15 December 2016
EMA/25469/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Benepali

International non-proprietary name: etanercept

Procedure No. EMEA/H/C/004007/II/0019/G

Note

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

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1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Samsung Bioepis UK Limited (SBUK) submitted to the European Medicines Agency on 25 August 2016 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.2.b	C.I.2.b - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Change(s) require to be further substantiated by new additional data to be submitted by the MAH	Type II	I, II, IIIA and IIIB
C.I.2.b	C.I.2.b - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Change(s) require to be further substantiated by new additional data to be submitted by the MAH	Type II	I, II and IIIB

Extension of indication to include two new indications for the treatment of juvenile idiopathic arthritis and paediatric plaque psoriasis already approved for the reference medicinal product (Enbrel) for Benepali. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. Annex II, the Package Leaflet and Labelling are updated in accordance. The RMP (version 4.2) is also updated accordingly. Furthermore, the PI is brought in line with the latest QRD template version 10.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

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 applicant 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 applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Timetable	Actual dates
Submission date	25 August 2016
Start of procedure:	12 September 2016
CHMP Rapporteur Assessment Report	11 October 2016
PRAC Rapporteur Assessment Report	14 October 2016
PRAC Outcome	27 October 2016
CHMP members comments	21 October 2016
Updated CHMP Rapporteur Assessment Report	4 November 2016
Request for supplementary information (RSI) adopted by the CHMP on	10 November 2016
MAH's responses submitted to the CHMP on:	15 November 2016
Re-start of procedure	23 November 2016
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	30 November 2016
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	30 November 2016
CHMP members comments	5 December 2016
PRAC members comments	N/A
Joint PRAC/CHMP Rapporteurs' updated assessment report on the MAH's responses circulated on	7 December 2016
CHMP Opinion	15 December 2016

2. Scientific discussion

2.1. Introduction

The MAH is submitting as part of this application two type II variations (Category C.I.2.b) to apply for Benepali to be registered for two paediatric indications already approved for the reference product Enbrel: Juvenile idiopathic arthritis and Paediatric plaque psoriasis.

The MAH proposes to group the two submitted variations since the variation type and justification for claiming for extrapolation of both indications are the same. Adding to that, the mechanism of action of etanercept regarding the proposed indications (JIA and paediatric psoriasis) is TNF-a binding, which shares the same mechanism as to the approved indications of Benepali such as RA and psoriasis.

2.2. Non-clinical aspects

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

2.2.1. Discussion on non-clinical aspects

Biosimilarity has been demonstrated on non-clinical level with the initial marketing authorisation of Benepali. Extrapolation of these data to the newly applied indications is considered adequate to support this application from a non-clinical point of view.

2.2.2. Conclusion on the non-clinical aspects

This application is considered acceptable from a non-clinical perspective.

2.3. Clinical aspects

2.3.1. Pharmacokinetics

No new pharmacokinetic data was submitted.

2.3.2. Pharmacodynamics

No new pharmacodynamic data was submitted.

2.3.3. Discussion on clinical pharmacology

Pharmacokinetic equivalence, between the biosimilar product and innovator was demonstrated at the time of the initial MA. This data can be extrapolated from adult studies to the paediatric target population regarding the applied two new indications for the treatment of juvenile idiopathic arthritis and paediatric plaque psoriasis.

2.3.4. Conclusions on clinical pharmacology

Comparative Pharmacokinetics of Benepali to the reference product in healthy volunteers was demonstrated with the initial MAA, supported by pharmacokinetic measurements in a subset of RA patients.

2.4. Clinical efficacy

No new clinical studies were submitted.

2.4.1. Discussion on clinical efficacy

The newly applied indications are already approved for the reference product Enbrel.

This application relies on the data submitted for the reference product Enbrel in the proposed indications. 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.

Biosimilarity to Enbrel has already been demonstrated at the time of the initial MA.

Sufficient knowledge of pharmacodynamics properties of Enbrel, including binding to its target receptor(s) and intrinsic activity demonstrate the same mechanism of action across all the indications.

Therefore safety and efficacy results from the studies presented at the initial MAA are sufficient for extrapolation to the applied paediatric indications, already approved for the references product.

Dosing in both pediatric indications is based on body weight. As Benepali, in contrast to Enbrel, is only available as a 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 50 mg dose.

2.4.2. Conclusions on the clinical efficacy

This application is considered acceptable from a clinical point of view.

2.5. Clinical safety

No new safety data was submitted.

2.5.1. Discussion on clinical safety

The main safety issues for TNF-α inhibitors, including etanercept, are related with their immunosuppressive action. Long-term inhibition of TNF-α could lead to a serious impairment of defence mechanisms against infections (in particular opportunistic infections) and against the development of neoplasms.

With the initial marketing authorisation, safety / tolerability of Benepali has been compared against the safety / tolerability profile of Enbrel: Key safety information is derived from the clinical Phase III study SB4-G31-RA in RA patients as an appropriate study population for showing biosimilarity, supported by the

clinical Phase I study SB4-G11-NHV in healthy subjects. Overall, there was no apparent and meaningful difference in safety and tolerability in the clinical studies.

2.5.2. Conclusions on clinical safety

This application is considered acceptable from a safety point of view.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

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

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.2 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 4.2 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	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 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)
Important identified risks – specific indications	Change in morphology and/or severity of psoriasis Worsening of CHF in adult subjects Inflammatory bowel disease in JIA
Important potential risks – all indications	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
Important potential risks – specific indications	Impaired growth and development in juvenile subjects Acute ischemic CV events in adult subjects 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

Abbreviations: ANCA= anti-neutrophil cytoplasmic antibodies; CHF=congestive heart failure; CIDP=chronic inflammatory demyelinating polyneuropathy; CV=cardiovascular; GBS=Guillain-Barré Syndrome; TB=tuberculosis.

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, worsening of congestive heart failure (CHF), 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 the long-term	Malignancy, serious and opportunistic infections, lupus-like reactions, sarcoidosis and/or granulomas, injection site reactions, allergic reactions, severe cutaneous adverse reactions, systemic	Planned for April 2016	Final report planned for 2027 Annual interim reports with PSUR/RMP

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)
	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.	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, worsening of CHF, 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.		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, worsening of CHF, autoimmune renal disease, pemphigus/pemphigoid, amyotrophic	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)
		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.		
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, worsening of CHF, 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	Korean Post-marketing	Malignancy, serious and opportunistic infections, lupus-like	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)
Category 3	Surveillance of BRENZYS®	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, worsening of CHF, 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.		

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 Section 4.8 Undesirable effects	None proposed
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	**SmPC**	None proposed

(CIDP and GBS)	Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects	
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	None proposed
Autoimmune hepatitis	**SmPC** Section 4.8 Undesirable effects	None proposed
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	None proposed
Important Identified Risks: Specific Indications		
Change in morphology and/or severity of psoriasis	**SmPC** Section 4.8 Undesirable effects	None proposed
Worsening of 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
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	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

2.7. Update of the Product information

As a consequence of the new indications in juvenile idiopathic arthritis and in paediatric plaque psoriasis, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. Annex II, the Package Leaflet and Labelling are updated in accordance.

Dosing in both pediatric indications is based on body weight. As Benepali, in contrast to Enbrel, is only available as a 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 50 mg dose.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed and accepted by the CHMP.

3. Benefit-Risk Balance

This application concerns an extension of indication to include two new indications for the treatment of juvenile idiopathic arthritis and paediatric plaque psoriasis, already approved for the reference medicinal product (Enbrel) for Benepali.

The reference medicinal product may have more than one therapeutic indication. When biosimilar

comparability has been demonstrated in one indication, extrapolation of clinical data to other indications of the reference product is possible. 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.

No new clinical studies were submitted in this application. Biosimilarity of Benepali to Enbrel has been demonstrated on physiochemical, biological, non-clinical and clinical grounds with the initial marketing authorisation in January 2016. Knowledge of pharmacodynamic properties of Enbrel, including binding to its target receptor(s) and intrinsic activity demonstrate the same mechanism of action across all the indications.

Results from the data presented at the initial MAA are sufficient for extrapolation to the applied paediatric indications, already approved for the references product.

The benefit-risk balance for the newly proposed indications of Benepali is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.2.b	C.I.2.b - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Change(s) require to be further substantiated by new additional data to be submitted by the MAH	Type II	I, II, IIIA and IIIB
C.I.2.b	C.I.2.b - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Change(s) require to be further substantiated by new additional data to be submitted by the MAH	Type II	I, II and IIIB

Extension of indication to include two new indications for the treatment of juvenile idiopathic arthritis and paediatric plaque psoriasis already approved for the reference medicinal product (Enbrel) for Benepali. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. Annex II and the Package Leaflet are updated in accordance. The RMP (version 4.2) is also updated accordingly. Furthermore, the PI is brought in line with the latest QRD template version 10.

The group of variations leads to amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

This CHMP recommendation is subject to the following amended conditions:

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.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, 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.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include two new indications for the treatment of juvenile idiopathic arthritis and paediatric plaque psoriasis already approved for the reference medicinal product (Enbrel) for Benepali. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. Annex II and the Package Leaflet are updated in accordance. The RMP (version 4.2) is also updated accordingly.

Furthermore, the PI is brought in line with the latest QRD template version 10.

The group of variations leads to amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Summary

Please refer to the published assessment report Benepali H-C- 4007-II-19-G: EPAR - Assessment Report – Variation