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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Benepali

International non-proprietary name: etanercept

Procedure No. EMEA/H/C/004007/X/0016

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

λz Lambda_z,	Terminal rate constant
ACR	American College of Rheumatology
ACR20	20% improvement according to the ACR criteria
ACR50	50% improvement according to the ACR criteria
ACR70	70% improvement according to the ACR criteria
ADCC	Antibody-dependent cell-mediated cytotoxicity
ANCOVA	Analysis of covariance
AS	Ankylosing spondylitis
AUC	Area under the concentration-time curve
AUC_T	Area under the concentration-time curve over the dosing interval
AZA	Azathioprine
biw	Twice a week
BLA	Biologic License Application
BMWP	Biosimilar Medicinal Products Working Party
bw	Body weight
CDAI	Clinical disease activity index
CDC	Complement-dependent cytotoxicity
cfu	Colony forming unit
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CL	Total body clearance
C_{max}	Maximum serum concentration
$C_{max,ss}$	Maximum serum concentration at steady state
CPMP	Committee for Proprietary Medicinal Products
CRP	C-reactive protein
CSR	Clinical study report
DAS	Disease activity score
db	Double-blind
DMARD	Disease-modifying anti-rheumatic drugs
EGA	Evaluator's global assessment
EM(E)A	European medicines Agency
enr	Enrolled
eow	Every other week
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	The European League Against Rheumatism
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GH	General health
h	Hour(s)
HAQ	Health assessment questionnaire
HMW	High molecular weight
i.v.	Intravenous
ICH	International Conference on Harmonisation
IgG1	Immunoglobulin G, subtype 1
JIA	Juvenile idiopathic arthritis
kg	Kilogram
L	Litre
LMW	Low molecular weight
LRV	Log_{10} reduction value
mAb	Monoclonal antibody
max	maximum
mc	Multicentre
mg	Milligram
min	minimum

mL	Millilitre
MTX	Methotrexate
N, n	Number
n.r.	Not reported
N/A	Not applicable
ND	No data available
NSAID	Non-steroid anti-inflammatory drugs
PD	Pharmacodynamic(s)
PGA	Patient's global assessment
PI	Product information
PK	Pharmacokinetic(s)
PP	Per-protocol
Ps	Psoriasis
PsA	Psoriatic arthritis
PUVA	Psoralen combined with ultraviolet A (UVA)
q4	Every 4 weeks
q8	Every 8 weeks
q6	Every 6 weeks
QoL	Quality of life
qw	Every week
ra	Randomised
RA	Rheumatoid arthritis
RF	Rheumatoid factor
Rt	Retention time
s.c.	Subcutaneous
SD	Standard deviation
SDAI	Simplified disease activity index
SE	Standard error
SF-36	Medical outcomes study short-form health survey
SJC	Swollen joint count
SmPC	Summary of product characteristics
SOC	System organ class
STD	Study
sTNF	Soluble tumour-necrosis factor alpha
T½	Terminal elimination half life
TB	Tuberculosis
TJC	Tender joint count
tm	Transmembrane
tmTNF	Membrane bound tumour necrosis factor
TNF	Tumour necrosis factor
TNFR	Tumour-necrosis factor receptor
TNFß	Tumour-necrosis factor beta
TNFα	Tumour-necrosis factor alpha
USA	United States of America
VAS	Visual analogue scale
Vc	Volume of distribution in the central compartment
Vp	Volume of distribution in the peripheral compartment
V_{ss}	Volume of distribution at steady state
WGET	Wegener's Granulomatosis Etanercept Trial
Wk(s)	Week(s)
y	Year(s)

1. Background information on the procedure

1.1. Submission of the dossier

Samsung Bioepis UK Limited (SBUK) submitted on 28 July 2016 an extension of the marketing authorisation.

The MAH applied for an additional strength: 25 mg associated with one new presentation: 25 mg solution for injection 4 pre-filled syringes.

The MAH applied for the following indication for Benepali 25 mg:

Rheumatoid arthritis

Benepali in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.

Benepali can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Benepali is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Benepali, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Juvenile idiopathic arthritis

Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

Etanercept has not been studied in children aged less than 2 years.

Psoriatic arthritis

Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. Etanercept has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.

Axial spondyloarthritis

Ankylosing spondylitis

Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Non-radiographic axial spondyloarthritis

Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).

Plaque psoriasis

Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA) (see section 5.1).

Paediatric plaque psoriasis

Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(s) (c) change or addition of a new strength/potency- Extensions of marketing authorisations

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The MAH did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

- The application was received by the EMA on 28 July 2016.
- The procedure started on 18 August 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 November 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 14 November 2016
- During the meeting on 1 December 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 15 December 2016, the CHMP agreed on the consolidated List of Questions to be

sent to the MAH. The final consolidated List of Questions was sent to the MAH on 15 December 2016.

- The MAH submitted the responses to the CHMP consolidated List of Questions on 20 January 2017.
- The Rapporteur circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on 27February 2017.
- The Rapporteur circulated the updated Joint Assessment Report on the responses to the List of Questions to all CHMP members on 16 March 2017.
- During the meeting on 23 March 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension of the marketing authorisation for Benepali on 23 March 2017.

2. Scientific discussion

2.1. Problem statement

Samsung Bioepis UK Limited submitted on 28 July 2016 an extension application to the marketing authorisation for Benepali (H/C/004007) to add a new strength of 25 mg solution for injection in a prefilled syringe.

The current application for Benepali 25 mg applied for the treatment of the following indications:

Rheumatoid arthritis

Benepali in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.

Benepali can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Benepali is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Benepali, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Juvenile idiopathic arthritis

Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

Etanercept has not been studied in children aged less than 2 years.

Psoriatic arthritis

Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. Etanercept has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.

Axial spondyloarthritis

Ankylosing spondylitis

Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Non-radiographic axial spondyloarthritis

Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).

Plaque psoriasis

Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA) (see section 5.1).

Paediatric plaque psoriasis

Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

About the product

Benepali is a biological medicinal product similar to the reference product, Enbrel. Benepali was authorised in the European Union in January 2016. The active substance of Benepali is etanercept, an immunosuppressant (ATC code: L04AB01).

Etanercept is a recombinant human tumour necrosis factor receptor p75Fc fusion protein. It interferes with the soluble TNF-α by mimicking the inhibitory effects of naturally occurring soluble TNF receptors that deactivate TNF-α and therefore down-regulate immune responses. Etanercept acts as a decoy receptor for TNF-α, reducing TNF-α affects and hence represents a competitive TNF-α inhibitor (EPAR Enbrel, 2014; Goffe and Cather, 2003). Etanercept may also modulate biological responses controlled by molecules further down the inflammatory cascade (e.g., cytokines, adhesion molecules, proteinases etc.) that are induced or regulated by TNF-α.

The already authorised dosage form is presented in a single-use pre-filled syringe (PFS) and pre-filled pen (PFP) containing 50 mg of etanercept per mL to be administered via subcutaneous (SC) injection.

The MAH claims the same therapeutic indications for the proposed biosimilar Benepali 25 mg as granted for Enbrel 25 mg in the EU.

Type of Application and aspects on development

The legal basis for this extension application is a similar biological application under Article 10(4) of Directive 2001/83/EC as amended.

2.2. Quality aspects

2.2.1. Introduction

Benepali has been developed as a similar biological medicinal product (biosimilar) to the reference medicinal product Enbrel having the tumour necrosis factor-α (TNF-α) inhibitor etanercept as active substance. The purpose of this line-extension application is to introduce an additional strength of 25 mg solution for injection in pre-filled syringe to the existing Marketing Authorization of 50 mg solution for injection in pre-filled syringe (PFS). Benepali 50 mg is additionally available in a pre-filled pen presentation (PFP).

The composition and presentation of Benepali 25 mg and Benepali 50 mg pre-filled syringes are identical with the exception of filling volume. Benepali 25 mg is presented in single-use pre-filled syringes containing 25 mg etanercept per 0.5 mL. The target fill volume for Benepali 25 mg is 0. 51 mL and it was selected since this is the target fill volume applied for the reference product Enbrel.

2.2.2. Active Substance

General information

Benepali (etanercept) is a homodimer of a chimeric protein, produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells, which consists of 934 amino acids, 467 amino acids for each chain. The homodimer has a molecular weight of approximately 130 kDa. Each etanercept single chain contains a total of 22 Cystein (Cys) residues. These Cys residues are linked by multiple intra-chain and inter-chain disulphide bonds. Etanercept is a highly glycosylated fusion protein with each monomer containing 3 N-linked glycosylation sites and 13 potential O-linked glycosylation sites.

No changes to the manufacture of the active substance are proposed with the present submission.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Benepali finished product (FP) is a clear to slightly opalescent, colourless or pale yellow, sterile and preservative-free solution for injection. It is intended for subcutaneous administration, and is presented in a pre-filled syringe (PFS; Benepali 25 mg and Benepali 50 mg) and a pre-filled pen (PFP; Benepali 50 mg). The PFS consists of a clear type I glass barrel with stainless steel needle, rubber needle cover and rubber plunger. The immediate container in the PFP is the same PFS, and the PFP is the PFS assembled into a pen device.

The active substance in Benepali FP is etanercept and the active substance and finished product formulations are identical. The excipients contained in the active substance and finished product are sucrose, sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate heptahydrate and water for injections. All excipients comply with compendial monographs.

The excipients and formulation are similar to the reference product Enbrel®, with the exception of L-arginine hydrochloride and the concentrations of sodium chloride and sodium phosphate that are adjusted relative to Enbrel.

Compatibility of the active substance and excipients has been studied in formulation development and formulation robustness studies. Benepali FP 25 mg strength is manufactured using the similar process parameters for 50 mg FP, with minor modifications. The differences include the volume of pooled bulk drug substance (BDS), filling weight, and stopper position and the input parameters were adjusted according to the changes. The results from risk assessment showed that there is low risk associated with the changes in these parameters in terms of product quality.

Container closure system

The FP is presented in a 1 ml syringe with fixed needle and needle shield. This packaging is standard for PFS presentations. The glass complies with Ph. Eur. 3.2.1, the silicone oil lubricant with Ph. Eur. 3.1.8 and the rubber part of the needle shield with Ph. Eur. 3.2.9. The identification of the needle shield rubber is determined by tests for density, ash, UV and IR spectra. The outer rigid polypropylene shell of the needle shield is not in contact with the Benepali solution for injection.

The plunger rod and the backstop on the syringe are functional parts of the container that are not in contact with the solution for injection. The plunger rod and backstop materials have been confirmed to comply with FDA 21 CFR regulations for materials with alimentary contact.

Manufacture of the product and process controls

The PFS manufacturing process involves thawing of the active substance, followed by sterile filtration through a 0.22 µm filter and aseptic syringe filling, and plunger placement. Following manufacture of the bulk PFS, the bulk packaged PFSs are shipped to the secondary packaging site for further processing.

There are no intermediates in the Benepali FP manufacturing process. The same principles for input and output definitions applied for active substance are also applied for FP process controls. For the input parameters, critical-, key- and non-key control parameters have been defined for each step in the process as well as the outputs; critical and process consistency in-process controls and in-process tests. The criticality is associated with impact on the defined critical quality attributes (CQAs) of the Benepali FP. The input parameters have action limits and operating ranges and the level of action if limits are exceeded have been defined. For the output parameters, most of the in-process controls/tests have action limits applied and some have established in-process specifications. The definitions for the limits have been described.

Process validation

The manufacturing process validation involves the following studies: 1) process validation of the complete manufacturing process from thawing of the active substance to visual inspection of the final PFSs, 2) filter validation, 3) aseptic fill validation, and 4) filling needle cleaning validation.

Manufacturing process consistency was demonstrated by the manufacture of three consecutive FP batches in commercial scale. No new data were presented for filter validation, aseptic fill validation, and filling needle

cleaning validation, as these are deemed covered by the previous validation programme for manufacture of Benepali 50 mg FP.

Product specification

The finished product specification includes test methods for identity, glycan content, biological activity, purity and impurities, endotoxin. Other general tests (appearance, pH, osmolality) are also included in the specification. The analytical procedures used for release and shelf life testing of Benepali and finished product have been appropriately described and validated.

The release and shelf-life specifications specifications for Benepali finished product are summarized in the following table:

The specifications of Benepali 50 mg FP and Benepali 25 mg FP are identical with the exception of extractable volume. No changes were made to the analytical procedures. The specifications for control of Benepali 25 mg FP are appropriately justified.

The impurities present or potentially present in the FP are the same as those identified and controlled in the active substance. Microbial contaminants and endotoxin are tested as part of FP release testing. In addition, testing for particulates s carried out as part of FP release testing, and characterisation testing for sub-visible particles was carried out for the FP.

Batch analysis data have been presented for the three process validation batches of Benepali 25 mg FP. The provided batch data comply with the release specifications.

Stability of the product

For 25 mg Process Validation Run (PVR) batches (00001, 00002, and 00003), 6 months data at the long-term and the accelerated storage conditions have been provided. For 00001 PVR batch, 3 months data (completed) at the stress storage condition are also available.

Overall, it is confirmed that no critical changes were observed at long-term conditions during 6 months for 25 mg Benepali FP PVR. There were also no significant changes over 6 months under accelerated conditions. The potency and impurities at the initial time point were similar; while upon stress the curves were practically superimposable, confirming the similar instability trends and degradation pathway at 40 ± 2ºC/75 ± 5% RH between 25 mg and 50 mg Benepali FP from Patheon.

To confirm the comparable stability, data comparison between 50 mg Benepali FP and 25 mg Benepali FP under long-term, accelerated, and stress storage condition was conducted to assess the comparability of stability profile. Although there were some variations in the results of TNF-α binding assay and TNF-α neutralising assay, degradation patterns in the test items were comparable between 50 mg Benepali FP and 25 mg Benepali FP from Patheon under long-term, accelerated, and stress storage condition. Overall, the results of the comparability and comparative stability studies indicate 50 mg Benepali FP and 25mg Benepali FP from Patheon are comparable in terms of degradation profile.

Based on the comparability assessment results, the claimed shelf-life of 30 months when stored at 2°C - 8°C for Benepali 25 mg FP is considered acceptable.

Comparability exercise for finished medicinal drug product

Similarity to Enbrel® was demonstrated in the course of the initial marketing authorization application of Benepali (i.e. Benepali 50 mg strength). The comparability exercise is also applicable for the 25 mg strength and thus no new data was presented.

Adventitious agents

The adventitious agents safety evaluation performed in the course of the initial marketing authorization of Benepali and the approval of the 50 mg strength is still relevant for the 25 mg strength. No changes are proposed that would affect safety with respect to adventitious agents.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The composition and presentation of Benepali 25 mg and Benepali 50 mg pre-filled syringes are identical with the exception of filling volume. Thus, the present submission mainly concerns manufacture of the finished product. No updates were provided with respect to the manufacture of the active substance, adventitious agents safety evaluation or biosimilarity assessment. Concerning these aspects, the information previously provided for the 50 mg strength is still relevant for the new strength. Taken together, the provided information regarding the additional strength of 25 mg PFS is considered sufficient and adequate**.**

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

This line extension application to introduce an additional strength of 25 mg PFS is approvable from the quality point of view.

2.3. Non-clinical aspects

The current line extension application was submitted to add a new strength of 25 mg solution for injection in a prefilled syringe to the marketing authorization of Benepali. Accordingly, no new additional non-clinical data was submitted for this line extension.

During the initial marketing authorisation application the similarity between Benepali and Enbrel was demonstrated on a non-clinical level.

Therefore, further studies regarding pharmacology, pharmacokinetics, genotoxicity, reproduction toxicology and carcinogenicity were not submitted for this line extension application, which was considered acceptable by the CHMP.

2.3.1. Ecotoxicity/environmental risk assessment

The MAH provided a justification for not submitting any environmental risk assessment studies based on the fact that Benepali is a protein and therefore unlikely to pose a significant risk to the environment which is in accordance with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2).

2.3.2. Discussion on non-clinical aspects

A set of non-clinical assays testing the properties of the biosimilar Benepali in comparison with the reference product Enbrel, was performed during the initial MAA. This data was generally considered in line with current European guidance on development of biosimilars, including the EMA "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" (EMEA/CHMP/BMWP/42832/2005 Rev. 1) and "Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues" (EMEA/CHMP/BMWP/403543/2010).

The current line extension application to the marketing authorization for Benepali was submitted to add a new strength of 25 mg solution for injection in a prefilled syringe. Accordingly, no new additional non-clinical data were submitted for this line extension.

2.3.3. Conclusion on the non-clinical aspects

Originally submitted comparative pharmacodynamics, pharmacokinetic and toxicology data demonstrated biosimilarity between Benepali and the reference product Enbrel. The provided non-clinical comparability exercise testing strategy was considered as appropriate. Relevant regulatory guidelines were taken into consideration.

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.4. Clinical aspects

2.4.1. Introduction

The current line extension concerned the introduction of a new strength of Benepali. The 25 mg strength was presented in single-use pre-filled syringe containing 25 mg etanercept per 0.5 mL.

No new clinical studies were performed. Reference is made to the clinical data of the Benepali 50 mg single use PFS and the authorised 25 mg strength of the reference product Enbrel.

Benepali is already authorized presented in a single-use PFS and PFP containing 50 mg etanercept per mL to be administered via SC injection.

For the 25 mg strength the same indications were claimed as for the 50 mg strength. The lower dose will allow the option of a twice weekly administration of Benepali, which is in line with the reference product Enbrel.

Dosing in both pediatric indications is based on body weight. As Benepali, in contrast to Enbrel, is only available as a 25mg/50 mg single dose, the presentation is applicable only for pediatric patients with body weight equal or greater than 62.5 kg. A wording has been included in the PI, in section 4.2, stating that other etanercept products are available for pediatric patients that require less than a full 25mg/50 mg dose.

In accordance with the procedure applied for including the two paediatric indications juvenile idiopathic arthritis and paediatric plaque psoriasis (EMEA/H/C/004007/II/0019/G) recently approved for the 50 mg Benepali strength, the product information was updated accordingly.

2.4.2. Pharmacokinetics

The PK similarity was demonstrated between 50 mg/ml Benepali (SB4) and 50 mg/ml Enbrel in the initial marketing authorization application (EMEA/H/C/004007). Further PK studies with the introduction of the 25 mg strength were not considered necessary.

2.4.3. Pharmacodynamics

The clinical evidence of similarity for Benepali was demonstrated during the initial marketing authorization application (EMEA/H/C/004007). Further PD studies with the introduction of the 25 mg strength were not considered necessary.

2.4.4. Discussion on clinical pharmacology

The PK and PD similarity between Benepali and the reference product Enbrel was demonstrated at the time of the initial MA.

Compared to the approved strength (i.e. Benepali 50 mg), no changes were proposed to the manufacturing process of the new 25 mg strength with the exception of the filling volume (i.e. 1 ml and 0.5 ml, respectively). The composition and control of the drug product remain unchanged.

Therefore, comparative PK data demonstrating similarity of Benepali 50 mg to Enbrel can be extrapolated to the lower 25 mg dose.

2.4.5. Conclusions on clinical pharmacology

No new clinical pharmacology data have been submitted in this application, which was considered acceptable by the CHMP.

2.5. Clinical efficacy

This line extension introducing a lower dose of 25 mg of Benepali PFSs containing 25 mg etanercept per 0.5 mL corresponds to Enbrel containing 25 mg etanercept.

The applicant claims the same therapeutic indications for the proposed biosimilar Benepali 25 mg as granted for Enbrel 25 mg in the EU and also approved for the 50 mg strength of Benepali.

The introduction of the lower strength will allow a twice weekly administration of Benepali, which is approved for the reference product Enbrel 25 mg.

Therefore, no new clinical studies were performed for this line extension application.

2.5.1. Discussion on clinical efficacy

Biosimilarity of Benepali to Enbrel was demonstrated for the approved 50 mg strength, presented as solution for injection in a PFS and PFP during the initial application (EMEA/H/C/004007).

Compared to the approved strength (i.e. Benepali 50 mg), no changes were proposed to the manufacturing process of the new 25 mg strength with exception of the filling volume (i.e. 1 ml and 0.5 ml, respectively). The composition of the drug product remains unchanged.

For the applied 25 mg strength the same indiactions were claimed as for Benepali 50 mg. The introduction of the lower strength will allow a twice weekly administration of Benepali, which was approved for the reference product Enbrel 25 mg. Therefore the equivalence of a twice weekly regimen of 25 mg etanercept vs once weekly 50 mg was not assessed per se in this procedure.

No new clinical studies were performed. The applicant refers to the clinical data of the already authorised Benepali 50 mg solution for injection in PFS, which is considered acceptable.

According to the variation recently approved by EC (EMEA/H/C/004007/II/0019/G) for the 50 mg Benepali strength the MAH applied for the inclusion of two new indications for the treatment of juvenile idiopathic arthritis and paediatric plaque psoriasis.

For the treatment of adolescent patients with juvenile idiopathic arthritis fulfilling the criteria stated in section 4.1 of the SPC, a full 25 mg pre-filled syringe twice weekly for paediatric patients weighing 62.5 kg or more will be feasible. This is in line with the 50 mg strength and is considered acceptable.

In line with Enbrel, the dosage recommendation regarding paediatric plaque psoriasis is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly. According to these recommendations, treatment with the Benepali 25 mg pre-filled syringe will be in fact only possible for children weighing exactly 31.25 kg, which doesn't seem to be feasible.

Nevertheless, the indication and dosage recommendation is in line with the SmPC of Enbrel 25 mg pre-filled syringe. As with the 50 mg strength, treatment eligibility for children weighing ≥ 62.5 kg and alternative treatment options for paediatric patients weighing less than 62.5 kg are stated in section 4.2. Therefore the indication is considered acceptable.

The extrapolation of clinical efficacy data from the already approved Benepali 50 mg strength is appropriate, as similar efficacy had been demonstrated. According to the EMA guideline on "Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues", extrapolation from one disease model to other indications may be accepted based on the totality of the data i.e. quality, non-clinical and clinical evidence.

2.5.2. Conclusions on the clinical efficacy

The extrapolation of clinical efficacy data from the already approved Benepali 50 mg strength is appropriate, as similar efficacy had been demonstrated.

No new clinical efficacy data have been submitted in this application, which was considered acceptable by the CHMP.

2.6. Clinical safety

The MAH referred to the safety information of the already approved 50 mg strength of Benepali. Extrapolation of data gained from the Benepali 50 mg application is considered appropriate.

2.6.1. Discussion on clinical safety

No safety aspects were identified regarding the implementation of the additional new strength of 25 mg solution for injection in a prefilled syringe, which could diverge from the already approved 50 mg strength. Benepali 25 mg claims the same indications as already approved for the 50 mg strength, with the difference of a twice weekly administration regimen, which has already been approved for the reference product, Enbrel. An extrapolation of data gained from Benepali 50 mg was therefore considered appropriate.

2.6.2. Conclusions on the clinical safety

No new clinical safety data have been submitted in this application, which was considered acceptable by the CHMP.

2.6.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	<u>All indications</u> Malignancy (including lymphoma and leukaemia) Serious and opportunistic infections (including TB, Legionella, Listeria, parasitic infection) Lupus-like reactions Sarcoidosis and/or granulomas Injection site reactions Allergic reactions Severe cutaneous adverse reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome) Systemic vasculitis (including ANCA positive vasculitis) Macrophage activation syndrome Central demyelinating disorders

Summary of safety concerns	
	Peripheral demyelinating events (CIDP and GBS) Aplastic anaemia and pancytopenia Interstitial lung disease (including pulmonary fibrosis and pneumonitis) Autoimmune hepatitis Liver events in patients with history of viral hepatitis (including hepatitis B virus reactivation) <u>Specific indications:</u> Change in morphology and/or severity of psoriasis CHF in adult subjects Inflammatory bowel disease in JIA
Important potential risks	<u>All indications:</u> Autoimmune renal disease Pemphigus/pemphigoid Amyotrophic lateral sclerosis Myasthenia gravis Encephalitis/leukoencephalomyelitis Progressive multifocal leukoencephalopathy Liver failure Hepatic cirrhosis and fibrosis Severe hypertensive reactions Adverse pregnancy outcomes Potential for medication errors (pre-filled pen) Potential for male infertility Weight gain <u>Specific indications:</u> Impaired growth and development in juvenile subjects Acute ischemic CV events in adult subjects

Summary of safety concerns	
	Potential for off-label use and medication error in children.
Missing information	Use in hepatic and renal impaired subjects Use in different ethnic origins Use in pregnant women

Pharmacovigilance plan

Study/activity Type, title and category *(1-3)*	*Objectives*	*Safety concerns addressed*	Status (planned, *started)*	Date for submission of interim or final reports (planned *or actual)*
1. BSRBR-RA Category 3	An established nationwide register for patients with rheumatological disorders treated with biologic agents. The register is designed as a national prospective study whose primary purpose is to assess long-term toxicity from the use of these agents in routine practice.	Malignancy, serious and opportunistic infections, lupus-like reactions, sarcoidosis and/or granulomas, injection site reactions, allergic reactions, severe cutaneous adverse reactions, systemic vasculitis, macrophage activation syndrome, central demyelinating disorders, peripheral demyelinating events, aplastic anaemia and pancytopenia, interstitial lung disease, autoimmune hepatitis, liver events in patients with history of viral hepatitis, change in morphology and/or severity of psoriasis, CHF in adult subjects, autoimmune renal disease, pemphigus/pemphigoid, amyotrophic lateral sclerosis, myasthenia gravis, encephalitis/leukoencephalomyelitis, progressive multifocal leukoencephalopathy, liver failure, hepatic cirrhosis and fibrosis, severe hypertensive reactions, adverse pregnancy outcomes, potential for male infertility, weight gain, acute ischemic CV events, and use in pregnant women.	Planned for April 2016	Final report planned for 2027 Annual interim reports with PSUR/RMP updates where applicable
2. RABBIT Category 3	A prospective, observational cohort study whose objectives are to evaluate	Malignancy, serious and opportunistic infections, lupus-like reactions, sarcoidosis and/or granulomas, injection site reactions, allergic reactions, severe cutaneous	Planned for April 2016	Final report planned for 2027 Annual interim

Study/activity Type, title and category *(1-3)*	*Objectives*	*Safety concerns addressed*	Status (planned, *started)*	Date for submission of interim or final reports (planned *or actual)*
	the long-term effectiveness, safety, and costs associated with tumour necrosis factor-inhibitor therapies in the treatment of RA and to compare this to a cohort of RA patients who are treated with non-biologic DMARDs	adverse reactions, systemic vasculitis, macrophage activation syndrome, central demyelinating disorders, peripheral demyelinating events, aplastic anaemia and pancytopenia, interstitial lung disease, autoimmune hepatitis, liver events in patients with history of viral hepatitis, change in morphology and/or severity of psoriasis, CHF in adult subjects, autoimmune renal disease, pemphigus/pemphigoid, amyotrophic lateral sclerosis, myasthenia gravis, encephalitis/leukoencephalomyelitis, progressive multifocal leukoencephalopathy, liver failure, hepatic cirrhosis and fibrosis, severe hypertensive reactions, adverse pregnancy outcomes, potential for male infertility, weight gain, acute ischemic CV events, and use in pregnant women.		reports with PSUR/RMP updates where applicable
3. ARTIS Category 3	A national prospective, observational, uncontrolled cohort study whose objectives are to evaluate the risk of selected AEs in RA, juvenile Idiopathic arthritis, and other rheumatic disease patients treated with etanercept.	Malignancy, serious and opportunistic infections, lupus-like reactions, sarcoidosis and/or granulomas, injection site reactions, allergic reactions, severe cutaneous adverse reactions, systemic vasculitis, macrophage activation syndrome, central demyelinating disorders, peripheral demyelinating events, aplastic anaemia and pancytopenia, interstitial lung disease, autoimmune hepatitis, liver events in patients with history of viral hepatitis, change in morphology and/or severity of psoriasis, CHF in adult subjects, autoimmune renal disease, pemphigus/pemphigoid, amyotrophic lateral sclerosis, myasthenia gravis, encephalitis/leukoencephalomyelitis, progressive multifocal leukoencephalopathy, liver failure, hepatic cirrhosis and fibrosis, severe hypertensive reactions, adverse pregnancy outcomes, potential for	Planned for April 2016	Final report planned for 2027 Annual interim reports with PSUR/RMP updates where applicable

Study/activity Type, title and category *(1-3)*	*Objectives*	*Safety concerns addressed*	Status (planned, *started)*	Date for submission of interim or final reports (planned *or actual)*
		male infertility, weight gain, acute ischemic CV events, and use in pregnant women.		
4. BADBIR Category 3	A nationwide registry which seeks to assess the long-term safety of biologic treatments for psoriasis. Recommended by NICE that all patients in the UK receiving new therapies for psoriasis be registered in BADBIR.	Malignancy, serious and opportunistic infections, lupus-like reactions, sarcoidosis and/or granulomas, injection site reactions, allergic reactions, severe cutaneous adverse reactions, systemic vasculitis, macrophage activation syndrome, central demyelinating disorders, peripheral demyelinating events, aplastic anaemia and pancytopenia, interstitial lung disease, autoimmune hepatitis, liver events in patients with history of viral hepatitis, change in morphology and/or severity of psoriasis, CHF in adult subjects, autoimmune renal disease, pemphigus/pemphigoid, amyotrophic lateral sclerosis, myasthenia gravis, encephalitis/leukoencephalomyelitis, progressive multifocal leukoencephalopathy, liver failure, hepatic cirrhosis and fibrosis, severe hypertensive reactions, adverse pregnancy outcomes, potential for male infertility, weight gain, acute ischemic CV events, and use in pregnant women.	Planned for May 2016	Final report planned for 2027 Annual interim reports with PSUR/RMP updates where applicable
5. SB4-KO41- PMS Category 3	Korean Postmarketing Surveillance of BRENZYS	Malignancy, serious and opportunistic infections, lupus-like reactions, sarcoidosis and/or granulomas, injection site reactions, allergic reactions, severe cutaneous adverse reactions, systemic vasculitis, macrophage activation syndrome, central demyelinating disorders, peripheral demyelinating events, aplastic anaemia and pancytopenia, interstitial lung disease, autoimmune hepatitis, liver events in patients with history of viral hepatitis, change in morphology and/or severity of psoriasis, CHF in adult subjects, autoimmune renal disease, pemphigus/pemphigoid,	Started	Final report planned for 2019 Q

Study/activity Type, title and category *(1-3)*	*Objectives*	*Safety concerns addressed*	Status (planned, *started)*	Date for submission of interim or final reports (planned *or actual)*
		amyotrophic lateral sclerosis, myasthenia gravis, encephalitis/leukoencephalomyelitis, progressive multifocal leukoencephalopathy, liver failure, hepatic cirrhosis and fibrosis, severe hypertensive reactions, adverse pregnancy outcomes, potential for male infertility, weight gain, acute ischemic CV events, and use in pregnant women.		

Risk minimisation measures

Safety concern	Routine risk minimisation *measures*	Additional risk minimisation *measures*
Important Identified risks: All Indications		
Malignancy (including lymphoma and leukaemia)	**SmPC** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects	None proposed
Serious and opportunistic infections (including TB, Legionella, Listeria, parasitic infection)	**SmPC** Section 4.3 Contraindications Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects	Patient Alert Card
Lupus-like reactions	**SmPC** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects	None proposed
Sarcoidosis and/or granulomas	**SmPC** Section 4.8 Undesirable effects	None proposed
Injection site reactions	**SmPC** Section 4.8 Undesirable effects	None proposed
Allergic reactions	**SmPC** Section 4.3 Contraindications Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects	None proposed
Severe cutaneous adverse reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome)	**SmPC** Section 4.8 Undesirable effects	None proposed
Systemic vasculitis (including ANCA positive vasculitis)	**SmPC** Section 4.4 Special warnings and precautions for use	None proposed

Safety concern	Routine risk minimisation *measures*	Additional risk minimisation *measures*
	Section 4.8 Undesirable effects	
Macrophage activation syndrome	**SmPC** Section 4.8 Undesirable effects	None proposed
Central demyelinating disorders	**SmPC** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects	None proposed
Peripheral demyelinating events (CIDP and GBS)	**SmPC** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects	None proposed
Aplastic anaemia and pancytopenia	**SmPC** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects	None proposed
Interstitial lung disease (including pulmonary fibrosis and pneumonitis)	**SmPC** Section 4.8 Undesirable effects	
Autoimmune hepatitis	**SmPC** Section 4.8 Undesirable effects	
Liver events in patients with history of viral hepatitis (including HBV reactivation)	**SmPC** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects	
Important Identified Risks: Specific Indications		
Change in morphology and/or severity of psoriasis	**SmPC** Section 4.8 Undesirable effects	None proposed
CHF in adult subjects	**SmPC** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects	Patient Alert Card
Inflammatory bowel disease in JIA subjects	**SmPC** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects	None proposed
Important Potential Risks: All Indications		
Autoimmune renal disease	None proposed	None proposed
Pemphigus/pemphigoid	None proposed	None proposed
Amyotrophic lateral sclerosis	None proposed	None proposed
Myasthenia gravis	None proposed	None proposed
Encephalitis/leukoencephalomyelitis	None proposed	None proposed
Progressive multifocal leukoencephalopathy	None proposed	None proposed
Liver failure	None proposed	None proposed
Hepatic cirrhosis and fibrosis	None proposed	None proposed
Severe hypertensive reactions	None proposed	None proposed
Adverse pregnancy outcomes	**SmPC** Section 4.6 Fertility, Pregnancy and Lactation	None proposed
Potential for medication errors (PFP)	Clear Package Leaflet Instructions for use of the PFP	Educational programme for healthcare professionals and patients.
Potential for male infertility	None proposed	None proposed

Safety concern	Routine risk minimisation *measures*	Additional risk minimisation *measures*
Weight gain	None proposed	None proposed
Important Potential Risks: Specific Indications		
Impaired growth and development in juvenile subjects	None proposed	None proposed
Acute ischemic cardiovascular events in adult subjects	None proposed	None proposed
Potential for off label use and medication error in children	**SmPC** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Package leaflet Children and adolescents Side effects in children and adolescents	Patient Alert Card Educational programme for healthcare professionals and patients.
Important Missing Information: All Indications		
Use in hepatic and renal impaired subjects	**SmPC** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use	None proposed
Use in different ethnic origins	None proposed	None proposed
Use in pregnant women	**SmPC** Section 4.6 Fertility, Pregnancy and Lactation	None proposed

Conclusion

The CHMP and PRAC considered that the risk management plan version 5.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Benepali 50 mg pre-filled syringe. The bridging report submitted by the MAH has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Benepali (etanercept) is included in the additional monitoring list as a new biological product.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH submitted a line extension application to the marketing authorisation for Benepali (C/H/004007) to add a new strength of 25 mg solution for injection in a prefilled syringe.

The legal basis for this extension application is a similar biological application under Article 10(4) of Directive 2001/83/EC as amended.

The already authorised dosage form is presented in a single-use PFS and PFP containing 50 mg etanercept per mL to be administered via SC injection.

This line extension introducing a lower dose of 25 mg of Benepali PFSs containing 25 mg etanercept per 0.5 mL corresponds with Enbrel containing 25 mg etanercept.

The applicant claims the same therapeutic indications for the proposed biosimilar Benepali 25 mg as granted for Enbrel 25 mg in the EU. The indications comprise the use in moderate to severe rheumatoid arthritis (RA), psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, plaque psoriasis, non-radiographic axial spondyloarthritis and paediatric plaque psoriasis. These indications are also in line with the approved 50 mg strength of Benepali.

3.1.2. Available therapies and unmet medical need

The introduction of the lower dose will allow a twice weekly administration of Benepali in the claimed indications. This administration regimen is also approved for the 25 mg strength of the reference product.

3.1.3. Main clinical studies

No new clinical studies were presented by the applicant for the introduction of the 25 mg strength, presented in a prefilled syringe. Extrapolation to the data of the already approved 50 mg strength of Benepali demonstrating similarity to Enbrel is considered appropriate.

Biosimilarity of Benepali 50 mg was demonstrated in the initial marketing authorisation application.

3.2. Favourable effects

Compared to the approved strength (i.e. Benepali 50 mg), no changes were proposed to the manufacturing process of the new 25 mg strength with exception of the filling volume (i.e. 1 ml and 0.5 ml, respectively). The composition and control of the drug product remain unchanged.

Benepali is a biosimilar of Enbrel which has been approved in the course of procedure EMEA/H/C/004007/0000. Similarity of Benepali to Enbrel was demonstrated with regards to the primary, secondary and tertiary structure, glycosylation, post-translational modifications (PTMs) and biological activities. No changes questioning the initial similarity assessment were proposed with the present submission.

No new additional non-clinical data were submitted for this line extension. Originally submitted comparative pharmacodynamics, pharmacokinetic and toxicology data demonstrated biosimilarity between Benepali and the reference product Enbrel. The provided non-clinical comparability exercise testing strategy was considered as appropriate. Relevant regulatory guidelines were taken into consideration.

No new clinical data were submitted by the applicant. The applicant refers to the clinical data of the authorized Benepali 50 mg single use PFS and the authorised 25 mg strength of the reference product Enbrel. The lower strength will allow the option of a twice weekly administration of Benepali for most indications, which is in line with the recommendations of the reference product Enbrel 25 mg strength.

3.3. Uncertainties and limitations about favourable effects

There remain no uncertainties and limitations about favourable effects.

3.4. Unfavourable effects

No major unfavourable effects were identified.

3.5. Uncertainties and limitations about unfavourable effects

There remain no uncertainties and limitations about unfavourable effects.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

From a quality perspective, no major issues or risks were identified. Similarity to the reference product is not questioned, as the proposed manufacturing change is related to filling volume only. Taken together, the new strength can be approved.

No new clinical and non-clincal studies were presented. The applicant refers to the data gained from the clinical and non-clinical biosimilarity program of the 50 mg strength of Benepali where biosimilarity of Benepali to Enbrel had already been demonstrated. The extrapolation is considered acceptable, as the indications are the same as for the Benepali 50 mg strength, as well as for the 25 mg strength of Enbrel. No efficacy or safety concerns arise from the introduction of the additional 25 mg strength.

3.6.2. Balance of benefits and risks

The overall B/R of Benepali 25 mg solution for injection in pre-filled syringe is considered positive.

3.7. Conclusions

The overall B/R of Benepali is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, the CHMP considers by consensus that the risk-benefit balance of, Benepali 25 mg solution for injection in pre-filled syringe is favourable in the following indication:

Rheumatoid arthritis

Benepali in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.

Benepali can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Benepali is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Benepali, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Juvenile idiopathic arthritis

Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

Etanercept has not been studied in children aged less than 2 years.

Psoriatic arthritis

Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. Etanercept has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.

Axial spondyloarthritis

Ankylosing spondylitis

Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Non-radiographic axial spondyloarthritis

Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).

Plaque psoriasis

Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA) (see section 5.1).

Paediatric plaque psoriasis

Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

is positive.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Benepali subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

1. Prior to launch in each Member State, the MAH shall agree the final educational material with the competent authority in that Member State, consisting of information provided to all healthcare professionals expected to prescribe the product on the correct and safe use of the pre-filled pen/pre-filled syringes and to inform them that the product is not for use in children and adolescents who weigh less than 62.5 kg, and a Patient Alert Card which is to be given to patients using Benepali.

2. The healthcare professional's educational material should contain the following key elements:

- 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 use in children and adolescents who weigh less than 62.5 kg
- Instructional materials to share with patients.

3. The Patient Alert Card should contain the following key elements for patients treated with Benepali:

- The risk of opportunistic infections and tuberculosis (TB)
- The risk of Congestive Heart Failure (CHF)
- Benepali is not for use in children and adolescents who weigh less than 62.5 kg.