EU Risk Management Plan for Benepali (Etanercept)

RMP version to be assessed as part of this application:

RMP Version number: 11.0

Data lock point for this RMP: Jul 10, 2025

Date of final sign off: Sep 08, 2025

Rationale for submitting an updated RMP:

The primary purpose of this RMP revision is to remove the important risks of “Aplastic Anaemia and Pancytopenia”, “Congestive Heart Failure in Adult Subjects” and “Acute Ischaemic Cardiovascular Events in Adults Subjects” to be aligned with the originator’s RMP.

Summary of significant changes in this RMP:

<Safety concerns>

Removal of “Aplastic Anaemia and Pancytopenia”, “Congestive Heart Failure in Adult Subjects” and “Acute Ischaemic Cardiovascular Events in Adults Subjects” to be aligned with the originator’s RMP.

<Risk minimisation measure>

Updated to reflect changes in version 11.0.

Other RMP versions under evaluation: None

Details of the currently approved RMP:

Version number: 10.0

Approved with procedure: EMA/VR/0000263971

Date of approval (opinion date): Jul 10, 2025

Qualified Person responsible for Pharmacovigilance (QPPV) oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

In the absence of QPPV, deputy QPPV's signature is provided below:

Name: Yana Luciana Corrieri

Signature: Signed by: Yana Corrieri Signer Name: Yana Corrieri Signing Reason: I approve this document Signing Time: 22-Sep-2025 | 00:20:38 PDT CA8D8528F8B54CE1B191B60678F0AD43

Date: : 22-Sep-2025 | 00:20:40 PDT

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
AE	Adverse events
ADR	Adverse drug reaction
AMI	Acute myocardial infarction
AS	Ankylosing spondylitis
AUC	Area under the curve
BADBIR	British Association of Dermatologists Biologic Interventions Register
CHMP	
CI	Congestive heart failure
CIDP	Committee for Medicinal Products for Human Use
CNS	Confidence interval
CV	Chronic inflammatory demyelinating polyneuropathy
DMARD	Central nervous system
DNA	Cardiovascular
EMA	Disease modifying anti-rheumatic drugs
EPAR	Deoxyribonucleic acid
EU	European Medicines Agency
FcRN	European Public Assessment Reports
FRET	European Union
GBS	Fc Receptor
GVP	Fluorescence Resonance Energy Transfer
HIV	Guillain-Barré syndrome
HLT	Good Pharmacovigilance Practices
IP	Human immunodeficiency virus
JIA	High level term
kDA	Investigational product
LT	Juvenile idiopathic arthritis
MAH	Kilodaltons
MedDRA	Lymphotoxin

MI	Marketing Authorisation Holder
MTX	Medical Dictionary for Regulatory Activities
NICE	Myocardial infarction
PFP	Methotrexate
PFS	National Institute for Health and Care Excellence
PK	Pre-filled pen
PL	Pre-filled syringe
PML	Pharmacokinetic
PRAC	Package Leaflet
PsA	Progressive multifocal leukoencephalopathy
PSUR	Pharmacovigilance Risk Assessment Committee
PT	Psoriatic arthritis
PV	Periodic Safety Update Report
QPPV	Preferred term
RA	Pharmacovigilance
RABBIT	Qualified Person responsibe for Pharmacovigilance
RMP	Rheumatoid arthritis
ROW	Rheumatoid Arthritis Observation of Biologic Therapy
SAE	Risk Management Plan
SmPC	Rest of the World
SMQ	Serious adverse event
SOC	Summary of Product Characteristics
TB	Standardised Medical Query
Th	System organ class
TNF	Tuberculosis
TNFR	T helper cell
US	Tumour Necrosis Factor
UK	Tumour necrosis factor receptor
	United States of America
	United Kingdom

PART I: PRODUCT(S) OVERVIEW

Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Etanercept
Pharmacotherapeutic group(s) (ATC Code)	L04AB01
Marketing Authorisation Holder	Samsung Bioepis NL B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Benepali
Marketing authorisation procedure	Centralized
Brief description of the product	Chemical class: Etanercept is a human tumour necrosis factor (TNF) receptor (TNFR) p75 Fc fusion protein produced by recombinant deoxyribonucleic acid (DNA) technology in a Chinese hamster ovary mammalian expression system. Etanercept is a dimer of a chimeric protein genetically engineered by fusing the extracellular ligand binding domain of human TNFR-2 (TNFR2/p75) to the Fc domain of human immunoglobulin (Ig) G1. This Fc component contains the hinge, CH_2 and CH_3 regions, but not the CH_1 region of IgG1. Etanercept contains 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons (kDa). The specific activity of etanercept is 1.7×10^6 units/mg.
	Summary of mode of action: Etanercept is a competitive inhibitor of TNF binding to its cell surface receptors, and thereby inhibits the biological activity of TNF (dominant cytokine in the inflammatory process of rheumatoid arthritis). Elevated levels of TNF are found in the synovium and psoriatic plaques of patients with psoriatic arthritis and in serum and synovial tissue of patients with ankylosing spondylitis. In plaque psoriasis, infiltration by inflammatory cells, including T-cells, leads to increased TNF levels in psoriatic lesions compared with levels in uninvolved skin.

	Important information about its composition: TNF and lymphotoxin are pro-inflammatory cytokines that bind to two distinct cell surface receptors: the 55-kDa (p55) and 75-kDa (p75) TNFRs. Both TNFRs exist naturally in membrane-bound and soluble forms. Soluble TNFRs are thought to regulate TNF biological activity. TNF and lymphotoxin exist predominantly as homotrimers, with their biological activity dependent on cross-linking of cell surface TNFRs. Dimeric soluble receptors, such as etanercept, possess a higher affinity for TNF than monomeric receptors and are considerably more potent competitive inhibitors of TNF binding to its cellular receptors. In addition, use of an immunoglobulin Fc region as a fusion element in the construction of a dimeric receptor imparts a longer serum half-life. Much of the joint pathology in rheumatoid arthritis and ankylosing spondylitis and skin pathology in plaque psoriasis is mediated by pro-inflammatory molecules that are linked in a network controlled by TNF. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biologic responses controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.
Hyperlink to the Product Information	Product Information
Indication(s) in the EEA	**Current**: Rheumatoid arthritis Psoriatic arthritis Ankylosing spondylitis Plaque psoriasis Non-radiographic axial spondyloarthritis Juvenile idiopathic arthritis (including polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis, adolescent psoriatic arthritis, adolescent enthesitis- related arthritis) Paediatric plaque psoriasis
	Proposed (if applicable): N/A
Dosage in the EEA	Current: **Adults** Rheumatoid arthritis 25 mg etanercept administered twice weekly is the recommended dose. Alternatively, 50 mg administered once weekly has been shown to be safe and effective.

	Psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis The recommended dose is 25 mg etanercept administered twice weekly, or 50 mg administered once weekly. For all of the above indications, available data suggest that a clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period. Plaque psoriasis The recommended dose of etanercept is 25mg administered twice weekly or 50 mg administered once weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25mg twice weekly or a dose of 50 mg once weekly. Treatment with Benepali should continue until remission is achieved, for up to 24 weeks. Continuous therapy beyond 24 weeks may be appropriate for some adult patients. Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with Benepali is indicated, the same guidance on treatment duration should be followed. The dose should be 25mg twice weekly or 50 mg once weekly. **Paediatric population** Juvenile idiopathic arthritis The recommended dose is 0.4 mg/kg (up to a maximum of 25 mg per dose), given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses or 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly. Discontinuation of treatment should be considered in patients who show no response after 4 months. Paediatric plaque psoriasis (age 6 years and above) The recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with Benepali is indicated, the above guidance on treatment duration should be followed. The dose should be 0.8 mg/kg (up to a maximum 50 mg per dose) once weekly. **Method of administration** Benepali is for subcutaneous use.
	Proposed: N/A
Pharmaceutical form(s) and strengths	Current: 25mg solution for injection in pre-filled syringe (PFS) 50 mg solution for injection in PFS 50 mg solution for injection in pre-filled pen (PFP)

	Proposed: N/A
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

This module is not required for a biosimilar in accordance with Good Pharmacovigilance Practices (GVP) Module V – Risk management systems Figure V.3, Requirements for new marketing applications.[1]

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity

As detailed in Table 1, reproductive toxicity, developmental toxicity or genotoxicity studies were not conducted as these routine toxicological studies are not required for biosimilars (in line with Committee for Medicinal Products for Human Use [CHMP] 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[1]).

Table 1: Summary of key safety findings from non-clinical studies and their relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Repeat dose toxicity: Benepali, the reference drugs (EU Enbrel or US Enbrel), or a vehicle control were administered subcutaneously twice weekly for 4 weeks to cynomolgus monkeys (3/sex) at dose levels of 1 or 15 mg/kg. In most animals, Benepali, EU Enbrel, and US Enbrel were well tolerated up to 15 mg/kg/dose with no reference- or Benepali-related effects on mean body weight, electrocardiography data, clinical pathology parameters, or ophthalmic findings, consistent with previous preclinical and clinical studies with Enbrel and other TNF-α inhibitors. Furthermore, there were no reference- or Benepali-related effects on the mean numbers of peripheral blood leukocyte subtypes, with the exception of 1 animal treated with Benepali at 15 mg/kg who showed a significant decrease in the number of peripheral blood leukocytes at study termination compared to pre-test. At terminal necropsy, microscopic findings attributed to Benepali or Enbrel was found in only 2 animals. Microscopic signs of acute/chronic inflammation/adhesion of the pericardium and heart were seen in 1 animal receiving US Enbrel at 1 mg/kg. The animal required early study termination on Day 17 due to severe clinical signs such as lethargy and breathing difficulties. In the other instance, microscopic changes in macrophages involving mainly spleen and liver were seen in 1 animal receiving Benepali at 15 mg/kg. In both cases, it was determined that these findings were likely due to pre-existing infections or conditions, which may have been exacerbated by the	The immunosuppressive properties of Benepali and Enbrel are well known and are part of the mechanism of action of these drugs. The Summary of Product Characteristics (SmPC) for Enbrel[1] and the proposed SmPC for Benepali include a special warning that patients should be evaluated for infections before, during, and after treatment with Enbrel/Benepali. In addition, the SmPCs for these products state that physicians should exercise caution when considering the use of Enbrel/Benepali in patients with a history of recurring or chronic infections or with underlying conditions that may predispose patients to infections, such as advanced or poorly controlled diabetes.

Key safety findings (from non-clinical studies)	Relevance to human usage
immunosuppressive properties of Enbrel/Benepali. The immunogenicity profile of Benepali was similar to those of EU Enbrel and US Enbrel. No significant differences were observed in measures of systemic exposure between Benepali, EU Enbrel and US Enbrel.	
Reproductive/Developmental toxicity: No reproductive studies were performed with Benepali in line with the EU guidance on biosimilar products (CHMP 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), which indicates that routine toxicological studies, such as reproduction toxicology, are not required.	Benepali has been developed as a biosimilar to Enbrel. Consequently, the reproductive/developmental toxicity package developed for Enbrel should be considered when considering this type of toxicity.
Genotoxicity/Carcinogenicity: No genotoxicity/carcinogenicity studies were performed with Benepali. Carcinogenicity studies were not conducted in line with the CHMP 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.	Benepali has been developed as a biosimilar to Enbrel. Consequently, the genotoxicity/carcinogenicity package developed for Enbrel should be considered when considering this type of toxicity.
Hepatotoxicity/Nephrotoxicity: No studies of hepatotoxicity or nephrotoxicity were performed with Benepali.	
Cardiotoxicity: No cardiotoxicity studies have been conducted in support of the safety profile of Benepali.	No effects on the cardiovascular (CV) system have been noted in non-clinical studies for the reference product, Enbrel. Since Benepali is being developed as a biosimilar, the safety profile of Enbrel can be considered with respect to cardiotoxicity. The SmPC for Enbrel and Benepali include the following warning in relation to congestive heart failure (CHF): Physicians should use caution when using Enbrel/Benepali in patients who have CHF. There have been post-marketing reports of worsening of CHF, with and without identifiable precipitating factors, in patients taking etanercept. Two large clinical trials evaluating the use of etanercept in the treatment of CHF were terminated early due to lack of efficacy. Although not conclusive, data from one of these trials suggest a possible tendency

Key safety findings (from non-clinical studies)	Relevance to human usage
	toward worsening CHF in those patients assigned to etanercept treatment.
Drug interactions: On the basis of the specificity of etanercept and the extensive clinical experience with the reference product, no non-clinical studies pertinent to drug interaction were conducted.	

Safety pharmacology

Safety pharmacology studies were not performed in line with the CHMP 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. Benepali has been developed as a biosimilar to Enbrel. Consequently, the safety pharmacology package developed for Enbrel should be considered when considering this type of toxicity.
Three in-vitro binding assays on tumour necrosis factor-alpha (TNF-α), lymphotoxin (LT)-α3 and neonatal Fc receptor (FcRn), and a cell based assay using the 293-Nuclear factor kappa B (NF-κB)-Luc cell line were performed because they are closely related to the mechanism of action of etanercept. The results from these studies are summarised in Table 2.

Table 2: Summary of comparative *in vitro* non-clinical pharmacology studies

Study title	Key findings
TNF-α binding assay	The relative binding activity of Benepali to TNF-α ligand was analysed by a fluorescence resonance energy transfer (FRET) assay. Based on the mean ± k standard deviation (SD) value of 23 different batches of European Union (EU) sourced Enbrel (EU Enbrel), the similarity range was set as 88%-114%. The results showed that Benepali and Enbrel were similar in terms of TNF-α binding.
LT-α3 binding assay	The relative binding activity of Benepali to LT-α3 ligand was analysed by a FRET assay. Based on the mean ± k SD value of 23 different batches of EU Enbrel, the similarity range was set as 84%-121%. The results showed that Benepali and Enbrel were similar in terms of LT-α3 binding.
FcRn Binding Assay	The FcRn binding affinity was analysed using Biacore. Based on the mean ± k SD value of 14 different batches of reference products, the similarity range of the KD of FcRn binding was set as 5936-12035 nM. The KD value of Benepali was 9603-12088 nM.

Study title	Key findings
	Although one batch was slightly outside the similarity range, results from a pharmacokinetic (PK) study in rats and a toxicology study in monkeys (see Table 3 and Table 1) suggested that the minor difference in FcRn binding affinity between Benepali and the reference products did not affect the PK profiles. Therefore, the FcRn binding affinities of Benepali and the reference products were similar.
NF-κB reporter gene assay	The inhibition level of NF-κB signalling was analysed by a reporter gene assay using the 293-NF-κB-Luc cell lines. By binding to TNF-α, etanercept prevents TNF-α binding to TNF receptor (TNFRs) on the cell surface and thus blocks the NF-κB signal pathway. NF-κB binds to the NF-κB binding motif connected to the luciferase reporter gene. Based on the mean ± k SD value of 14 different batches of EU Enbrel, the similarity range was set as 80%-129%. The results showed that Benepali and Enbrel were similar in terms of NF-κB signalling.

Two non-clinical studies have been performed, as summarised in Table 3, to assess the PK, efficacy and safety of Benepali in comparison to Enbrel and one non-clinical study, as summarised in Table 1, has been performed to assess the toxicity of Benepali in comparison to Enbrel. A PK study in rats was performed to evaluate the PK similarity of Benepali and Enbrel following single dose administration of 1 mg/kg Benepali or EU Enbrel by subcutaneous injection. In addition, the efficacy and side effects of Benepali were compared to those of EU Enbrel and United States of America (US) sourced Enbrel (US Enbrel) in a collagen antibody-induced, BALB/c mouse arthritis model. The key findings from these studies are summarised in Table 3 below.

Table 3: Summary of comparative *in vivo* pharmacokinetic and pharmacodynamics studies

Study title	Key findings
PK Study of Benepali in SD Rat (11-RK-331N)	Following single dose administration of 1 mg/kg Benepali or EU Enbrel by subcutaneous injection to male SD rats, the serum concentration-time profiles were similar between the Benepali and EU Enbrel-treated groups at 1 mg/kg. Moreover, there were no significant differences in maximum observed concentration (C_{max}), area under the curve (AUC) from the time of dosing to the last measurable concentration (AUC_{last}), time of maximum observed concentration (T_{max}) and terminal half-life ($T_{1/2}$) between the Benepali and EU Enbrel-treated groups at 1 mg/kg. In conclusion, these results suggest that PK profiles of Benepali injected subcutaneously at doses of 1 mg/kg are similar to those of EU Enbrel.

Study title	Key findings
Evaluation of Benepali for Suppression of Collagen Antibody-Induced Arthritis in BALB/c Mice (CAIA-e007)	The efficacy and side effects of Benepali were compared to those of EU Enbrel and US Enbrel in a collagen antibody-induced, BALB/c mouse arthritis model. A vehicle-treated control group was also included. Each article was tested at 1, 5, and 10 mg/kg given intraperitoneally once daily at 3-day intervals for 5 doses. Following arthritis induction with ArthritoMab/lipopolysaccharide, treatment responses to Benepali, EU Enbrel and US Enbrel indicated maximal or near maximal efficacy at 1 mg/kg. All test articles suppressed the development of arthritis by significantly reducing footpad volumes and clinical scores with no significant differences among treated groups. Thus, the effects of Benepali on arthritis progression in the mouse model were similar to those of EU Enbrel and US Enbrel. No deaths or group mean body weight losses occurred during this study. Distal tail necrosis was documented in 1-3 mice from each group on Day 8 due to the vein dilation technique, but did not impair the overall health of the animals. No other adverse effects were observed during the study.

The only non-clinical safety study was a comparative 4 week subcutaneous injection repeat dose subchronic toxicity study in cynomolgus monkeys designed to characterise the safety profile of Benepali compared to Enbrel. The toxicity profiles for both Benepali and Enbrel (EU and US sourced) were similar.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Safety data are available for Benepali or Enbrel in 2 clinical studies:

- Study SB4-G11-NHV, a randomised, single-blind, three-part, two-period, two-sequence, single-dose, cross-over study to compare the pharmacokinetics (PK), safety, tolerability and immunogenicity of 3 formulations of etanercept (Benepali, European Union [EU] sourced Enbrel [EU Enbrel] and United States of America [US] sourced Enbrel [US Enbrel]) in healthy male subjects.
- Study SB4-G31-RA, a randomised, double-blind, parallel group, multicentre clinical study to evaluate the efficacy, safety, PK and immunogenicity of Benepali compared to Enbrel in subjects with moderate to severe RA despite methotrexate (MTX) therapy. The study includes an open-label extension period (in Czech Republic and Poland) consisting of 48 weeks of active treatment and 4 weeks of safety follow-up to evaluate the long-term safety, tolerability, immunogenicity and efficacy of Benepali in subjects with RA treated previously with Benepali or Enbrel. Both the randomised, double-blind study and the extension period have been completed.

Exposure data are presented separately for the healthy volunteer study (SB4-G11-NHV) because subjects who received Benepali received a single dose of Benepali only. For this reason, exposure data are not tabulated for study SB4-G11-NHV, but are summarised in the paragraph below.

Study SB4-G11-NHV consisted of 3 parts. In each study part, 46 subjects were assigned in a 1:1 ratio to one of 2 sequences. In Part A, 46 subjects were randomised to receive a single dose of Benepali or EU Enbrel in Period 1 followed by the cross-over treatment in Period 2. In Part B, 46 subjects were randomised to receive a single dose of Benepali or US Enbrel in Period 1 followed by the crossover treatment in Period 2. In Part C, 46 subjects were randomised to receive a single dose of EU Enbrel or US Enbrel in Period 1 followed by the crossover treatment in Period 2. In Part A, 46 subjects received one 50 mg dose of Benepali and in Part B, 45 subjects received one 50 mg dose of Benepali. All subjects exposed to Benepali were male and all except 1 subject were white. The age of subjects exposed to Benepali ranged from 19 to 54 years.

Exposure data are available from a single Phase III clinical study in patients with RA. In the study SB4-G31-RA, patients with moderate to severe RA who had had an inadequate response to MTX and who had been on a stable dose of MTX for at least 4 weeks before screening were randomised in a 1:1 ratio to receive either Benepali 50 mg (n=299) or EU Enbrel 50 mg (n=297) once weekly for 52 weeks via subcutaneous injection. Benepali or EU Enbrel was co-administered with oral or parenteral MTX (10-25 mg/week) and folic acid (5-10 mg/week).

In 2 countries (Czech Republic and Poland), willing subjects who met pre-defined criteria could continue in an open-label extension period, consisting of 48 weeks of Benepali treatment. Those who were originally receiving EU Enbrel in the 52 week randomized double-blind period were switched to Benepali.

Exposure to Benepali in the study SB4-G31-RA is presented by duration of exposure in Table SIII.1 by age group and gender in Table SIII.2 and by ethnic or racial origin in Table SIII.3. The

total clinical exposure for Benepali is approximately 494.173 patient-years (Table SIII.1). Exposure is not presented by dose as all patients received the same dose of Benepali (50 mg). Exposure is not presented by special populations (e.g., pregnant women, lactating women, renal impairment, hepatic impairment, cardiac impairment, and immunocompromised) because these populations have been excluded from clinical studies.

Table SIII.1: Duration of exposure

Indication: Rheumatoid Arthritis		
Duration of exposure	**Patients**	**Person time**
Up to 3 months	418	104.482
3-6 months	407	100.562
6-9 months	400	98.403
9-12 months	388	80.192
Total person time		494.173

Table SIII.2: Age group and gender

Age group	**Patients**		**Person time**	
	M	**F**	**M**	**F**
< 65 years	55	306	62.584	368.285
≥ 65 to < 75 years	13	43	15.403	47.592
≥ 75 years	1	0	0.310	-
Total	69	349	78.297	415.877

Table SIII.3: Ethnic origin

Ethnic origin	**Patients**	**Person time**
White	397	476.055
Asian	12	10.962
American Indian or Alaskan Native	5	4.904
Hispanic or Latino	4	2.252
Total	418	494.173

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Hypersensitivity to the active substance or to any of the excipients

Reason for exclusion: Patients cannot be treated with Benepali if they have a known or suspected allergy or intolerance to Benepali or any components of the investigational product (IP).

Sepsis or risk of sepsis

Reason for exclusion: Patients cannot be treated with Benepali if they have sepsis or are at risk of acquiring sepsis.

Active infections, including chronic or localised infections

Reason for exclusion: Patients cannot be treated with Benepali if they have an active infection, including chronic or localized infection.

Live/live-attenuated vaccine within 8 weeks prior to randomisation

Reason for exclusion: The SmPC for Enbrel and the proposed SmPC for Benepali contain the following language[2,3]

"Live vaccines should not be given concurrently with Enbrel/Benepali. No data are available on the secondary transmission of infection by live vaccines in patients receiving Enbrel/etanercept."

Abnormal renal or hepatic function at screening

Reason for exclusion: Even though this is not considered a contraindication to Benepali treatment, exclusion of subjects with abnormal renal or hepatic function from clinical trials facilitates the evaluation and interpretation of new hepatic/renal events because any occurrences would not be confounded by pre-existing abnormal renal or hepatic function. This allows any possible relationship between the occurrence of such events and Benepali treatment to be evaluated.

Abnormal haematological parameters at screening

Reason for exclusion: The following text regarding haematologic reactions is included in Section 4.4 of the SmPC for Enbrel and the proposed SmPC for Benepali[2,3]

"Rare cases of pancytopenia and very rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients treated with Enbrel/etanercept. Caution should be exercised in patients being treated with Enbrel/Benepali who have a previous history of blood dyscrasias. All patients and parents/caregivers should be advised that if the patient develops signs and symptoms suggestive of blood dyscrasias or infections (e.g., persistent fever, sore throat, bruising, bleeding, paleness) whilst on Enbrel/Benepali, they should seek immediate medical

advice. Such patients should be investigated urgently, including full blood count; if blood dyscrasias are confirmed, Enbrel/Benepali should be discontinued."

In addition, thrombocytopenia, anaemia, leukopenia, neutropenia, pancytopenia and aplastic anaemia are included in the tabulated list of ADRs in Section 4.8 of the SmPC for Enbrel and the proposed SmPC for Benepali.[2,3]

Positive serological test for hepatitis B or hepatitis C or a known history of infection with human immunodeficiency virus (HIV)

Reason for exclusion: Although the presence of these laboratory abnormalities is not considered a contraindication to Benepali treatment, the exclusion of subjects with such serological results or known HIV infection assists in the evaluation and interpretation of occurrences of infectious hepatitis during clinical studies. This allows any possible relationship between the occurrence of such events and Benepali treatment to be evaluated without confounding medical history.

Section 4.4 of the SmPC for Enbrel and the proposed SmPC for Benepali includes a statement that the safety and efficacy of Enbrel/etanercept in patients with immunosuppression have not been evaluated.[2,3]

Current diagnosis of active tuberculosis (TB), recent exposure to TB or evidence of a latent TB infection

Reason for exclusion: The SmPC for Enbrel and the proposed SmPC for Benepali include the following contraindication in Section 4.3[2,3]:

Treatment with Enbrel/Benepali should not be initiated in patients with active infections, including chronic or localised infections. Furthermore, Section 4.4 of the SmPCs includes warnings concerning TB and recommends evaluation of all patients for active and latent infection prior to initiation of Enbrel/Benepali treatment. If active TB is diagnosed, Enbrel/Benepali therapy must not be initiated. If inactive (latent) TB is diagnosed, treatment for latent TB must be started with anti-TB therapy before the initiation of Enbrel/Benepali, in accordance with local recommendations. In this situation, the benefit/risk balance of Enbrel/Benepali therapy should be very carefully considered.

Have a history of an infected joint prosthesis which has not been removed or replaced

Reason for exclusion: This may represent a possible chronic infection and patients with an infection should not be treated with Benepali.

Bone marrow hypoplasia which, in the opinion of the Investigator, will put the subject at risk if they are enrolled

Reason for exclusion: The following text regarding haematologic reactions is included in Section 4.4 of the SmPC for Enbrel and the proposed SmPC for Benepali[2,3]:

"Rare cases of pancytopenia and very rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients treated with Enbrel/etanercept. Caution should be exercised in patients being treated with Enbrel/Benepali who have a previous history of blood dyscrasias.

All patients and parents/caregivers should be advised that if the patient develops signs and symptoms suggestive of blood dyscrasias or infections (e.g., persistent fever, sore throat, bruising, bleeding, paleness) whilst on Enbrel/Benepali, they should seek immediate medical advice. Such patients should be investigated urgently, including full blood count; if blood dyscrasias are confirmed, Enbrel/Benepali should be discontinued."

In addition, thrombocytopenia, anaemia, leukopenia, neutropenia, pancytopenia and aplastic anaemia are included in the tabulated list of adverse drug reactions (ADRs) in Section 4.8 of the SmPC for Enbrel and the proposed SmPC for Benepali.[2,3]

Significant systemic RA involvement (e.g., vasculitis, pulmonary fibrosis, etc.) which, in the opinion of the Investigator, will put the subject at risk if they are enrolled

Reason for exclusion: This exclusion criterion was included to allow the investigator to use his/her judgement and exclude significant systemic RA involvement that could put the subject at risk if they were enrolled in the study.

History of any malignancy within the 5 years prior to screening except completely excised and cured squamous carcinoma of the uterine cervix, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma

Reason for exclusion: Section 4.8 of the SmPC for Enbrel and the proposed SmPC for Benepali describes reports of various malignancies in clinical studies with etanercept and from post-marketing data.

In addition, the following are listed in the tabulated list of ADRs: non-melanoma skin cancers, lymphoma, melanoma, leukaemia, and Merkel cell carcinoma.[2,3]

History of lymphoproliferative disease including lymphoma

Reason for exclusion: Section 4.8 of the SmPC for Enbrel and the proposed SmPC for Benepali describes reports of lymphoma in clinical studies with etanercept and from post-marketing data.

In addition, lymphoma is included in the tabulated list of ADRs in Section 4.8.[2,3]

History of CHF (NYHA Class III/IV) or unstable angina

Reason for exclusion: Section 4.4 of the SmPC for Enbrel and the proposed SmPC for Benepali includes the following language[2,3]:

"Physicians should use caution when using Enbrel/Benepali in patients who have CHF. There have been post-marketing reports of worsening of CHF, with and without identifiable precipitating factors, in patients taking Enbrel/etanercept. Two large clinical trials evaluating the use of Enbrel/etanercept in the treatment of CHF were terminated early due to lack of efficacy. Although not conclusive, data from one of these trials suggest a possible tendency toward worsening CHF in those patients assigned to Enbrel/etanercept treatment."

Uncontrolled diabetes mellitus or uncontrolled hypertension

Reason for exclusion: Section 4.4 of the SmPC for Enbrel and the proposed SmPC for Benepali includes the following language[2,3]:

"There have been reports of hypoglycaemia following initiation of Enbrel/etanercept in patients

receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients."

History of organ transplantation

Reason for exclusion: To avoid modulation of cellular immune responses and possible additional immunosuppression over agents used to prevent organ rejection, which could increase the frequency of infections or other serious adverse events (SAEs).

Physical incapacitation (American College of Rheumatology [ACR] Functional Class IV or wheelchair-/bed-bound)

Reason for exclusion: Subjects with physical incapacitation were excluded as they would not have been able to attend the study visits or fulfil the requirements of the study and would have confounded the efficacy assessment.

History of demyelinating disorders (such as multiple sclerosis or Guillain-Barré syndrome (GBS))

Reason for exclusion: Although not considered a contraindication to treatment, exclusion of subjects with a history of demyelinating disease was intended to ensure that any new events were not confounded by the presence of previously diagnosed demyelinating disease. This allowed any possible relationship between new-onset demyelinating disease and treatment with Benepali to be better evaluated. Sections 4.4 and 4.8 of the SmPC for Enbrel and the proposed SmPC for Benepali include information regarding demyelinating disease.[2,3]

The following language is included in Section 4.4:

"There have been rare reports of central nervous system (CNS) demyelinating disorders in patients treated with Enbrel/etanercept. Additionally, there have been very rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), demyelinating polyneuropathy, and multifocal motor neuropathy). Although no clinical trials have been performed evaluating Enbrel/etanercept therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity. A careful risk/benefit evaluation, including a neurologic assessment, is recommended when prescribing Enbrel/Benepali to patients with pre-existing or recent onset of demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease."

Any other disease or disorder which, in the opinion of the Investigator, will put the subject at risk if they are enrolled

Reason for exclusion: This exclusion criterion was included to allow the Investigator to use his/her judgement and exclude other medical conditions not specified that could put the subject at risk if they were enrolled in the study. It is in keeping with good medical practice not to enrol patients in clinical studies who have serious diseases or disorders other than the disease state under study.

Have or have had a substance abuse (alcohol or drug) problem within the 3 years prior to screening

Reason for exclusion: This represents a standard exclusion criterion in clinical trials of an IP.

Usually, such patients will not be included in clinical trials because they often have no compliance with study procedures and IP. Additionally, they may have other diseases which may appear suddenly.

During the study periods, 'importance' of individual exclusion criterion was not discussed. Also, whether or not each criterion is subject for 'missing information' was not assessed. Instead, as a biosimilar of Enbrel, missing information of Benepali is aligned with that of reference product, based on the EMA guide on similar biological medicinal products. In response to the the EMA comments from Benepali Periodic Safety Update Report (PSUR) no.5 Assessment Report, the following safety concerns have been removed:

- Missing information "use in pregnant women", "use in hepatic and renal impairment patients", and "use in patients of different ethnic groups"
- Important identified risk "injection-site reactions"

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare (i.e., > 1/10,000 to < 1/1000) or very rare (i.e., < 1/10,000) adverse reactions, adverse reactions that are dose-related, due to prolonged exposure, long latency, or adverse reactions which occur in other claimed indications: adult psoriatic arthritis (PsA), adult ankylosing spondylitis (AS), plaque psoriasis, and non-radiographic axial spondyloarthritis, juvenile idiopathic arthritis (JIA) and paediatric plaque psoriasis.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.3: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Paediatric population	Not included in the clinical development program
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program

Type of special population	Exposure
Population with relevant different ethnic origin	Most subjects enrolled in the two clinical studies (SB4-G11-NHV and SB4-G31-RA) were Caucasian in origin (all but 1 subject in study SB4-G11-NHV and 93.3% of Benepali-treated patients in study SB4-G31-RA) but these studies also enrolled subjects of other racial or ethnic origins. There are no known obvious safety or tolerability differences with regard to race and/or ethnic origin in etanercept.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Benepali sales data was obtained from the marketing partners (EU: Biogen, United Kingdom (UK): Biogen, Rest of the World (ROW): Organon, Yuhan, Bionovis) from the date of launch to Dec 31, 2022. In EU, the United Kingdom, Canada, Australia, Korea, Switzerland, Israel, and Brazil, Benepali was sold as both PFP and PFS form for this period. The PFS is authorised to contain either 25 mg (in EU, UK, Switzerland, and the United States only) or 50 mg etanercept; the PFP contains 50 mg etanercept. Exposure was estimated using the World Health Organisation Defined Daily Dose for etanercept (7 mg/day).

SV.1.2 Exposure

Cumulatively, from the International Birth Date of Sep 07, 2015 to Dec 31, 2024 approximately [redacted] units of etanercept 50mg and [redacted] units of etanercept 25mg were sold, equivalent to 781,032 and 10,429 patient-years respectively. Table SV.1 presents the exposure data by region.

Table SV.1: Exposure table by region

Region	SB4 50mg		SB4 25mg	
	Units Sold (PFP and/or PFS)	Estimated Exposure (Patient-Years)[a]	Units Sold (PFS)	Estimated Exposure (Patient-Years)[a]
EU	[redacted]	441,964	[redacted]	8,079
UK	[redacted]	212,788	[redacted]	2,345
Switzerland	[redacted]	1,292	[redacted]	5
Canada	[redacted]	29,869	-	-
Australia	[redacted]	18,266	-	-
Brazil	[redacted]	70,238	-	-
Israel	[redacted]	655	-	-
Republic of Korea	[redacted]	5,960	-	-
Total	[redacted]	781,032	[redacted]	10,429

[a]Total number of patient years = [redacted])*(25 or 50 mg/unit) / (7mg)*[redacted] patient days/years)

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

No information is available regarding the potential for misuse of etanercept for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable as the risks are aligned with those of the reference product.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Based on the EMA guide on similar biological medicinal products, the RMP should take into account the risks associated with the use of the reference product. The following risks are the safety concerns of both Benepali and the reference product, Enbrel.

Important identified risks	Important potential risks	Missing information
• Malignancy (including lymphoma and leukaemia) • Serious and opportunistic infections (including TB, Legionella, Listeria, parasitic infection) • Demyelinating disorders • Aplastic anaemia and pancytopenia • CHF in adult subjects	• Encephalitis/leukoencephalomyelitis • Progressive multifocal leukoencephalopathy • Impaired growth and development in juvenile subjects • Acute ischemic CV events in adult subjects	None

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

The following important identified risks have been removed from the RMP to be aligned with Originator`s RMP

- Congestive heart failure in adult subjects
- Aplastic anaemia and pancytopenia

The following important potential risk has been removed from the RMP to be aligned with Originator`s RMP

- Acute ischemic CV events in adult subjects

SVII.3 Details of important identified risks, important potential risks, and missing information

Based on the European Medicines Agency (EMA) guide on similar biological medicinal

products[1], the RMP should take into account identified and potential risks associated with the use of the reference product. So, this section will contain all the important identified risks and important potential risks described in the European Public Assessment Report (EPAR) for the reference product, Enbrel, and from the scientific literature.

The SB4-G31-RA study was conducted in patients with moderate to severe RA. There was no safety concern newly detected from this study and it has been concluded that the Benepali safety profile was comparable with that of Enbrel.

The reference product, Enbrel, has been used in clinical practice for more than 10 years and the risk profile is well known.

For each risk presented in this section, the clinical trial safety database was searched for specified events using Standardized Medical Query (SMQ)/High level group terms, preferred terms (PTs), High level and search stems for that risk based on Medical Dictionary for Regulatory Activities (MedDRA) version 16.0. (Refer to Annex 7 for the specific adverse event terms and/or stems used for risks analysis.)

SVII.3.1 Presentation of important identified risks and important potential risks

Malignancy (including lymphoma and leukaemia)

Potential mechanisms: The exact mechanism is unknown, but tumour necrosis factor-alpha (TNF-α) plays an important role in the immune response. Therefore, it might be proposed that suppression with a TNF-α blocking agent such as etanercept might contribute to a reduced immune response increasing the risk of developing malignancies.

Evidence source(s) and strength of evidence: Study SB4-G31-RA; proposed Summary of Product Characteristics (SmPC) for Benepali, section 4.4 ‘Special warnings and precautions for use’; referenced scientific publications.

Characterisation of the risk:

- Frequency with 95 % confidence interval (CI)

Frequency in the Benepali clinical study (SB4-G31-RA)

There were 5 events of malignancy in 5 patients treated with Benepali (subject incidence: 1.196 %; 95% CI: 0.390 %, 2.769 %), 1 event each of adenocarcinoma gastric, hepatic cancer, breast cancer, basal cell carcinoma, and lung cancer metastatic. This corresponded to an exposure adjusted event rate of 1.012 events per 100 patient-years (95% CI: 0.329 , 2.361). There was 1 event of malignancy (invasive ductal breast carcinoma) in 1 patient treated with Enbrel (subject incidence: 0.337%; 95% CI: 0.009%, 1.862%), corresponding to an exposure adjusted event rate of 0.380 events per 100 patient-years (95% CI: 0.010, 2.117).

No cases of lymphoproliferative disorders including lymphoma were reported in the Benepali clinical study (SB4-G31-RA).

Table 1: Subject incidence and exposure-adjusted rate of malignancy (including lymphoma and leukaemia)[a]

Indication	Drug	Total Subjects N	No. of Subjects with Event N1 (%)[b]	95% CI of Event Rate	Exposure (Patient-years) E	No. of Events n	Exp-Adj Event Rate[c]	Exp-Adj Rate 95% CI
RA	Enbrel 50 mg	297	1 (0.337)	0.009, 1.862	263.238	1	0.380	0.010, 2.117
	Benepali 50 mg	418	5 (1.196)	0.390 , 2.769	494.173	5	1.012	0.329 , 2.361

[a] One patient with neoplasm was excluded since it turned out to be foot osteophyte with rheumatoid nodule.
[b] Subject incidence = N1/N × 100.
[c] Exposure-adjusted (Exp-Adj) event rate per 100 patient-years = n/E × 100.

- Seriousness/outcomes

In the Benepali clinical study (SB4-G31-RA), 4 events of malignancy (adenocarcinoma gastric, hepatic cancer, breast cancer, and lung cancer metastatic) in the Benepali treatment group were considered serious (0.809 events per 100 patient-years; 95% CI: 0.221 , 2.072). In the Enbrel treatment group, the event of invasive ductal breast carcinoma was considered serious (0.380 events per 100 patient-years; 95% CI: 0.010, 2.117).

Table 2: Subject incidence and exposure-adjusted rate of malignancy (including lymphoma and leukaemia) that were SAEs

Indication	Drug	Total Subjects N	No. of Subjects with Event N1 (%)[a]	95% CI of Event Rate	Exposure (Patient-years) E	No. of Events n	Exp-Adj Event Rate[b]	Exp-Adj Rate 95% CI
RA	Enbrel 50 mg	297	1 (0.337)	0.009, 1.862	263.238	1	0.380	0.010, 2.117
	Benepali 50 mg	418	4 (0.957)	0.261 ,2.432	494.173	4	0.809	0.221 , 2.072

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-Adj) event rate per 100 patient-years = n/E × 100.

In the Benepali treatment group, the outcomes of the malignancy events were fatal for the event of adenocarcinoma gastric and hepatic cancer, resolved with sequelae for the event of breast cancer, not resolved for the event of lung cancer metastatic, and resolved for the event of basal cell carcinoma. In the Enbrel treatment group, the outcome of the event of invasive ductal breast carcinoma was resolved with sequelae.

- Severity and nature of risk

In the Benepali clinical study (SB4-G31-RA), 3 of the reported events in the Benepali treatment group (adenocarcinoma gastric, hepatic cancer and lung cancer metastatic) were considered severe in severity (0.607 events per 100 patient-years; 95% CI: 0.125, 1.774). In the Enbrel treatment group, the event of invasive ductal breast carcinoma was considered

severe in severity (0.380 events per 100 patient-years; 95% CI: 0.010, 2.117).

Table 3: Subject incidence and exposure-adjusted rate of malignancy (including lymphoma and leukaemia) that was severe

Indication	Drug	Total Subjects N	No. of Subjects with Event N1 (%)[a]	95% CI of Event Rate	Exposure (Patient-years) E	No. of Events n	Exp-Adj Event Rate[b]	Exp-Adj Rate 95% CI
RA	Enbrel 50 mg	297	1 (0.337)	0.009, 1.862	263.238	1	0.380	0.010, 2.117
	Benepali 50 mg	418	3 (0.718)	0.148 , 2.083	494.173	3	0.607	0.125 , 1.774

[a] Subject incidence = N1/N × 100.

[b] Exposure-adjusted (Exp-Adj) event rate per 100 patient-years = n/E × 100.

- Impact on individual patient

Malignancy can directly affect a patient's physical functioning and lifespan and have a severe effect on the patient's quality of life. Potential effects will depend on the individual patient and other factors including, site of malignancy, tolerance to treatment and degree of social and emotional support. The gravity of the diagnosis and fear about the effects of malignancy can also cause psychological distress.

Risk factors and risk groups: The overall risk of malignancy including cutaneous and non-cutaneous cancers has been reported to be higher in patients with rheumatoid arthritis (RA) compared with healthy subjects.[4,5]

In addition, the proposed SmPC for Benepali states that there is an increased background risk for lymphoma and leukaemia in RA patients with long-standing, highly active, inflammatory disease.

Studies have shown that patients with RA have an approximately 2-fold increased risk of lymphoma and leukaemia, a 20% to 50% increased risk of respiratory tract cancer, and a 70% increased risk of non-melanoma skin cancers, but a decreased risk for breast and colorectal cancer.[3,4,6]

Preventability: No preventable measures.

The potential role of TNF-blocking therapy in malignancy is not known.

Impact on the risk-benefit balance of the product: Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place

Public health impact: Not applicable.

Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, parasitic infection)

Potential mechanisms: Due to suppression of an immune response, the immune system is unable to mount an efficient response against infection. This may lead to serious consequences, a life-threatening situation or even death.

Evidence source(s) and strength of evidence: Study SB4-G31-RA; referenced scientific

publications.

Characterisation of the risk:

- Frequency with 95 % confidence interval (CI)

Frequency in the Benepali clinical study (SB4-G31-RA)

There were 24 events of serious or opportunistic infections in 15 patients treated with Benepali (subject incidence: 3.589 %; 95% CI: 2.022 %, 5.850 %), corresponding to an exposure adjusted event rate of 4.857 events per 100 patient-years (95% CI: 3.112, 7.226). There were 19 events of serious or opportunistic infections in 17 patients treated with Enbrel (subject incidence: 5.724 %; 95% CI: 3.369 %, 9.007 %), corresponding to an exposure adjusted event rate of 7.218 events per 100 patient-years (95% CI: 4.346, 11.271). There were no cases of tuberculosis (TB).

Table 4: Subject incidence and exposure-adjusted rate of serious and opportunistic infections

Indication	Drug	Total Subjects N	No. of Subjects with Event N1 (%)[a]	95% CI of Event Rate	Exposure (Patient-years) E	No. of Events n	Exp-Adj Event Rate[b]	Exp-Adj Rate 95% CI
RA	Enbrel 50 mg	297	17 (5.724)	3.369 , 9.007	263.238	19	7.218	4.346 , 11.271

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-Adj) event rate per 100 patient-years = n/E × 100.

- Seriousness/outcomes

In the Benepali clinical study (SB4-G31-RA), the events liver abscess, pneumonia, bronchitis and peritonitis of the Benepali treatment group were considered serious (0.809 events per 100 patient-years; 95% CI: 0.221, 2.072). In the Enbrel treatment group, 5 events were considered serious (1.899 events per 100 patient-years; 95% CI: 0.617, 4.433), 1 event each of appendicitis, pneumonia, and erysipelas and 2 events of cellulitis.

The outcome of all serious or opportunistic infections in the Benepali treatment group was recovered/resolved.

Table 5: Subject incidence and exposure-adjusted rate of serious and opportunistic infections that were SAEs

Indication	Drug	Total Subjects N	No. of Subjects with Event N1 (%)	95% CI of Event Rate	Exposure (Patient-years) E	No. of Events n	Exp-Adj Event Rate	Exp-Adj Rate 95% CI
RA	Enbrel 50 mg	297	5 (1.684)	0.549 3.885	263.238	5	1.889	0.617 4.433
	Benepali 50mg	418	3 (0.718)	0.148 2.083	494.172	4	0.809	0.221,2.072

- Severity and nature of risk

In the Benepali clinical study (SB4-G31-RA), the events of pneumonia was considered severe in severity. In the Enbrel treatment group, 2 events (appendicitis and erysipelas) were considered severe in severity (0.760 events per 100 patient-years; 95% CI: 0.092, 2.745).

Table 6: Subject incidence and exposure-adjusted rate of serious and opportunistic infections that were severe

Indication	Drug	Total Subjects N	No. of Subjects with Event N1 (%)[a]	95% CI of Event Rate	Exposure (Patient-years) E	No. of Events n	Exp-Adj Event Rate[b]	Exp-Adj Rate 95% CI
RA	Enbrel 50 mg	297	2 (0.673)	0.082, 2.411	263.238	2	0.760	0.092, 2.745
	Benepali 50 mg	418	1 (0.239)	0.006, 1.326	494.173	1	0.202	0.005,1.127

[a] Subject incidence = N1/N × 100.

[b] Exposure-adjusted (Exp-Adj) event rate per 100 patient-years = n/E × 100.

- Impact on individual patient

Serious and opportunistic infections can influence the patient's quality of life and overall health. Some of these infections might lead to hospitalisation, long-lasting antimicrobial therapy, and sometimes even result in death. It is important to identify the infection as early as possible. In patients who are incapable of mounting a normal immune response, such infections might be difficult to cure.

Risk factors and risk groups: The patients who are on concomitant immunosuppressive therapy, in addition to their underlying disease, can be predisposed to infection.

Preventability: No preventable measures to prevent serious infections.

The SmPC and package leaflet (PL) for Benepali contain all relevant information concerning serious and opportunistic infections. The patient should be evaluated for infections before, during and after treatment with Benepali.

Impact on the risk-benefit balance of the product: Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place

Public health impact: Not applicable.

Demyelinating disorders

Potential mechanisms: TNF blockade augments the number of peripheral T cells which in turn enhances auto-immune responses by changing the function of antigen presenting cells, potentiating signalling of T-cell receptor and/or reducing the apoptosis of autoreactive T-cells that may target neurons. This sequence of events leads to development of drug-induced demyelination.[7,8]

Evidence source(s) and strength of evidence: Study SB4-G31-RA; proposed SmPC for Benepali, Section 4.4 'Special warnings and precautions for use'; referenced scientific publications.

Characterisation of the risk:

- Frequency with 95 % confidence interval (CI)

Frequency in the Benepali clinical study (SB4-G31-RA)

There were no reports of central demyelinating disorders in either the Benepali or Enbrel treatment groups.

- Seriousness/outcomes

There were no reports of serious central demyelinating disorders in either the Benepali or Enbrel treatment groups.

- Severity and nature of risk

There were no reports of severe central demyelinating disorders in either the Benepali or Enbrel treatment groups.

- Impact on individual patient

Central demyelinating disorders can have a significant impact on a patient's quality of life given the severe nature of the symptoms of conditions such as multiple sclerosis, and the negative impact on a patient's physical functioning, as well as increased morbidity and mortality.

Risk factors and risk groups: Patients with pre-existing or recent-onset central demyelinating disorders.

Preventability: According to the proposed SmPC for Benepali, Section 4.4 'Special warnings and precautions for use', a careful risk/benefit evaluation, including a neurologic assessment, is recommended when prescribing Benepali to patients with pre-existing or recent onset of demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease.

Impact on the risk-benefit balance of the product: Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place

Public health impact: Not applicable.

Encephalitis/leukoencephalomyelitis

Potential mechanisms: The exact mechanism is unknown.

Evidence source(s) and strength of evidence: Study SB4-G31-RA.

Characterisation of the risk:

- Frequency with 95 % confidence interval (CI)

Frequency in the Benepali clinical study (SB4-G31-RA)

There were no reports of encephalitis/leukoencephalomyelitis in either the Benepali or Enbrel treatment groups.

- Seriousness/outcomes

There were no reports of serious encephalitis/leukoencephalomyelitis in either the Benepali or

Enbrel treatment groups.

- Severity and nature of risk

There were no reports of severe encephalitis/leukoencephalomyelitis in either the Benepali or Enbrel treatment groups.

- Impact on individual patient

Encephalitis/leukoencephalomyelitis can significantly impact a patient's quality of life given the co-morbidities associated with these CNS inflammatory conditions.

Risk factors and risk groups: Patients with pre-existing or recent onset of encephalitis/leukoencephalomyelitis.

Preventability: Prescribers should exercise caution in considering the use of Benepali in patients with pre-existing or recent-onset encephalitis/leukoencephalomyelitis.

Impact on the risk-benefit balance of the product: Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place

Public health impact: Not applicable.

Progressive multifocal leukoencephalopathy

Potential mechanisms: Not applicable.

Evidence source(s) and strength of evidence: Study SB4-G31-RA; referenced scientific publications.

Characterisation of the risk:

- Frequency with 95 % confidence interval (CI)

Frequency in the Benepali clinical study (SB4-G31-RA)

There were no reports of progressive multifocal leukoencephalopathy (PML) in either the Benepali or Enbrel treatment groups.

- Seriousness/outcomes

There were no reports of serious PML in either the Benepali or Enbrel treatment groups.

- Severity and nature of risk

There were no reports of severe PML in either the Benepali or Enbrel treatment groups.

- Impact on individual patient

PML can significantly impact a patient's quality of life given the severity of this condition, its life-threatening and often fatal nature, and associated co-morbidities.

Risk factors and risk groups: C Patients on concomitant immunosuppressive therapy that, along with their underlying disease, could predispose them to PML.

Preventability: No preventable measures.

Impact on the risk-benefit balance of the product: Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place

Public health impact: Not applicable.

Impaired growth and development in juvenile subjects

Potential mechanisms: Not applicable.

Evidence source(s) and strength of evidence: Referenced scientific publications

Characterisation of the risk:

- Frequency with 95 % confidence interval (CI)

No information available.

- Seriousness/outcomes

No information available.

- Severity and nature of risk

No information available.

- Impact on individual patient

Potential impact of impaired growth and development in a juvenile subject could be significant given the nature of this condition and the impact it can have on the patient's psycho-social development.

Risk factors and risk groups: There are currently no known risk groups or risk factors in patients following the administration of etanercept for events in growth and development.

Preventability: An effect on growth and development following exposure to etanercept cannot be identified pre-emptively.

Impact on the risk-benefit balance of the product: Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place

Public health impact: Not applicable.

SVII.3.2 Presentation of the missing information

Not applicable

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Malignancy (including lymphoma and leukaemia) Serious and opportunistic infections (including TB, Legionella, Listeria, parasitic infections) Demyelinating disorders
Important potential risks	Encephalitis/leukoencephalomyelitis Progressive multifocal leukoencephalopathy Impaired growth and development in juvenile subjects

Abbreviations: TB=tuberculosis

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for Demyelination, Guillain-Barré Syndrome, Lymphoma, Mycosis Fungoides, Progressive Multifocal Leukoencephalopathy and Malignancy:

Specific follow-up questionnaires (Annex 4) will be used in case the Marketing Authorisation Holder (MAH) receives any reports on Demyelination, Guillain-Barré Syndrome, Lymphoma, Mycosis Fungoides, Progressive Multifocal Leukoencephalopathy and Malignancy.

Other forms of routine pharmacovigilance activities: none

III.2 Additional pharmacovigilance activities

RABBIT summary

Study short name and title: RABBIT - Rheumatoid Arthritis Observation of Biologic Therapy

Rationale and study objectives: A national register for the long-term observation of therapy with biologics in adult patients with rheumatoid arthritis (RA) whose main goal is the investigation of long-term safety of biologic disease modifying anti-rheumatic drugs (DMARDs) in patients with RA.

Study design: National prospective observational cohort study

Study population: Adult patients in Germany with RA

Milestones:

- Protocol submission: Completed
- Study start: Apr 2016 (completed)
- Study end: 2028 (planned)
- Final report: 2029 (planned)

BADBIR summary

Study short name and title: BADBIR - British Association of Dermatologists Biologic Interventions Register

Rationale and study objectives: A nationwide registry which seeks to assess the long-term safety of biologic treatments for psoriasis. Recommended by National Institute for Health and Care Excellence (NICE) that all patients in the United Kingdom (UK) receiving new therapies for psoriasis be registered in BADBIR.

Study design: National prospective observational cohort study

Study population: Patients in the UK who are on long-term biologic treatments for psoriasis

Milestones:

- Protocol submission: Completed
- Study start: May 2016 (completed)
- Study end: 2025 (planned)
- Final report: 2026 (planned)

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
N/A				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A				
Category 3 - Required additional pharmacovigilance activities				
RABBIT - Rheumatoid Arthritis Observation of Biologic Therapy	A prospective, observational cohort study whose objectives are to evaluate 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.	Malignancy, serious and opportunistic infections, demyelinating disorders, aplastic anaemia and pancytopenia, CHF in adult subjects, encephalitis/leukoencephalomyelitis, progressive multifocal leukoencephalopathy, and acute ischemic CV events.	Protocol submission	Completed[a]
			Study start date	April 2016
			Study end date	2028 (planned)
			Final report	2029 (planned) Biennial interim reports will be submitted during the study period as individual reports. Summaries of study progress will be presented in PSURs and RMP updates, where applicable.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
BADBIR - British Association of Dermatologists Biologic Interventions Register	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, demyelinating disorders, aplastic anaemia and pancytopenia, CHF in adult subjects, encephalitis/leukoencephalomyelitis, progressive multifocal leukoencephalopathy, and acute ischemic CV events.	Protocol submission	Completed[a]
			Study start date	May 2016
			Study end date	2025 (planned)
			Final report	2026 (planned) Biennial interim reports will be submitted during the study period as individual reports. Summaries of study progress will be presented in PSURs and RMP updates, where applicable.

[a] The general protocol provided by each registry has already been submitted. Any revisions of the protocol will be submitted with forthcoming RMP updates. The final report plan is now proposed in the due date sections.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

No post-authorisation efficacy studies are currently planned or imposed as specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
N/A				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A				

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Malignancy (including lymphoma and leukaemia)	Routine risk communication: SmPC section 4.4 and 4.8, and PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Prescription only medication
Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, parasitic infection)	Routine risk communication: SmPC section 4.3, 4.4, and 4.8, and PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Prescription only medication
Demyelinating disorders	Routine risk communication: SmPC section 4.4 and 4.8, and PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Prescription only medication
Encephalitis/ Leukoencephalomyelitis	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information:

Safety concern	Routine risk minimisation activities
	Prescription only medication
Progressive multifocal leukoencephalopathy	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Prescription only medication
Impaired growth and development in juvenile subjects	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Prescription only medication

V.2. Additional Risk Minimisation Measures

Patient Card

Objectives:

To provide the following important safety information that patients need to be aware of before and during Benepali treatment and to let patient know what to do when such safety events are suspected.

- Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, parasitic infection)

Rationale for the additional risk minimisation activity:

Patient card is provided to Benepali prescribing physicians for distribution to patients receiving Benepali. This card provides important safety information for patients, including information relating to infections

Target audience and planned distribution path:

Patient card is provided to Benepali prescribing physicians for distribution to patients receiving Benepali.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Not applicable

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Malignancy (including lymphoma and leukaemia)	Routine risk minimisation measures: SmPC sections 4.4 and 4.8, and PL sections 2 and 4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific AE follow-up form for lymphoma, mycosis fungoides/cutaneous T-cell lymphoma, malignancy occurring in patients ≤ 30 years old Additional pharmacovigilance activities[a]: Registry participation
Serious and opportunistic infections (including TB, Legionella, Listeria, parasitic infection)	Routine risk minimisation measures: SmPC section 4.3, 4.4, and 4.8, and PL sections 2 and 4 Additional risk minimisation measures: Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities[a] Registry participation
Demyelinating disorders	Routine risk minimisation measures: SmPC section 4.4 and 4.8, and PL sections 2 and 4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific AE follow-up form for demyelination and Guillain-Barré syndrome Additional pharmacovigilance activities[a] Registry participation
Encephalitis/ leukoencephalomyelitis	<Routine risk minimisation measures:> None <Additional risk minimisation measures:> None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities [a] Registry participation

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Progressive multifocal leukoencephalopathy	<Routine risk minimisation measures:> None <Additional risk minimisation measures:> None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific AE follow-up form for progressive multifocal leukoencephalopathy Additional pharmacovigilance activities [a]: Registry participation
Impaired growth and development in juvenile subjects	<Routine risk minimisation measures:> None <Additional risk minimisation measures:> None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

[a] Final report due for individual activities: Registry (RABBIT – 2029) & (BADBIR-2026)

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR BENEPALI

This is a summary of the risk management plan (RMP) for Benepali. The RMP details important risks of Benepali, how these risks can be minimised, and how more information will be obtained about Benepali's risks and uncertainties (missing information).

Benepali's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Benepali should be used.

This summary of the RMP for Benepali should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Benepali's RMP.

I. The medicine and what it is used for

Benepali is authorised for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis, and paediatric plaque psoriasis (see SmPC for the full indication). It contains etanercept as the active substance and it is given by injection.

Further information about the evaluation of Benepali’s benefits can be found in Benepali’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/benepali

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Benepali, together with measures to minimise such risks and the proposed studies for learning more about Benepali's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Benepali, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse events is collected continuously and analysed regularly, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Benepali are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Benepali. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Malignancy (including lymphoma and leukaemia) Serious and opportunistic infections (including TB, *Legionella, Listeria* and parasitic infection) Demyelinating disorders
Important potential risks	Encephalitis/leukoencephalomyelitis Progressive multifocal leukoencephalopathy Impaired growth and development in juvenile subjects
Missing information	Not applicable

II.B Summary of important risks

II.B.1 Important identified risks

Malignancy (including lymphoma and leukaemia)	
Evidence for linking the risk to the medicine	Study SB4-G31-RA; proposed Summary of Product Characteristics (SmPC) for Benepali, section 4.4 'Special warnings and precautions for use'; referenced scientific publications.
Risk factors and risk groups	Overall risk of malignancy including cutaneous and non-cutaneous cancers in subjects with RA and PsO has been reported to be higher than that observed in healthy subjects. In addition, the proposed SmPC for Benepali states that there is an increased background risk for lymphoma and leukaemia in RA patients with long-standing, highly active, inflammatory disease. Studies have shown that patients with RA have an approximately 2-fold increased risk of lymphoma and leukaemia, a 20% to 50% increased risk of respiratory tract cancer, and a 70% increased risk of non-melanoma skin cancers, but a decreased risk for breast and colorectal cancer.[4,6] The increase in lymphoma risk is limited to those RA patients who have long-standing and very severe disease.[12]
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8 PL Sections 2 and 4 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, parasitic infection)	
Evidence for linking the risk to the medicine	Study SB4-G31-RA; referenced scientific publications.
Risk factors and risk groups	The patients who are on concomitant immunosuppressive therapy, in addition to their underlying disease, can be predisposed to infection.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.3, 4.4, and 4.8 PL Sections 2 and 4 Additional risk minimisation measures Patient cards are provided to etanercept prescribing physicians for distribution to patients receiving etanercept. This card provides important safety information for patients, including information relating to infections
Additional pharmacovigilance activities	Additional pharmacovigilance activities Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

Demyelinating disorders	
Evidence for linking the risk to the medicine	Study SB4-G31-RA; proposed SmPC for Benepali, Section 4.4 'Special warnings and precautions for use'; referenced scientific publications.
Risk factors and risk groups	In RA, the primary autoimmune condition may be a contributing factor to the development of demyelinating disorders, other inflammatory rheumatic disorders, particularly SpAs, are not classically associated with immune neurological disorders. Potential risk factors for central demyelinating disorders include vitamin D deficiency and certain childhood infections including Epstein-Barr virus.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4 and 4.8 PL Sections 2 and 4 Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

II.B.2 Important potential risks

Encephalitis/leukoencephalomyelitis	
Evidence for linking the risk to the medicine	Study SB4-G31-RA.
Risk factors and risk groups	Subjects on concomitant immunosuppressive therapy, or with medical conditions that cause immunosuppression that, in addition to their underlying disease, could predispose them to infections.
Risk minimisation measures	Routine risk minimisation measures None Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

Progressive multifocal leukoencephalopathy	
Evidence for linking the risk to the medicine	Study SB4-G31-RA; referenced scientific publications.
Risk factors and risk groups	Patients on concomitant immunosuppressive therapy that, along with their underlying disease, could predispose them to PML.
Risk minimisation measures	Routine risk minimisation measures None Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

Impaired growth and development in juvenile subjects	
Evidence for linking the risk to the medicine	Referenced scientific publications
Risk factors and risk groups	There are currently no known risk groups or risk factors in patients following the administration of etanercept for events in growth and development.
Risk minimisation measures	Routine risk minimisation measures None Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities None

II.B.3 Missing information

Not applicable

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Benepali.

II.C.2 Other studies in post-authorisation development plan

RABBIT

Purpose of the study: A prospective, observational cohort study whose objectives are to evaluate 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.

BADBIR

Purpose of the study: 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.

Annex 4 - Specific adverse drug reaction follow-up forms

Specific adverse event follow-up forms: Demyelination, Guillain-Barré Syndrome, Lymphoma, Mycosis Fungoides, Progressive Multifocal Leukoencephalopathy, Malignancy

Questionnaire: Demyelination

This form is designed to provide information of patients who have demyelination potentially associated with the Product: Benepali, Brenzys, or Etoloce.

A. Patient Information	*Enter all dates in the format MMM/DD/YYYY, e.g., DEC/28/2012.
Initials/Identifiers:	Date of birth: M M M D D Y Y Y Y
Sex: ☐ Male ☐ Female	Product/Manufacturer/Lot#:

B. Prior Relevant Medical History			Tick if none ☐
Tick if relevant	Medical History	Date	Method of Diagnosis
☐	Multiple Sclerosis	M M M D D Y Y Y Y	
☐	Optic neuritis	M M M D D Y Y Y Y	
☐	Other demyelinating neurologic disorders (please list):	M M M D D Y Y Y Y	

If prior medical history includes multiple sclerosis, please indicate the following:	
Specific diagnosis	☐ Primary progressive ☐ Relapsing remitting ☐ Secondary progressive
History of relapse	☐ Yes (please indicate frequency: _____) ☐ No
Has the frequency of relapse changed since starting the Product?	☐ Yes (please explain: _____) ☐ No

Did the patient ever experience neurologic symptoms prior to starting the Product?

☐ Yes
☐ No
If yes, please provide the descriptions:

Does the patient have a family history of demyelinating disorders?

☐ Yes
☐ No
If yes, please specify the condition and family relationship:

Did the patient ever have a brain or spinal MRI scan prior to starting the Product?

☐ Yes
☐ No
If yes, please specify the findings and reason for the scan:

Questionnaire: Demyelination

B. Prior Relevant Medical History

Tick if none ☐

Does the patient have a history of brain injury or lesions prior to starting the Product?

☐ Yes
☐ No
If yes, please describe the details:

C. Risk Factors

Has the patient received other TNF-α inhibitor?

☐ Yes
☐ No

If yes, please provide the following information:

TNF-α inhibitor drug product (if etanercept, include brand name):
Indication:
Dose:
Start date:
Stop date:

Drug treatment associated with demyelinating neurologic disorders — Tick if none ☐

Product Name	Start Date (MMM/DD/YYYY)	Stop Date (MMM/DD/YYYY) ☐ Tick if ongoing
		☐
		☐
		☐
		☐

Radiation therapy	☐ Yes (please provide start/stop dates: _____) ☐ No
Occupational exposure	☐ Yes (please specify: _____) ☐ No
Environmental exposure	☐ Yes (please specify: _____) ☐ No
Other	☐ Yes (please specify: _____) ☐ No

D. Diagnostic Test Results (if more than once, please write on Section F. Additional Comments)

Tick if relevant	Test	Test Date	Results
☐	MRI	M M M D D Y Y Y Y	
☐	Lumbar Puncture	M M M D D Y Y Y Y	
☐	Cerebrospinal fluid analysis	M M M D D Y Y Y Y	
☐	Visual evoked potential	M M M D D Y Y Y Y	
☐	Other:	M M M D D Y Y Y Y	

Test results may be attached, if available.
Results Attached: ☐ Yes ☐ No

Questionnaire: Demyelination

E. Outcome
Was the Product discontinued?
☐ Yes ☐ No If yes, please indicate the below: Patient's neurologic condition ☐ Improved ☐ Worsen ☐ Remained stable
Was the Product restarted?
☐ Yes ☐ No If yes, please provide the result to the patient's neurologic condition:
Was the patient treated for the neurologic condition?
☐ Yes ☐ No If yes, please specify in details:
What is the patient's current status?

F. Additional Comments

Signature(s)			
Reporter's _____	name:	Signature: _____	Date: _____

Questionnaire: Guillain-Barré Syndrome (GBS)

This form is designed to provide information of patients who have Guillain-Barré syndrome (GBS) potentially associated with the Product: Benepali, Brenzys, or Etoloce.

A. Patient Information

*Enter all dates in the format MMM/DD/YYYY, e.g., DEC/28/2012.

Initials/Identifiers: Date of birth: M M M D D Y Y Y Y

Sex: ☐ Male ☐ Female Product/Manufacturer/Lot#:

B. Relevant Medical History/Risk Factors

Tick if none ☐

☐ Previous history of Guillain-Barré

☐ Recent surgery, specify:
_____

☐ Recent vaccination, type:
_____

☐ Malignancy, type:_____

☐ Connective tissue disease, type:
_____

☐ Pregnancy, expected date of delivery:
M M M D D Y Y Y Y

☐ Recent infection, onset:
M M M D D Y Y Y Y

Time interval between infection and GBS symptoms:
_____

Type of infection:
_____

Has the patient received other TNF-α inhibitor?

☐ Yes
☐ No

If yes, please provide the following information:

TNF-α inhibitor drug product (if etanercept, include brand name):
Indication:
Dose:
Start date:
Stop date:.

C. Clinical Manifestations (check all that apply)

Pain: ☐ Yes ☐ No
- ☐ Severe
- ☐ Throbbing
- ☐ Aching
- ☐ Other (please specify):

Weakness: ☐ Yes ☐ No
- ☐ Symmetrical
- ☐ Lower limbs (manual muscle test grade):
  R_____ L_____
- ☐ Upper limbs (manual muscle test grade):
  R_____ L_____
- ☐ Trunk muscles

Sensory changes: ☐ Yes ☐ No
- ☐ Paraesthesia
- ☐ Numbness or similar sensory changes (specify):

Dysreflexia: ☐ Yes ☐ No
- ☐ Reflexes decreased
- ☐ Reflexes absent
- ☐ Hypotonia

Autonomic changes: ☐ Yes ☐ No
- ☐ Tachycardia
- ☐ Paroxysmal hypertension
- ☐ Anhidrosis and/or diaphoresis
- ☐ Bradycardia
- ☐ Orthostatic hypotension
- ☐ Facial flushing

Cranial nerve involvement: ☐ Yes ☐ No
- ☐ Facial weakness
- ☐ Dysphasia
- ☐ Dysarthrias
- ☐ Slurred speech
- ☐ Oropharyngeal weakness
- ☐ Difficulty swallowing

Papilledema: ☐ Yes ☐ No
- ☐ Increased CSF pressure
- ☐ Headache
- ☐ Pseudotumor cerebri syndrome

Respiratory involvement: ☐ Yes ☐ No
- ☐ Respiratory weakness
- ☐ Dyspnea on exertion
- ☐ Shortness of breath

Paralysis:: ☐ Yes ☐ No

Type (specify all areas):

Questionnaire: Guillain-Barré Syndrome (GBS)

D. Laboratory Data

☐ Electrodiagnostic test, specify: _____ Date: M M M D D Y Y Y Y

Provide or attach results:

☐ Cerebrospinal fluid analysis results: Date: M M M D D Y Y Y Y

Provide or attach results:

E. Treatments

☐ No treatment ☐ IV Immunoglobulin ☐ Plasmapheresis ☐ Ventilation assistance

☐ Other (please specify):

F. Outcome

Is there any explanation for the event?

What is the current status of the patient?

G. Additional Comments

Signature(s)

Reporter's name: _____ Signature: _____ Date: _____

Questionnaire: Lymphoma

This form is designed to provide follow-up information of patients with lymphoma potentially associated with the Product: Benepali, Brenzys, or Etoloce.

A. Patient Information	*Enter all dates in the format MMM/DD/YYYY, e.g., DEC/28/2012.
Initials/Identifiers:	Date of birth: M M M D D Y Y Y Y
Sex: ☐ Male ☐ Female	Product/Manufacturer/Lot#:

Questionnaire: Lymphoma

B. Relevant History/Risk Factors

Tick if none ☐

Please indicate if the patient received any of the following immunosuppressive medications. Please include dates if therapy received and dosing/frequency.

Tick if drug was taken	Drug	Dosage	Frequency	Start date (MMM/DD/YYYY)	Stop date (MMM/DD/YYYY) ☐ Tick if ongoing
☐	Adalimumab				☐
☐	Azathioprine				☐
☐	Cyclophosphamide				☐
☐	Cyclosporine				☐
☐	Etanercept (Brand name:_____)				☐
☐	Gold				☐
☐	Infliximab				☐
☐	Leflunomide				☐
☐	Methotrexate				☐
☐	6-Mercaptopurine				☐
☐	Other (please specify): _____				☐

Is there a family history of cancer? ☐ Yes ☐ No ☐ Unknown

If yes, please check all that apply:

☐ Maternal Specify Type(s): _____

☐ Paternal, Specify Type(s): _____

☐ Sibling, Specify Type(s): _____

☐ Other:_____ Specify Type(s): _____

History of immune deficiency? ☐ Yes ☐ No

If yes, specify type(s): _____

History of HIV? ☐ Yes ☐ No

History of prior organ transplant? ☐ Yes ☐ No

Date of organ transplant (MMM/DD/YYYY): _____

Specify type of organ transplant: _____

History of any chronic inflammatory disease/or history of other chronic disease(s)? ☐ Yes ☐ No

If yes, specify type(s): _____

History of: ☐ Cirrhosis ☐ Hepatitis B ☐ Hepatitis C ☐ Helicobacter Pylori

Occupational exposures (please specify.):

Environmental exposures (please specify.):

C. Lymphoma Information

☐ Hodgkin's ☐ Non-Hodgkin's ☐ T-cell ☐ B-cell ☐ Other: _____

Date of diagnosis (MMM/DD/YYYY): _____

Stage of lymphoma at the time of diagnosis: _____

Questionnaire: Lymphoma

What treatment was initiated after diagnosis?

Chemotherapy ☐ Yes ☐ No (please specify type):_____

Radiation ☐ Yes ☐ No

Bone marrow transplant ☐ Yes ☐ No

If yes, please provide information on Epstein Barr Virus (EBV) status of donor: _____

Other (please specify): _____

Epstein Barr Virus (EBV) Testing: ☐ Yes (date of EBV testing: _____) ☐ No

If yes, check the following:

Type of EBV test: ☐ Blood test ☐ In situ hybridization ☐ Immunohistologic analysis ☐ Other: _____

Result of EBV testing: _____

Please attach pathology report including immunotype, cytogenic, histologic subtype, if available.

Attachment: ☐ Yes ☐ No

Current stage of lymphoma:

Current treatment for lymphoma:

D. Product Information

Was the patient diagnosed with lymphoma or other malignancy prior to receiving the Product?
☐ Yes ☐ No

Date patient initiated the Product: M M M D D Y Y Y Y

Primary diagnosis for which the Product is being used:

E. Outcome (please specify the patient's current status.)

F. Additional Comments

Signature(s)

Reporter's name: _____ Signature: _____ Date: _____

Questionnaire: Mycosis Fungoides (MF)

This form is designed to provide follow-up information of patients with mycosis fungoides (MF) potentially associated with the Product: Benepali, Brenzys, or Etoloce.

A. Patient Information

*Enter all dates in the format MMM/DD/YYYY, e.g., DEC/28/2012.

Initials/Identifiers: Date of birth: M M M D D Y Y Y Y

Sex: ☐ Male ☐ Female Product/Manufacturer/Lot#:

B. Relevant History/Risk Factors

Tick if none ☐

Please indicate if the patient received any of the following immunosuppressive medications; include dates of therapy and dosing/frequency.

Tick if drug was taken.	Drug	Dosage	Frequency	Start date (MMM/DD/YYYY)	Stop date (MMM/DD/YYYY) ☐ Tick if ongoing
☐	Adalimumab				☐
☐	Azathioprine				☐
☐	Cyclophosphamide				☐
☐	Cyclosporine				☐
☐	Etanercept (Brand name: _____)				☐
☐	Gold				☐
☐	Infliximab				☐
☐	Leflunomide				☐
☐	Methotrexate				☐
☐	6-Mercaptopurine				☐
☐	Other: _____ (Please specify)				☐

Is there a family history of cancer? ☐ Yes ☐ No ☐ Unknown

If yes, please check all that apply:

☐ Maternal Specify Type(s): _____

☐ Paternal, Specify Type(s): _____

☐ Sibling, Specify Type(s): _____

☐ Other:_____ Specify Type(s): _____

C. Patient Medical History

Immune deficiency? ☐ Yes ☐ No ☐ Unknown Type: _____

HIV? ☐ Yes ☐ No ☐ Unknown

Lyme disease? ☐ Yes ☐ No ☐ Unknown

Tobacco use? ☐ No ☐ Current ☐ Past Estimate use/duration: _____

Questionnaire: Mycosis Fungoides (MF)

C. Patient Medical History

Alcohol use? ☐ No ☐ Current ☐ Past Estimate use/duration: _____

Organ transplant? ☐ Yes ☐ No ☐ Unknown

Type of Organ: _____ Date: M M M D D Y Y Y Y

Chronic diseases? ☐ Yes ☐ No ☐ Unknown Type: _____

Primary occupation: _____ Duration: _____

Exposure to:

Solvents	☐ Yes	☐ No	☐ Unknown	Duration: _____	Most recent exposure: _____
Pesticides	☐ Yes	☐ No	☐ Unknown	Duration: _____	Most recent exposure: _____
Publishing/ Printing	☐ Yes	☐ No	☐ Unknown	Duration: _____	Most recent exposure: _____
Paper/ Wood industry	☐ Yes	☐ No	☐ Unknown	Duration: _____	Most recent exposure: _____

D. History of Skin Disorder

Tick if none ☐

Onset date: M M M D D Y Y Y Y

Chronic dermatitis? ☐ Yes ☐ No ☐ Unknown

Features of rash: ☐ Morbilliform ☐ Flaking/Peeling ☐ Plaques ☐ Ulcers/Exfoliation

Site of rash: ☐ Extremities ☐ Flexor surfaces ☐ Extensor surfaces ☐ Trunk

Clinical progression: ☐ None ☐ Slow ☐ Rapid

Change in presentation after initiation of TNF inhibitor: ☐ Yes ☐ No ☐ Unknown

Describe: _____

E. Current Skin Disorder

☐ Mycosis fungoides ☐ Sezary Syndrome ☐ Primary cutaneous anaplastic large cell lymphoma

☐ Lymphomatoid papulosis ☐ Other: _____

Onset of symptoms: M M M D D Y Y Y Y Date of diagnosis: M M M D D Y Y Y Y

Clinical appearance: _____

Stage of lymphoma at time of diagnosis: _____

Current stage of lymphoma: _____

Epstein Ban Virus (EBV) Testing: ☐ Yes ☐ No Date: M M M D D Y Y Y Y

Type of Test:

☐ Blood test ☐ In situ hybridization ☐ Immunohistologic analysis ☐ Other: _____

Result:

Questionnaire: Mycosis Fungoides (MF)

E. Current Skin Disorder

☐ Positive ☐ Negative

Please check the appropriate boxes which most closely describe the certainty of diagnosis of the disorder reported above:

Test Performed	Diagnostic of disorder reported	Consistent with diagnosis reported	Cannot rule out diagnosis reported	Not Performed
Histopathology	☐	☐	☐	☐
Immunohistology	☐	☐	☐	☐
Flow Cytometry	☐	☐	☐	☐
Immunogenotype (TCR-rearrangement)	☐	☐	☐	☐
Lymph node analysis	☐	☐	☐	☐

*** PLEASE ATTACH PATHOLOGY REPORT, INCLUDING THE ABOVE STUDIES.

Report Attached: ☐ Yes ☐ No

F. Treatment History for Cutaneous T-Cell Lymphoma

Topical therapy: ☐ Yes ☐ No

Please specify drugs: _____

Phototherapy: ☐ Yes ☐ No

Extracorporeal photophoresis: ☐ Yes ☐ No

Systemic treatments: ☐ Yes ☐ No

Please specify drugs: _____

Radiation therapy: ☐ Yes ☐ No

Chemotherapy: ☐ Yes ☐ No

Please specify drugs: _____

Bone marrow transplant: ☐ Yes ☐ No

Stem cell transplant: ☐ Yes ☐ No

Other: _____

G. Product Information

Was patient diagnosed with lymphoma prior to receiving the Product? ☐ Yes ☐ No

Date patient initiated the therapy: _____

Primary diagnosis for which the Product is being used: _____

H. Outcome (please specify the patient's current status.)

Questionnaire: Mycosis Fungoides (MF)

I. Additional Comments

Signature(s)			
Reporter's _____	name:	Signature: _____	Date: _____

Questionnaire: Progressive Multifocal Leukoencephalopathy (PML)

This form is designed to provide information of patients who have progressive multifocal leukoencephalopathy (PML) potentially associated with the Product: Benepali, Brenzys, or Etoloce.

A. Patient Information

*Enter all dates in the format MMM/DD/YYYY, e.g., DEC/28/2012.

Initials/Identifiers: Date of birth: M M M D D Y Y Y Y

Sex: ☐ Male ☐ Female Product/Manufacturer/Lot#:

B. Relevant Medical History

Does the patient have a history of: Tick if none ☐

☐ Neurologic disorder(s) ☐ Cancer ☐ Diabetes ☐ HIV infection ☐ Risk factor(s) for HIV infection ☐ Immune deficiency disorder ☐ Blood Transfusion	If any items are checked, provide specific diagnosis(es) and when condition(s) were diagnosed:

Does the patient have a family history of neurologic disease?

☐ Yes
☐ No
If yes, specify: _____

Please indicate if the patient received any of the following immunosuppressive medications; include dates of therapy and dosage/frequency.

Tick if drug was taken	Drug	Dosage	Frequency	Start date (MMM/DD/YYYY)	Stop date (MMM/DD/YYYY) ☐ Tick if ongoing
☐	Adalimumab				☐
☐	Anakinra				☐
☐	Azathioprine				☐
☐	Certolizumab				☐
☐	Corticosteroids				☐
☐	Cyclophosphamide				☐
☐	Cyclosporine				☐
☐	Etanercept (Brand name:_____)				☐
☐	Golimumab				☐
☐	Infliximab				☐
☐	Leflunomide				☐
☐	Methotrexate				☐
☐	Natalizumab				☐
☐	Rituximab				☐
☐	Tocilizumab				☐
☐	Other:_____ (Please specify)				☐

Questionnaire: Progressive Multifocal Leukoencephalopathy (PML)

C. Neurologic Event: Clinical Features

Does the patient have a progressive neurologic/neuropsychiatric syndrome? ☐ Yes ☐ No

Which of the following symptoms and/or signs are present?

- ☐ Limb weakness or incoordination
- ☐ Speech deficits
- ☐ Cognitive impairment
- ☐ Memory loss
- ☐ Gait disorder
- ☐ Focal sensory deficit
- ☐ Vision loss/Visual defects
- ☐ Seizure
- ☐ Dysesthesia
- ☐ Headache

Describe all available details of the clinical course of the patient's neurologic disease including outcomes and functional status.

Please indicate and explain any treatment(s) provided and response(s) to treatment.

If an autopsy was performed, please provide (or attach) results.

If there was any tests done as below, please describe:

Test	Test Date	Results (key findings) (If desired, attach results.)
CSF analysis	M M M D D Y Y Y Y	Positive JC Virus PCR? ☐ Yes ☐ No
MRI Brain	M M M D D Y Y Y Y	
Brain Tissue Evaluation (Biopsy / Autopsy)	M M M D D Y Y Y Y	

D. Outcome (Please specify the patient's current status.)

E. Additional Comments

Signature(s)

Reporter's name: _____ Signature: _____ Date: _____

Questionnaire: Malignancy

This form is designed to provide follow-up information of patients ≤ 30 years old with malignancy potentially associated with the Product: Benepali, Brenzys, or Etoloce.

A. Patient Information

*Enter all dates in the format MMM/DD/YYYY, e.g., DEC/28/2012.

Initials/Identifiers: Date of birth: M M M D D Y Y Y Y

Sex: ☐ Male ☐ Female Product/Manufacturer/Lot#:

Race/ Ethnicity: ☐ Asian ☐ White or Caucasian ☐ Hawaiian Native or Pacific Islander
☐ Black or African American ☐ American Indian or Native American
☐ Hispanic or Latino ☐ Other: _____

B. Product Information

Indication(s)

☐ Rheumatoid arthritis
☐ Psoriatic arthritis
☐ Ankylosing spondylitis
☐ Psoriasis
☐ Non-radiographic axial spondyloarthritis
☐ Other (please specify.):_____

Dosing Information

Dose: _____
Age at the first exposure: _____
Date of the first exposure: _____
Duration of the use : _____ (☐ Months ☐ Years)
Number of doses received to date: _____

Status of the Product Usage

☐ Continued/Ongoing
☐ Temporarily discontinued (provide stop and restart dates):

Stop Date: M M M D D Y Y Y Y

Restart Date: M M M D D Y Y Y Y

☐ Permanently discontinued (provide stop date):
M M M D D Y Y Y Y

Has the patient received other TNF-α inhibitor?

☐ Yes
☐ No

If yes, please provide the following information:

TNF-α inhibitor drug product (if etanercept, include brand name):
Indication:
Dose:
Start date:
Stop date:

Questionnaire: Malignancy

B. Product Information

Other immunosuppressant drugs, including glucocorticosterioids and anti-neoplastics, prior to or concomitant with the Product exposure (please provide start date and stop date for each)

Concomitant medications with the Product other than those already listed above (please provide start date and stop date for each)

C. Malignancy Event Information and Risk Factors

Date of malignancy diagnosis: M M M D D Y Y Y Y

Is this a new primary malignancy? ☐ Yes ☐ No ☐ Unknown

- If no, is this a recurrence of a previous malignancy? ☐ Yes ☐ No ☐ Unknown

Time from the treatment initiation (with the Product) to malignancy diagnosis:
_____(☐ Months ☐ Years)

Time from the treatment initiation (with other TNF-alpha inhibitor) to malignancy diagnosis (if applicable):
_____(☐ Months ☐ Years)

Histopathologic diagnosis as stated on the original diagnostic pathology report:
_____

Copy of pathology report included? ☐ Yes ☐ No

Copy of definitive surgical report included? ☐ Yes ☐ No

Describe the malignancy staging and findings that supported specified staging, including system used.

Presenting symptoms

Questionnaire: Malignancy

C. Malignancy Event Information and Risk Factors

List any relevant risk factors for malignancy from the patient's medical history, including prior illness (e.g., Epstein-Barr, human papilloma virus), tobacco use (provide pack-years), exposures, or medications.

List any preventive measures taken for malignancy, if any, including, mammograms, pap smears, or HPV vaccine.

Family history of malignancy

☐ Yes
☐ No
If yes, please complete the following:

Malignancy type: _____
Relationship to the family member: _____

Describe primary treatment for malignancy.

D. Outcome of Event

☐ Patient recovered and event resolved
☐ Event resolved with sequelae
☐ Event ongoing
☐ Fatal
If fatal outcome, please provide cause of death and relationship to the malignancy:
_____

E. Additional Comments

Signature(s)

Reporter's name: _____ Signature: _____ Date: _____

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Prior to the use of etanercept in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at reducing the risk of serious infections.

The MAH shall ensure that in each Member State where etanercept is marketed, all healthcare professionals who are expected to prescribe etanercept have access to/are provided with the following educational materials

Patient card

- Etanercept treatment may increase the risk of infection
- Signs or symptoms of the safety concern and when to seek attention from a healthcare professional
- Contact details of the etanercept prescriber