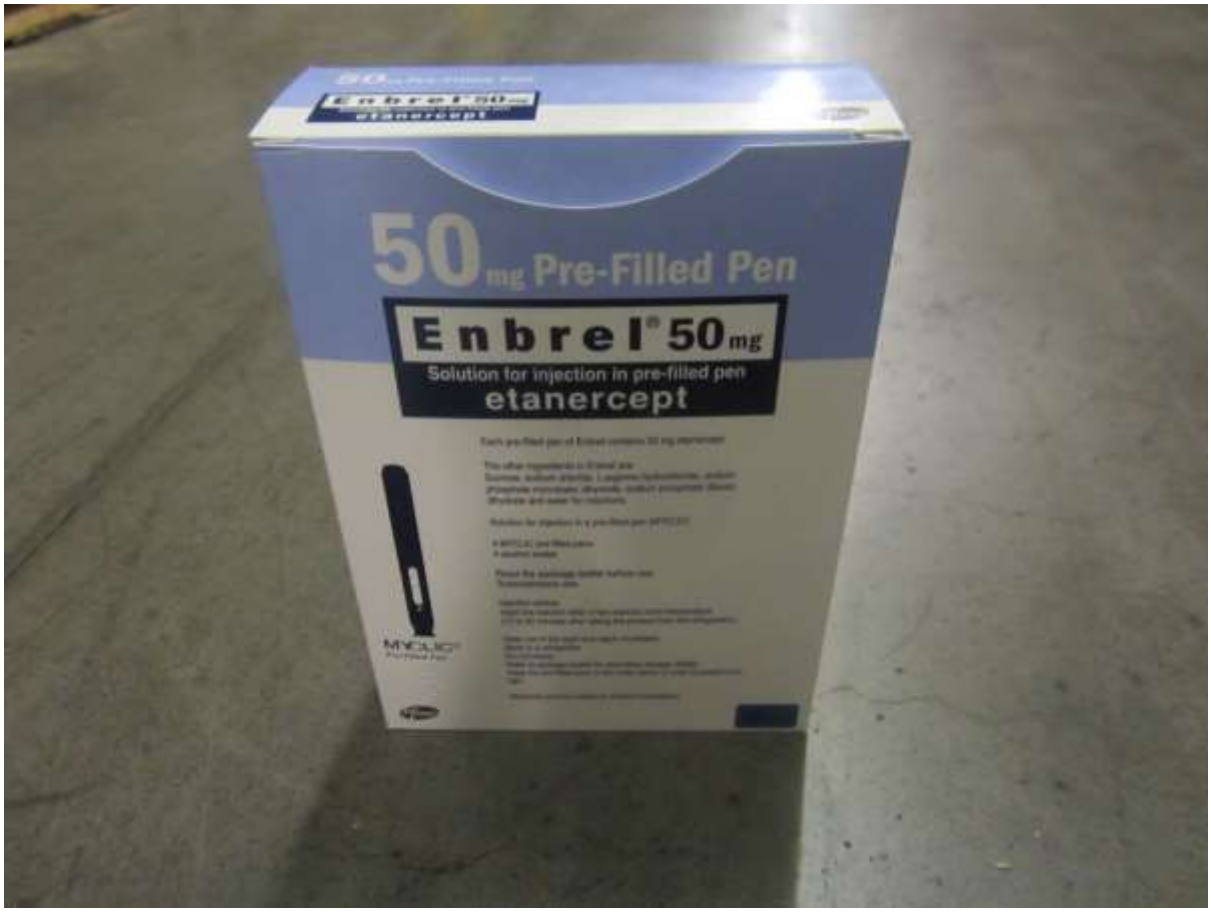
1. What are biosimilars and are they important? *Drug Ther Bull* May 2013; 51(5): 57-60.
2. Hooker N. Answers to commonly asked questions about biosimilars. London. UK Medicines Information. 2015.
3. UKMi Product Safety Assessment tool. Available at: http://www.ukmi.nhs.uk/activities/patientSafety/default.asp?pageRef=19UKM.
4. Biogen Limited. Summary of Product Characteristics for Benepali®▼ 50mg pre-filled pen/ pre-filled syringe. Date of Authorisation Nov 2015
5. Pfizer Ltd Summary of Product Characteristics for Enbrel® 50mg pre-filled pen/ pre-filled syringe. Last updated December 2015 Available from www.medicines.org.uk
6. Medicines and Healthcare Products Regulatory Agency. Biosimilar Products. *Drug Safety Update* 2008; 1(7): 8
7. Biogen Ltd. Package Information Leaflet Benepali® Nov 2015
8. Pfizer Ltd. Patent Information Leaflet Enbrel pre-filled pen December 2015
9. European Medicines Agency. European public assessment report: Benepali®▼. London, 2015.
10. Medicines and Healthcare Products Regulatory Agency. Tumour necrosis factor alpha inhibitors. Risk of tuberculosis - screen all patients before starting treatment and monitor them closely. *Drug Safety Update* April 2014.

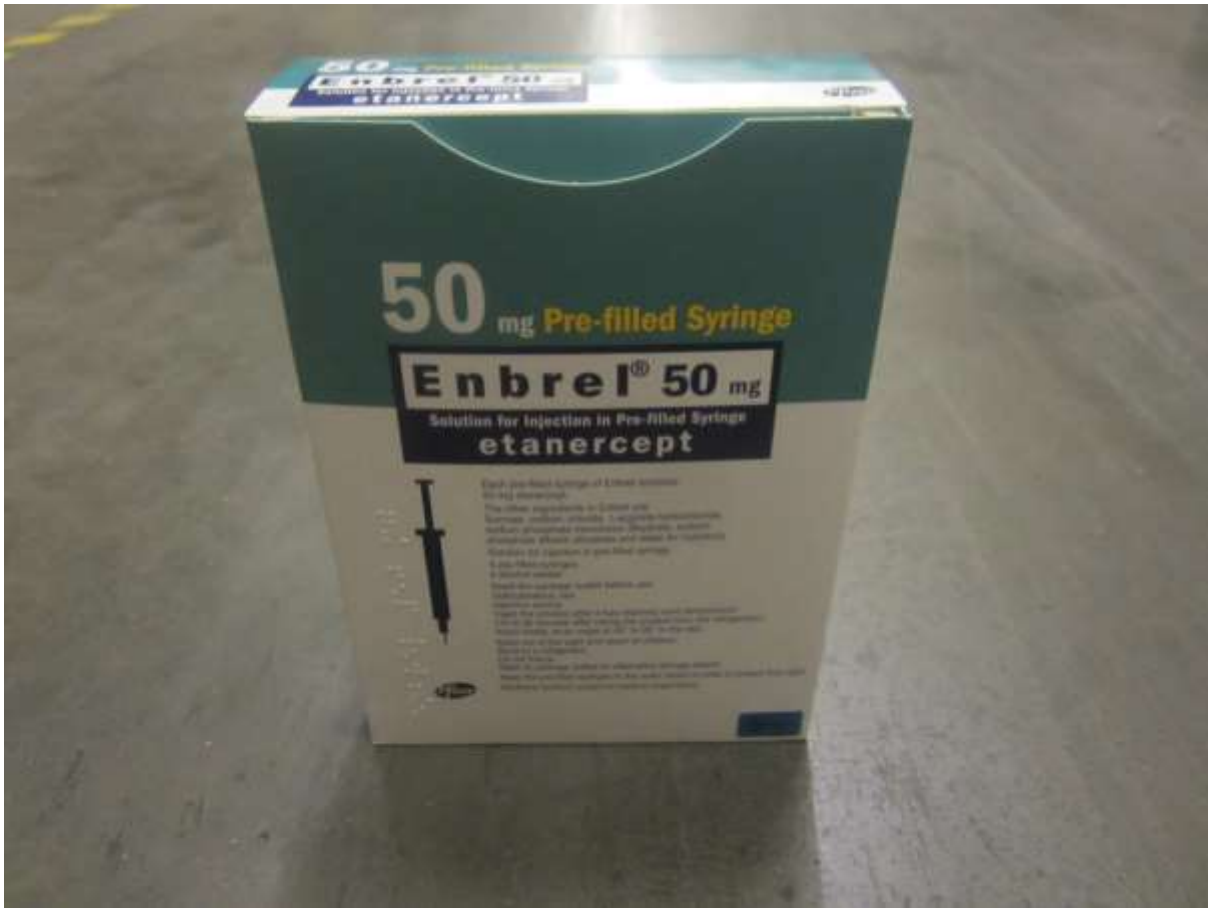
EXAMPLE PRODUCT PHOTOS/ PICTURES


Benepali 50 mg
solution for injection
in pre-filled pen
Etanercept
Subcutaneous use
4 pre-filled pens
Benepali 50mg
solution for injection
in pre-filled pen
Etanercept


Benepali 50 mg
solution for injection
in pre-filled syringe
Etanercept
Subcutaneous use
4 pre-filled syringes


Enbrel
MYCLIC


50 mg Pre-Filled Pen
Enbrel® 50 mg
Solution for injection in pre-filled pen
etanercept


50 mg Pre-filled Syringe
Enbrel® 50 mg
Solution for Injection in Pre-filled Syringe
etanercept