



**RISK MANAGEMENT PLAN**

**for**

**Fubelv<sup>®</sup> (etanercept)**

**Data lock point (DLP) for RMP: 26-Jul-2019**

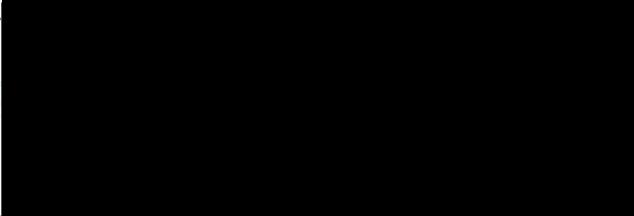

**Version Number: 0.2**

**Dated: 23-Jan-2026**



# Risk Management Plan – Etanercept

Risk Management Plan for:	Etanercept
RMP Version number:	0.2
Data lock point for this RMP:	26-Jul-2019
Date of final sign-off:	23-Jan-2026
Rationale for submitting an updated RMP:	In response to the EMA query, this RMP has been updated to remove Important identified risks ("Aplastic Anaemia and Pancytopenia," "Congestive Heart Failure in Adult Subjects,") and Important potential risk ("Acute Ischaemic Cardiovascular Events in Adult Subjects")" from the list of safety concerns to align with the reference product Enbrel (Pfizer Limited), RMP v 7.9 (dated 12-Jun-2025).
Summary of significant changes in this RMP:	<p><b>Part II Module VII:</b></p> <ul style="list-style-type: none"> <li>Updated the reason for the removal of the list of safety concerns and changes to the important identified risks and important potential risks.</li> <li>Module SVIII: Removed the safety concerns to align with the reference product Enbrel (Pfizer Limited), RMP v 7.9 (dated 12-Jun-2025).</li> </ul> <p><b>Part V:</b> Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)</p> <p><b>Part V.1 and Part V.3:</b> Removed "Aplastic Anaemia and Pancytopenia," "Congestive Heart Failure in Adult Subjects," and "Aute Ischaemic Cardiovascular Events in Adult Subjects" from the description of routine risk minimisation measures by safety concern.</p> <p><b>Part V.2:</b> Updates to the patient card</p> <p>"The risk of congestive heart failure (CHF) in adult subjects has been removed from the patient card, in alignment with the reference biologic Enbrel."</p> <p><b>Part VI:</b> Summary of the risk management plan has been updated to align with the reference</p>

Risk Management Plan for:	Etanercept
	<p>product Enbrel (Pfizer Limited), RMP v 7.9 (dated 12-Jun 2025).</p> <p><b>Part VII: Annexes</b></p> <p><b>Annex 6:</b> Updated additional risk minimisation measures to align with the reference product Enbrel (Pfizer Limited), RMP v 7.9 (dated 12-Jun-2025) i.e. removal of information regarding the risk of Congestive Heart Failure in Adult Subjects from the Patient Card.</p> <p><b>Annexe-8:</b> Updated with all the above-mentioned changes.</p>
<p>Other RMP versions under evaluation</p> <ul style="list-style-type: none"> <li>• RMP version number</li> <li>• Submitted on</li> <li>• Procedure number</li> </ul>	Not applicable
<p>Details of the currently approved RMP</p> <ul style="list-style-type: none"> <li>• Version number</li> <li>• Approved with procedure</li> <li>• Date of approval (Opinion date)</li> </ul>	Not applicable; this is the initial RMP
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**List of abbreviations**

<b>Term/Abbreviation</b>	<b>Explanation</b>
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical Classification System
BCIL	Biosimilar Collaborations Ireland Limited
CHF	Congestive heart failure
CHO	Chinese hamster ovary
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
CRP	C-reactive protein
CV	Cardiovascular
DLP	Data Lock Point
DMARD	Disease-Modifying Antirheumatic Drugs
DNA	Deoxyribonucleic Acid
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
GBS	Guillain-Barre Syndrome
HCP	Healthcare Professional
INN	International Non-proprietary Name
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MRI	Magnetic Resonance Imaging
NMSC	Non-Melanoma Skin Cancer
NOAEL	No Observable Adverse Effect Levels
NSAIDs	Nonsteroidal anti-inflammatory drugs
PC	Patient Card
PL	Package Leaflet
PML	Progressive multifocal leukoencephalopathy
PML	Progressive multifocal leukoencephalopathy
PSUR	Periodic Safety Update Report
PUVA	Psoralen and Ultraviolet-A light
QPPV	Qualified Person for Pharmacovigilance
RA	Rheumatoid Arthritis
RABBIT	Rheumatoid Arthritis: Beobachtung der Biologika-Therapie registry
RMP	Risk Management Plan
SAEs	Serious Adverse Events
SEER	Surveillance, Epidemiology, and End Results

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SFPHC	Serum Free Process High Capacity
SIR	Standardised Incidence Ratio
SmPC	Summary of Product Characteristics
TB	Tuberculosis
TNF	Tumour Necrosis Factor

**Part I: Product(s) Overview****Table 1:** Product overview

Active substance (s) (INN or common name):	Etanercept
Pharmacotherapeutic group (s): (Anatomical Therapeutic Chemical Classification System (ATC) Code):	Immunosuppressants, Tumour Necrosis Factor alpha (TNF- $\alpha$ ) inhibitors, ATC code: L04AB01
Marketing Authorisation Applicant:	Biosimilar Collaborations Ireland Limited
Medicinal products to which this RMP refers	3
Invented name (s) in the European Economic Area (EEA)	Fubelv 25 mg solution for injection in pre-filled syringe Fubelv 50 mg solution for injection in pre-filled syringe Fubelv 50 mg solution for injection in pre-filled pen (autoinjector)
Marketing authorisation procedure	Centralized procedure
Brief description of the product	<p><u>Chemical class:</u> Immunosuppressants, tumour necrosis factor alpha (TNF-<math>\alpha</math>) inhibitors</p> <p><u>Summary of mode of action:</u> 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.</p> <p><u>Important information about its composition:</u> Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system. Etanercept is a dimer of a chimeric protein genetically engineered by fusing the extracellular ligand binding domain of human tumour necrosis factor receptor-2 (TNFR2/p75) to the Fc domain of human IgG1. This Fc</p>

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	<p>component contains the hinge, CH2 and CH3 regions, but not the CH1 region of IgG1. Etanercept contains 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons. The specific activity of etanercept is <math>1.7 \times 10^6</math> units/mg.</p>
<p>Hyperlink to the Product Information</p>	<p>Fubelv® Product information (<a href="#">Module 1.3.1</a>)</p>
<p>Indication (s) in the EEA</p>	<p><u>Current:</u></p> <p><b><u>Rheumatoid arthritis</u></b></p> <p>Fubelv in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.</p> <p>Fubelv can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.</p> <p>Fubelv is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.</p> <p>Fubelv , alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.</p> <p><b><u>Juvenile idiopathic arthritis</u></b></p> <p>Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.</p> <p>Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.</p> <p>Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.</p> <p>Etanercept has not been studied in children aged less than 2 years.</p> <p><b><u>Psoriatic arthritis</u></b></p> <p>Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. Etanercept has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.</p>

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	<p><b><u>Axial spondyloarthritis</u></b></p> <ul style="list-style-type: none"> <li>• <i>Ankylosing spondylitis</i></li> </ul> <p>Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.</p> <ul style="list-style-type: none"> <li>• <i>Non-radiographic axial spondyloarthritis</i></li> </ul> <p>Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).</p> <p><b><u>Plaque psoriasis</u></b></p> <p>Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA).</p> <p><b><u>Paediatric plaque psoriasis</u></b></p> <p>Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.</p> <p>Proposed: Not applicable.</p>
<p>Dosage in the EEA</p>	<p><u>Current:</u></p> <p>Fubelv treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and plaque psoriasis. Patients treated with Fubelv should be given the Patient Card.</p> <p>Fubelv is available in strengths of 25 and 50 mg.</p> <p><u>Posology</u></p> <p><i>Rheumatoid arthritis</i></p> <p>The recommended dose is 50mg etanercept administered once weekly.</p> <p><i>Psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis</i></p> <p>The recommended dose is 50mg administered once weekly.</p> <p>For all 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.</p> <p><i>Plaque psoriasis</i></p> <p>The recommended dose of etanercept is 50 mg</p>

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	<p>administered once weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 50 mg once weekly. Treatment with Fubelv 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 Fubelv is indicated, the same guidance on treatment duration should be followed. The dose should be 25 mg twice weekly or 50 mg once weekly.</p> <p><u>Special population</u></p> <p><i>Renal and hepatic impairment:</i> No dose adjustment is required.</p> <p><i>Elderly:</i> No dose adjustment is required. Posology and administration are the same as for adults 18-75 years of age.</p> <p><i>Paediatric population:</i> Fubelv is only available as 25 mg prefilled syringe, 50 mg pre-filled syringe, and 50 mg pre-filled pen. Thus, it is not possible to administer Fubelv to paediatric patients that require less than a full 25mg or 50 mg dose. Paediatric patients who require a dose other than a full 25 mg or 50 mg should not receive Fubelv. If an alternate dose is required, other etanercept products offering such an option should be used. The dosage of etanercept is based on body weight for paediatric patients. Patients weighing less than 62.5 kg should be accurately dosed on a mg/kg basis using the powder and solvent for solution for injection presentations or powder for solution for injection presentations. Patients weighing 62.5 kg or more, may be dosed using a fixed-dose pre-filled syringe or pre-filled pen.</p> <p><u>Juvenile idiopathic arthritis:</u> 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. A 10 mg vial strength may be more appropriate for administration to children with JIA below the weight of 25 kg. No formal clinical trials have been conducted in children aged 2 to 3 years. However, limited safety data from a patient registry suggest that the safety profile in children from 2 to 3 years of age is similar to that seen in adults and children aged 4 years and older, when dosed every week with 0.8 mg/kg subcutaneously. There is generally no applicable use of etanercept in</p>
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	<p>children aged below 2 years in the indication juvenile idiopathic arthritis.</p> <p><i>Paediatric plaque psoriasis (age 6 years and above):</i></p> <p>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.</p> <p>If re-treatment with Fubelv is indicated, the above guidance on treatment duration should be followed. The dose should be 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly.</p> <p>There is generally no applicable use of etanercept in children aged below 6 years in the indication plaque psoriasis.</p>
	<p>Proposed: Not applicable.</p>
<p>Pharmaceutical form (s) and strengths</p>	<p><u>Current:</u></p> <p>Solution for injection</p> <p>Each pre-filled syringe contains 25 or 50 mg of etanercept.</p> <p>Each pre-filled pen contains 50 mg of etanercept.</p>
	<p>Proposed: Not applicable.</p>
<p>Is/will the product be subject to additional monitoring in the European Union (EU)?</p>	<p>No</p>

**Note:** The proposed invented name, Fubelv is submitted by BCIL under a duplicate Marketing Authorisation Application (MAA) for the same pharmaceutical product; same qualitative and quantitative composition in active substance, forms and strength as Nepexto.

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## **Part II: Safety Specification**

This RMP is prepared for initial application under centralised procedure (Article 10(4) for biosimilar product Fubelv (etanercept) with EU-licensed Enbrel (etanercept) as reference biologics. Relevant safety information is included in the respective modules below.

### **Part II: Module SI - Epidemiology of the indication(s) and target population(s)**

Not applicable as this RMP pertains to a similar biologic. (Ref: In accordance with the Good Pharmacovigilance Practices (GVP) - Biological medicinal products Error! Reference source not found. "All parts of an RMP are required for a biosimilar, except for RMP part II, module SI "Epidemiology of the target population).

### **Part II: Module SII - Non-clinical part of the safety specification**

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

#### **Toxicity**

##### Single-dose toxicity

The acute single-dose toxicity of Biosimilar Etanercept was assessed following a one-time subcutaneous or intravenous injection at a dose level of 0 (placebo) and 500 mg/kg to male and female Swiss albino mice. There was no test article-related clinical sign of toxicity, no mortality, no body weight change, and no gross pathological finding in treated animals, and Biosimilar Etanercept was well tolerated following a one-time subcutaneous or intravenous dose of 500 mg/kg (approximately 48.8 x equivalent human 50 mg dose [mouse conversion factor of 12.3 and human BW of 60 kg]).

Additionally, the acute single-dose toxicity of Biosimilar Etanercept was assessed following a one-time subcutaneous or intravenous injection at a dose level of 0 (placebo) and 250 mg/kg to Wistar rats. There was no test article-related clinical sign of toxicity, no mortality, no body weight change, and no gross pathological finding in treated animals, and Biosimilar Etanercept was well-tolerated following a one-time subcutaneous or intravenous injection of 250 mg/kg (approximately 48.8x equivalent of human 50 mg dose [rat conversion factor of 6.2 and human BW of 60 kg]).

##### Repeat-dose toxicity

The repeat-dose toxicity of Biosimilar Etanercept was assessed following once weekly repeat-dose subcutaneous administration to male and female Swiss albino mice at dose levels of 0, 10, 50, 100, and 500 mg/kg on Days 1, 8, 15, and 22. The effects of Biosimilar Etanercept were compared to those of Enbrel following dosing at 10 mg/kg. All mice survived until scheduled euthanasia.

There was no incidence of test article-related clinical signs, bodyweight changes, food consumption alterations, clinical parameter (haematology and chemistry) effects, organ weight changes, or gross anatomic findings at necropsy. Dose formulation analysis verified that all formulations were within acceptable variance of the nominal concentrations. There was significant dose-related granulocyte and MNC infiltration at the injection site in all etanercept-treated groups. Such changes were reported previously in the scientific discussion for Enbrel approval.

Additionally, the repeat-dose toxicity of Biosimilar Etanercept was assessed following once weekly repeat dose subcutaneous administration to male and female New Zealand White rabbits at dose levels of 0, 2.5, 12.5, and 25 mg/kg on Days 1, 8, 15, and 22. All rabbits survived until scheduled euthanasia. There was no incidence of test article-related clinical signs, body weight changes, food consumption alterations, clinical parameter (haematology and chemistry) effects, organ weight changes, gross anatomic findings at necropsy, or histopathological findings.

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Dose formulation analysis verified that all formulations were within acceptable variance of the nominal concentrations. Four weekly subcutaneous administrations of Biosimilar Etanercept to male and female New Zealand White rabbits at dose levels up to 25 mg/kg were well-tolerated with no adverse systemic test article-related effects. The No Observable Adverse Effect Levels (NOAEL) of Biosimilar Etanercept was 25 mg/kg (approximately 9.7 x equivalent of human 50 mg dose [rabbit conversion factor of 3.1 and human BW of 60 kg]) under the conditions of this study.

The repeat-dose toxicity of Biosimilar Etanercept was assessed following twice weekly repeat-dose subcutaneous administration to male and female cynomolgus monkeys at dose levels of 0.0, 1.0, 5.0, and 15 mg/kg (approximately 0.38, 1.9, and 5.8 x equivalent of human 50 mg dose, respectively [monkey conversion rate of 3.1 and human BW of 60 kg]) for 4 weeks. The effects of Biosimilar Etanercept administration were compared to those of Enbrel following twice weekly subcutaneous administration at 15 mg/kg. All animals survived until scheduled euthanasia. There was no incidence of test article-related clinical signs, food consumption changes, body weights, ophthalmoscopic and electrocardiographic findings, or haematology and coagulation parameters. Plasma etanercept levels were quantified for exposure on Days 1 and 22. Median time to maximum concentration (T<sub>max</sub>) was 24 and 36 hours in males and females, respectively (values ranging from 24 to 36 hours). No accumulation of etanercept was observed under these dosage regimens. All animals were negative for anti-drug antibodies (ADAs) pre-test. Biosimilar Etanercept induced etanercept-specific anti-drug antibodies in 3/6 and 2/10 animals in at 1 mg/kg and 15 mg/kg, respectively. There was no detectable ADA at 0 or 5 mg/kg Biosimilar Etanercept. As there was no dose related trend in ADA incidence with Biosimilar Etanercept-treated animals, intergroup differences in ADA incidence were considered reflective of inter-animal variability, and the immunogenicity of Biosimilar Etanercept was considered low. There was an enlarged spleen in one female at 15 mg/kg, and an increased spleen weight and slightly increased liver weight in one female treated at 15 mg/kg. Females treated at 15 mg/kg showed a reversible minimal decreased follicular development in the spleen.

In conclusion, Biosimilar Etanercept was well tolerated at dose levels up to 15 mg/kg (approximately 5.8 x equivalent of human 50 mg dose). The pharmacokinetic profile, low generation of ADA, and safety of Biosimilar Etanercept was comparable to that of Enbrel at 15 mg/kg in this study and to the expected results previously shown for US-licensed Enbrel in a 4-week cynomolgus monkey toxicity studies.

### Reproductive/developmental toxicity

Reproductive and Developmental Toxicity studies are not required for a biosimilar product.

### Genotoxicity

Genotoxicity studies are not required for a biosimilar product.

### Carcinogenicity

Carcinogenicity studies are not required for a biosimilar product.

## **The Evaluation of local irritation potential and immunogenicity of Biosimilar Etanercept**

Local tolerance was investigated in the course of the repeated dose toxicity studies in mice and cynomolgus monkey.

### Evaluation of Local tolerance in Cynomolgus monkey

No relevant differences were observed in the incidence or severity of any microscopic observations between Biosimilar Etanercept and the reference compound Enbrel when administered subcutaneously to Cynomolgus monkeys twice a week for a period of 4 weeks. Based on the results observed Biosimilar Etanercept was well tolerated at the site of injection

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in absence of any meaningful changes observed histopathologically at the injection site. Thus, Biosimilar Etanercept has similar local irritation potential as Enbrel.

### Evaluation of Local tolerance in Mice

Treatment-related local reaction of significant granulocytes and MNC infiltration was seen at the site of injection (subcutaneous tissue) in Biosimilar Etanercept -treated groups and Enbrel-treated group of mice. The incidence and/or severity of reactions at injection site were dose dependent.

These changes corroborated with those reported in the scientific discussion for the approval of Enbrel by the European Medicines Agency.

#### *Conclusion on Local Irritation Potential (Local Tolerance):*

Based on the results observed Biosimilar Etanercept was well tolerated at the site of injection in absence of any meaningful changes observed histopathologically at the injection site. Thus, Biosimilar Etanercept has similar local irritation potential as Enbrel.

#### *Conclusion on Preclinical Immunogenicity Potential of Biosimilar Etanercept:*

The following conclusion could be drawn after sample analysis.

- Etanercept Drug Substance administered subcutaneously at the doses of 1 and 15 mg/kg induced specific anti-drug antibodies against Etanercept, the incidence of which was of 3/6 and 2/10, respectively. No ADA positive samples were detected in the control group (placebo) or in the 5 mg/kg group.
- Enbrel administered subcutaneously at the dose of 15 mg/kg induced specific antidrug antibodies against Enbrel. The incidence was of 5/10.
- All samples resulted ADA negative at pretest.
- The observed immunogenicity results were expected and found to be in line with innovator data Enbrel.

## **Safety pharmacology**

No dedicated studies were performed.

## **Part II: Module SIII - Clinical trial exposure**

Fubelv<sup>®</sup> is another proposed invented name for etanercept in the EMA region. Etanercept is also already approved and marketed under the trade name of Nepexto<sup>®</sup>.

Biosimilar Etanercept (YLB113) has been tested proofing its similarity to EU-licensed Enbrel in two Phase 1 clinical trials and one pivotal Phase 3 clinical trial, comprising a total of 118 healthy subjects and 517 evaluable patients with moderate to severe rheumatoid arthritis. In the Japanese Phase 1 study YLB113-001, a single dose of 25 mg was used, whereas in the Indian Phase 1 study LBC14-155, a single dose of 50 mg was administered. In the pivotal study YB113-002, a dose of 50 mg was administered once a week together with methotrexate (MTX).

Following data represents exposure to YLB113 and LBC14 (Fubelv) only.

**Table 2: SIII.1: Duration of exposure**

<b>Duration of exposure (YLB113-001 and LBC14-155)</b>	<b>Patients</b>
Single dose 25 mg	60
Single dose 50 mg	58
<b>Total number of Healthy volunteers exposed to single dose</b>	<b>118</b>

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<b>Duration of exposure (YLB113-002)</b>	<b>Patients</b>
50 mg once a week for 24 weeks (Stage A), and 52 weeks (Stage B)	528
<b>Total number of patients with moderate to severe rheumatoid arthritis exposed to once-a-week dose</b>	<b>528</b>

**Table 3: SIII.2: Age group and gender**

<b>Age group and gender</b>	<b>Patients</b>
Healthy male volunteers in YLB113-001 Mean age 28 years	60 Males
Healthy male Indian volunteers in LBC14-155 Mean age 26 years	58 Males
Patients with moderate to severe rheumatoid arthritis in YLB113-002 Mean age 52.3 years	114 Males and 403 Females
<b>Total</b>	<b>646</b>

**Table 4: SIII.3: Dose**

<b>Dose of exposure</b>	<b>Patients</b>
Single dose s.c 25 mg (YLB113-001)	59
Single dose s.c 50 mg (LBC14-155)	38
50 mg once a week for 24 weeks (Stage A), and 52 weeks (Stage B)–[YLB113-002]	528
<b>Total</b>	<b>646</b>

**Table 5: SIII.4: Ethnic origin**

<b>Ethnic origin</b>	<b>Patients</b>
Japanese (YLB113-001)	59
Indian (LBC14-155)	38
Centres in Europe, Ukraine, India, Japan (YLB113-002)	528
<b>Total</b>	<b>646</b>

**Part II: Module SIV - Populations Not Studied in Clinical Trials**

There were no representatives of population group falling under exclusion criteria in YLB113-001, LBC-14-155 and YLB113–002 study. Safety data on use of etanercept in these population groups is limited.

**SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme**Important exclusion criteria for YLB113–002 trial:

- **Stage A:** To compare the efficacy, safety, and immunogenicity of YLB113 (Fubelv) and EU-licensed Enbrel.
- **Stage B:** To compare long-term safety, and immunogenicity of YLB113 (Fubelv) and Enbrel.
- **Stage C:** To compare the sustainability of effects of treatment in patients with rheumatoid arthritis after crossing over treatments between YLB113 (Fubelv) and Enbrel arms, post-completion of 24 weeks treatment (Stage A).

Subjects were excluded from the study if they met any of the following criteria:

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**Stage A and Stage B:**

1. Pregnant females or nursing mothers.
2. Females of childbearing potential and males who were not willing to use reliable and effective contraceptive measures during the course of the study and for at least 3 months after the last study visit.

**Stage C:**

Subjects whose DAS28 score had either not improved or those who were more inclined to participate in Stage B.

Reason for exclusion: Safety data for use in the patient population mentioned above is limited.

Is it considered to be included as missing information? Yes

Rationale: Not applicable

***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 adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

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

**Table 6: SIV - Exposure of special populations included or not in clinical trial development programmes**

<b>Type of Special Population</b>	<b>Exposure</b>
Pregnant Women	Not included in the clinical development program
Breastfeeding Women	
Patients with relevant comorbidities: <ol style="list-style-type: none"> <li>1. Subjects allergic to latex.</li> <li>2. Subjects suffering from acute or chronic, localized or disseminated infections within months prior to screening.</li> <li>3. Subjects with active tuberculosis (TB), prior history of unsuccessfully treated TB, latent TB, or those who were at risk of developing TB.</li> <li>4. Subjects with a history of septic arthritis of native joints within 12 months prior to screening, or any prior history of septic arthritis of a prosthetic joint.</li> <li>5. Subjects diagnosed with other rheumatic diseases, autoimmune disease, connective tissue disease, or immune deficiencies.</li> <li>6. Subjects with active or prior history of malignancies within 5 years prior to screening.</li> <li>7. Subjects with a prior history of blood dyscrasias.</li> </ol>	Not included in the clinical development program

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<p>8. Subjects with a history of alcohol, drug, or chemical abuse in the past 2 years prior to screening.</p> <p>9. Subjects who received any live or attenuated vaccines within 4 weeks of screening.</p> <p>10. Subjects previously treated with any other biologic response modifiers for any autoimmune indication.</p> <p>11. Subjects with serious systemic infections.</p> <p>12. Subjects with Class III or IV congestive heart failure.</p> <p>13. Subjects with clinically significant abnormal ECG findings.</p> <p>14. Subjects with abnormal screening laboratory values:</p> <ul style="list-style-type: none"><li>• Haemoglobin <math>\leq 8</math> g/dl</li><li>• Platelet count <math>\leq 125,000/\text{mm}^3</math></li><li>• White blood cell count <math>\leq 3500/\text{mm}^3</math></li><li>• Lymphocyte count <math>\leq 1000</math> cell/<math>\text{mm}^3</math></li><li>• Aspartate aminotransferase (AST)/alanine aminotransferase (ALT)/alkaline phosphatase (ALP) <math>\geq 3 \times</math> upper limit of Normal (ULN), or serum total bilirubin <math>\geq 2 \times</math> ULN.</li><li>• Serum creatinine <math>\geq 2</math> mg/d</li></ul> <p>15. Subjects with active or prior history of clinically significant or uncontrolled respiratory, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic (including demyelinating disorders), metabolic, pulmonary, cardiovascular disease, or a history of any autoimmune disease or psychiatric illness, or any other condition which, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results.</p> <p>16. Subjects who participated in any other investigational study within 3 months prior to screening or are likely to simultaneously participate in another therapeutic clinical study.</p> <p>17. Females of childbearing potential and males who were not willing to use reliable and effective contraceptive measures during the course of the study and for at least 3 months after the last study visit.</p> <p>18. Subjects who received systemic/intra-articular corticosteroids, excluding those who</p>	
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<p>received a <math>\leq 10</math> mg/day oral dose of prednisolone or equivalent corticosteroid, 2 weeks prior to screening.</p> <p>19. Subjects who received or who had received alkylating agents (e.g. cyclophosphamides) within 6 months prior to screening only if being received for conditions other than cancer or multiple sclerosis.</p> <p>20. Subjects who were using nonsteroidal anti-inflammatory drugs (NSAIDs) and were not on a stable dose within 2 weeks prior to screening.</p> <p>21. Subjects determined by the Investigator (or sub-investigator) to be ineligible for this study.</p>	
Population with relevant different ethnic origin	Not included in the clinical development program
Subpopulations Carrying Relevant Genetic Polymorphisms	Not included in the clinical development program

**Part II: Module SV - Post-authorisation Experience**

Fubelv® is another proposed invented name for etanercept in the EMA region. Etanercept is also already approved and marketed under the trade name of Nepexto®.

There is no post-authorisation experience with Fubelv till date.

**Part II: Module SVI - Additional EU Requirements for the Safety Specification**

**Potential for harm from overdose**

No dose-limiting toxicities were observed during clinical trials of rheumatoid arthritis patients. The highest dose level evaluated has been an intravenous loading dose of 32 mg/m<sup>2</sup> followed by subcutaneous doses of 16 mg/m<sup>2</sup> administered twice weekly. One rheumatoid arthritis patient mistakenly self-administered 62 mg etanercept subcutaneously twice weekly for 3 weeks without experiencing undesirable effects. There is no known antidote to etanercept.

**Potential for transmission of infectious agents**

There is a slight potential of transmission of infectious agents as Fubelv is a biologic produced antibody. The production lines are state of the art and have been proven efficient and clean for the production of batches for clinical trials. Currently, there is no data suggesting any transmission of infectious agents with Fubelv.

**Potential for medication errors**

The Biosimilar Autoinjector uses the SHL Molly® Auto Injector and Enbrel SureClick® Autoinjector uses the SHL DAI® Disposable Auto Injector (DAI) for the delivery of the drug products. SHL Molly® Auto Injector has been selected for Biosimilar Autoinjector because of its similarity in the user interface and advantage over SHL DAI® Disposable Auto Injector (DAI). The choice of SHL Molly® Auto Injector for Biosimilar Auto injector can be considered as an improvement over the Reference Medicinal Product, Enbrel SureClick® Autoinjector. The differences in the user interface between the two products are less likely to pose any long-term significant effect on the users' ability to use Biosimilar Autoinjector safely and effectively. The difference in the functionality of the safety guard, are only likely to cause some confusion on the initial use of Biosimilar Autoinjector if at all. The users are likely to be aware of any use errors caused by the differences. In line with update of the originator RMP (Enbrel RMP version 7.4 dated 11-Jun-2020), potential for medication error associated with usage of a pre-filled

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pen was removed from the list of safety concerns, as further outlined in below sections of this RMP.

**Potential for off-label use**

Etanercept has not been studied in children aged less than 2 years. The potential for off-label use in children less than 2 years is unlikely.

**Specific paediatric issues**

Impaired growth and development of juvenile subjects have been observed but currently available data could not identify specific risk factor for risk group.

**Potential for misuse for illegal purposes**

Fubelv does not belong to a pharmacological class associated with drug abuse. Although, the abuse potential of Fubelv was not specifically studied, there were no data that would suggest that Fubelv may lead to drug abuse.

**Part II: Module SVII - Identified and Potential Risks**

**SVII.1 Identification of Safety Concerns in the Initial RMP Submission**

Fubelv has been developed as a biosimilar to Enbrel, its risk/benefit profile is considered to be similar to that of Enbrel. The safety and tolerability of Enbrel have been studied in various Phase I –IV clinical studies. The results have demonstrated well accepted efficacy and safety profile. The innovator drug Enbrel is approved and available in the market globally since 1998; therefore, benefits are well proven, and the risks are known for the treatment of rheumatoid arthritis.

On 02-Feb-2000, the product Enbrel® was authorised by the European Commission according to EMA product number- EMEA/H/C/000262. Accordingly, the safety concerns for Fubelv® are based on the list of safety concerns as presented in the European Public Assessment Report (EPAR) for Enbrel® (date 12-Jun-2025) [1].

**Table 7: SVII.1 - Summary of safety concerns**

<b>Summary of safety concerns<sup>1</sup></b>	
Important Identified Risks	<ul style="list-style-type: none"> <li>• Malignancy (including lymphoma and leukemia)</li> <li>• Serious and opportunistic infections (including tuberculosis, Legionella, Listeria and parasitic infections)</li> <li>• Demyelinating disorders</li> </ul>
Important Potential Risks	<ul style="list-style-type: none"> <li>• Encephalitis/ leukoencephalomyelitis</li> <li>• Progressive multifocal leukoencephalopathy [PML]</li> <li>• Impaired growth and development of juvenile subjects</li> </ul>
Missing Information	<ul style="list-style-type: none"> <li>• None<sup>2</sup></li> </ul>

**SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP**

Not applicable, as all risks from reference biologics RMP have been considered in this RMP.

<sup>1</sup> The following safety concerns are aligned with the originator RMP v7.9.

<sup>2</sup> Missing information presented in the originator RMP is not considered relevant for the Fubelv RMP.

### **SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP**

All safety concerns in the RMP for the biosimilar product Fubelv® are solely based on the safety concerns for the reference biologics Enbrel® (Pfizer Europe MA EEIG), containing Etanercept. Same are listed under SVII.1. Important Identified Risk

#### **1. Malignancy (including lymphoma and leukaemia):**

Risk-benefit impact: Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been received in the post-marketing period. Based on current knowledge, a possible risk for the development of lymphomas, leukaemia or other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded. Caution should be exercised when considering TNF-antagonist therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy. Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including etanercept. Post-marketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with etanercept. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

#### **2. Serious and opportunistic infections (including tuberculosis, Legionella, Listeria and parasitic infections):**

Risk-benefit impact: Serious infections, sepsis, tuberculosis, and opportunistic infections, including invasive fungal infections, listeriosis and legionellosis, have been reported with the use of etanercept. In some cases, particular fungal and other opportunistic infections have not been recognised, resulting in delay of appropriate treatment and sometimes death. In evaluating patients for infections, the patient's risk for relevant opportunistic infections (e.g. exposure to endemic mycoses) should be considered. Patients should be evaluated for infections before, during, and after treatment with Fubelv, taking into consideration that the mean elimination half-life of etanercept is approximately 70 hours.

#### **3. Demyelinating Disorders**

Chronic inflammatory demyelinating polyneuropathy is an acquired demyelinating disease of the peripheral nerves in which myelin is presumably the target of the immune attack. Cases could be the result of a specific autoimmune response induced by anti-TNF $\alpha$ . Accordingly, inflammatory demyelinating neuropathy has previously been described as occurring with other immunotherapies such as interferon- $\alpha$ , tacrolimus (FK506), cyclosporine A, and suramin. All these therapies might be involved in the disequilibrium of the immune system and could exacerbate the deleterious pro-inflammatory and tissue-damaging activities of the immune system. The potential mechanism for central demyelinating disorders is currently not well understood.

#### **Important potential risks**

##### **1. Encephalitis/ leukoencephalomyelitis**

Risk-benefit impact: Etanercept may be associated with encephalitis/ leukoencephalomyelitis however, currently available data is insufficient to establish causal association between etanercept and encephalitis/ leukoencephalomyelitis.

##### **2. Progressive multifocal leukoencephalopathy [PML]**

Risk-benefit impact: Etanercept may be associated with PML however, currently available data is insufficient to establish causal association between etanercept and PML. There have been rare reports of CNS demyelinating disorders in patients treated with etanercept. Additionally, there have been very rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy). Clinical trials of other TNF antagonists in

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patients with multiple sclerosis have shown increases in disease activity. A careful risk/benefit evaluation, including a neurologic assessment, is recommended when prescribing Fubelv 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.

**3. Impaired growth and development of juvenile subjects**

Risk-benefit impact: Etanercept may be associated with impaired growth and development of juvenile subjects. However, currently available data is insufficient to establish causal association between Etanercept and impaired growth and development of juvenile subjects.

**SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP**

Not applicable as this is the initial RMP for Fubelv®.

**SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information**

**SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks**

**Table 8: SVII.2 - Important Identified Risk: Malignancy (including lymphoma and leukaemia)**

<p><b>Potential Mechanisms</b></p>	<p>The possibility exists for TNF-antagonists, including etanercept, to affect host defences against malignancies since TNF mediates inflammation and modulates cellular immune responses. In the studies by innovator for etanercept, malignancies most likely resulted from the fact that patients received etanercept for the vast duration of the trials. Except for the case of lymphoma and thyroid carcinoma, all cases were considered by the investigator to be unrelated to study drug. Plausible explanations for the higher incidence of skin cancers in etanercept-treated patients were: (1) the number of patients and the duration of time that patients received etanercept vastly exceeded that for placebo due to the designs of the trials; and (2) the potential for underlying skin cancers to be unmasked as the patient’s psoriatic plaques clear. Six (6) of these patients with cutaneous malignancies had a previous history of the event, and 8 had received prior phototherapy before the study. Except for 2 cases of basal cell carcinoma, all cases were considered by the investigator to be unrelated to the study drug.</p>
<p><b>Evidence Source(s) and Strength of Evidence</b></p>	<p>Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been received in the post-marketing period. Based on current knowledge, a possible risk for the development of lymphomas, leukaemia or other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded. Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including etanercept. Post-marketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with etanercept. Analysis of the risk attributable to etanercept of relatively rare events like malignancy can be assessed by comparing the rates observed in the two phase 3 studies to those of an appropriate historical population. The observed number of extracutaneous</p>

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	<p>cancers in the etanercept psoriasis database (10 extracutaneous malignancies/1038.7 patient-years = 1.0 per 100 patient-years) is not significantly different from the expected rate based on calculations using the general population database from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database (0.5 per 100 patient-years; 95% confidence interval [CI] = 0.2-1.1). The SEER database does not include non-melanoma skin cancers.</p>
<p><b>Characterisation of the Risk</b></p>	<p>Malignancies, some fatal, have been reported among children, adolescents, and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy ≤ 18 years of age), including etanercept, in the post-marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies typically associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded. This risk will be further characterised from analysis of data available from registry.</p>
<p><b>Risk Factors and Risk Groups</b></p>	<p>Based on current knowledge, a possible risk for the development of lymphomas, leukaemia or other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded. Several studies have confirmed that the risk of malignancy in psoriasis patients exceeds that in the normal population, and standardised incidence ratios of 1.78 (95% CI 1.32-2.40), 1.3 (95% CI 1.2-1.4), 1.37 (95% CI 1.28-1.47), and 1.35 (95% CI 1.22-1.49) have been reported.</p>
<p><b>Preventability</b></p>	<p>Caution should be exercised when considering TNF-antagonist therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.</p>
<p><b>Impact on the Risk-Benefit Balance of the Product</b></p>	<p>Based on current knowledge, a possible risk for the development of lymphomas, leukaemia or other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded. Caution should be exercised when considering TNF-antagonist therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy. Melanoma and nonmelanoma skin cancer (NMSC) have been reported in patients treated with TNF antagonists, including etanercept. Post-marketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with etanercept. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.</p>
<p><b>Public Health Impact</b></p>	<p>No increase in incidence of malignancy has been seen with the duration of treatment or in relation to predicted malignancy rates for the general population. However, this risk will be further monitored through registry and pharmacovigilance activities.</p>

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**Table 9: SVII.3 - Important Identified Risk: Serious and opportunistic infections (including tuberculosis, Legionella, Listeria and parasitic infections)**

<b>Potential Mechanisms</b>	The possibility exists for TNF-antagonists, including etanercept, to affect host defences against infections since TNF mediates inflammation and modulates cellular immune responses.
<b>Evidence Source(s) and Strength of Evidence</b>	The most serious infections that have been reported with medicinal products containing etanercept are invasive fungal infections, listeriosis and legionellosis, active tuberculosis, including miliary tuberculosis and tuberculosis with extra-pulmonary location. Rates of infections (the most frequently reported AE) were related to the duration of treatment. Upper respiratory tract infections were the most commonly reported type of infection. Increased cough and respiratory disorders ("colds") were found to be significantly more frequent ( $p < 0.05$ ) in the high dose group compared to placebo and to the mid dose group. A trend ( $p < 0.10$ ) toward association of fever with etanercept treatment overall and with high dose treatment as compared to placebo was noted. The majority of fevers were associated with infections or other inflammatory conditions. In the sepsis clinical trial, 108 patients with documented sepsis were treated with etanercept and 33 patients received placebo. In this study, the patient group was severely immunocompromised. A higher mortality was observed in the etanercept-treated than in the placebo-treated group when the infection was caused by gram-positive or unknown microbes, and the mortality rate was raised in the groups treated with high doses of etanercept. The increased mortality observed with increasing dose could not be explained by imbalances at enrolment. Mortality was not related to an identifiable direct toxicity of etanercept.
<b>Characterisation of the Risk</b>	Serious infections were rare and occurred in similar proportions of patients across treatment groups during the initial 12-week, placebo-controlled portion of the 3 studies by innovator. Only 1 serious infection (pneumonia) occurred during the extended blinded portion (weeks 13 to 24) of studies. Five (5) serious infections occurred during the withdrawal/retreatment/open-label period of one study and 2 serious infections occurred during the long-term, open-label period of other study. Overall, for serious infections, there were 6 cases of cellulitis, 3 cases of pneumonia, 2 cases of abscess, and 1 case each of furunculosis, pharyngitis, cholecystitis, osteomyelitis, and gastroenteritis reported. No reports of opportunistic infections or tuberculosis occurred in any study. This risk will be further characterised from analysis of data available from registry.
<b>Risk Factors and Risk Groups</b>	Patient on concomitant treatment with other immunosuppressant are at additional risk.
<b>Preventability</b>	Patients should be evaluated for infections before, during, and after treatment with Fubelv, taking into consideration that the mean elimination half-life of etanercept is approximately 70 hours. Administration of Fubelv should be discontinued if a patient develops a serious infection.

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<b>Impact on the Risk-Benefit Balance of the Product</b>	In evaluating patients for infections, the patient’s risk for relevant opportunistic infections (e.g. exposure to endemic mycoses) should be considered.
<b>Public Health Impact</b>	Patients who develop a new infection while undergoing treatment with Fubelv should be monitored closely. The safety and efficacy of etanercept in patients with chronic infections have not been evaluated. Physicians should exercise caution when considering the use of Fubelv 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.

**Table 10: SVII.4 - Important Identified Risk: Demyelinating disorders**

<b>Potential Mechanisms</b>	Whether TNF-α blockers directly cause demyelination (either with a progressive or a monophasic course) or they trigger pre-existing demyelinating predisposition, remains controversial.
<b>Evidence Source(s) and Strength of Evidence</b>	There have been rare reports of CNS demyelinating disorders in patients treated with etanercept. Additionally, there have been very rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy). Although no clinical trials have been performed evaluating etanercept therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity.
<b>Characterisation of the Risk</b>	Central and peripheral demyelinating events have been seen rarely and very rarely with etanercept use, respectively.
<b>Risk Factors and Risk Groups</b>	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.
<b>Preventability</b>	A careful risk/benefit evaluation, including a neurologic assessment, prescribing Fubelv to patients at risk.
<b>Impact on the Risk-Benefit Balance of the Product</b>	To be determined from analysis of registry data.
<b>Public Health Impact</b>	A careful risk/benefit evaluation, including a neurologic assessment, is recommended when prescribing Fubelv 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.

**Table 11: SVII.7 - Important Potential Risk: Encephalitis/ leucoencephalomyelitis**

<b>Potential Mechanisms</b>	The Potential mechanism may be immune mediated.
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<b>Evidence Source(s) and Strength of Evidence</b>	Currently available data is not sufficient. The impact of long-term treatment with etanercept on the development of immune mediated reaction is unknown.
<b>Characterisation of the Risk</b>	This risk will be further characterised based on analysis of data from the registry.
<b>Risk Factors and Risk Groups</b>	Currently available data could not identify specific risk factors for the risk group.
<b>Preventability</b>	Regular monitoring
<b>Impact on the Risk-Benefit Balance of the Product</b>	To be determined from analysis of registry data.
<b>Public Health Impact</b>	Currently available data is not sufficient.

**Table 12: SVII.8 - Important Potential Risk: Progressive Multifocal Leukoencephalopathy [PML]**

<b>Potential Mechanisms</b>	The potential mechanism is immune mediated reaction
<b>Evidence Source(s) and Strength of Evidence</b>	Currently available data is not sufficient.
<b>Characterisation of the Risk</b>	This risk will be further characterised based on analysis of data from the registry.
<b>Risk Factors and Risk Groups</b>	Currently available data could not identify specific risk factors for the risk group.
<b>Preventability</b>	Regular monitoring
<b>Impact on the Risk-Benefit Balance of the Product</b>	To be determined from analysis of registry data.
<b>Public Health Impact</b>	Currently available data is not sufficient

**Table 13: SVII.9 - Important Potential Risk: Impaired growth and development of juvenile subjects**

<b>Potential Mechanisms</b>	The potential mechanism is not clear
<b>Evidence Source(s) and Strength of Evidence</b>	Currently available data is not sufficient
<b>Characterisation of the Risk</b>	This risk will be further characterised via routine pharmacovigilance activities.
<b>Risk Factors and Risk Groups</b>	Currently available data could not identify specific risk factor for risk group.

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<b>Preventability</b>	Regular monitoring.
<b>Impact on the Risk-Benefit Balance of the Product</b>	Impact is to be determined via routine pharmacovigilance activities.
<b>Public Health Impact</b>	Currently available data is not sufficient

**SVII.3.2. Presentation of the Missing Information**

Not applicable

**Part II: Module SVIII - Summary of the Safety Concerns**

**Table 14: SVIII - Summary of safety concerns**

Important Identified Risks	<ul style="list-style-type: none"> <li>• Malignancy (including lymphoma and leukemia)</li> <li>• Serious and opportunistic infections (including tuberculosis, Legionella, Listeria and parasitic infections)</li> <li>• Demyelinating disorders</li> </ul>
Important Potential Risks	<ul style="list-style-type: none"> <li>• Encephalitis/ leukoencephalomyelitis</li> <li>• Progressive multifocal leukoencephalopathy [PML]</li> <li>• Impaired growth and development of juvenile subjects</li> </ul>
Missing Information	<ul style="list-style-type: none"> <li>• None</li> </ul>

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### **Part III: Pharmacovigilance Plan (including post-authorisation safety studies)**

The Pharmacovigilance System Master File contains details of the system and processes that the MAH/Applicant has in place to identify and/or characterize the risks recognised in the safety specification.

#### **III.1 Routine Pharmacovigilance Activities**

Routine pharmacovigilance activities including AE collection and reporting, PSURs and signal detection will be carried out.

##### *Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*

A key requirement for pharmacovigilance of biologicals is the need to ensure continuous product and batch traceability in clinical use. Communication should emphasize the importance of providing the product name (or INN and name of the marketing authorisation holder) and batch number(s) when reporting suspected adverse reactions.

Etanercept will either be supplied in a hospital setting (e.g. whether used in primary or tertiary care) or other methods will be used to collect exposure information when used in secondary or tertiary care, such as routine bar code scanning at all points in the supply chain. Both, product name and batch number shall be recorded by the healthcare professionals (HCPs). In line with GVP Guideline for Biological medicinal products (EMA/168402/2014), recording drug name and batch number is mentioned in Section 4.4 of the Summary of Product Information (SmPC). The product name and batch information are included in the product packaging; thus, this information is available to be recorded and reported at all levels in the supply chain from manufacturer release to prescription, dispensing and patient administration.

All adverse event (AE) reports for biological medicinal products including biosimilars are evaluated by the Applicant's dedicated medical expert. Once missing information has been identified (e.g. reporting adverse events without indication of product name and batch number) or reported AE would benefit from further investigation, send out of specific adverse reaction follow-up questionnaires (for the following risks: Amyotrophic Lateral Sclerosis, Demyelination, Guillain- Barré Syndrome, Lymphoma, Mycosis Fungoides, Progressive Multifocal Leukoencephalopathy, Juvenile idiopathic arthritis subtype, Malignancy, Adverse events in paediatric patients, see [Annex 4](#)) to HCPs will be initiated. Together with a "biologic-specific cover letter" mentioning importance of reporting batch number and product name for AE reporting for biosimilars.

Specific safety concerns will be taken into consideration for risk-benefit assessment of individual biosimilars. Moreover, new safety signals including batch-specific safety issues can be detected and reported in a timely manner.

The pharmacovigilance plan includes a discussion around clinical settings of product use and how this may impact on routine product name and batch recording and reporting and what additional activities or risk minimisation measures are required to support product traceability (e.g. bar coding). As outlined above, in order to improve traceability of the medicinal product, the SmPC will include a prominent statement that the name/batch number of the administered product should be clearly recorded in the patient file. Related wording will also be included in educational material, and product promotional material, as applicable.

The Specific adverse drug reaction follow-up forms are provided in [Annex 4](#) of the RMP.

#### **Other forms of routine pharmacovigilance activities for safety concerns:**

Not Applicable

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### **III.2 Additional Pharmacovigilance Activities**

None for Fubelv.

**Note:** Fubelv® is another proposed invented name for etanercept in the EMA region. Etanercept has also already been approved and marketed under the trade name Nepexto®.

Etanercept has been demonstrated to be relatively safe, although some specific safety issues require continuing surveillance, including serious bacterial and opportunistic infections and increased risk of lymphomas with continued use. For ongoing safety evaluation, the Biosimilar Etanercept (Nepexto) will continue to be monitored through the German Biologics RABBIT registry.

### **III.3 Summary Table of Additional Pharmacovigilance Activities**

Not applicable for Fubelv.

**Part IV: Plans for post-authorisation efficacy studies**

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

Not applicable.

**Part V: Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)****Risk Minimisation Plan****V.1 Routine Risk Minimisation Measures****Table 15: Part V.1 - Description of routine risk minimisation measures by safety concern**

Safety Concern	Routine Risk Minimisation Activities
1. Malignancy (including lymphoma and leukaemia).	<p><u>Routine risk communication:</u> SmPC sections 4.4 and 4.8 PL sections 2 and 4</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> SmPC section 4.4 PL section 2</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u> Legal status: prescription only medicine</p>
2. Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, and parasitic infections)	<p><u>Routine risk communication:</u> SmPC sections 4.3, 4.4 and 4.8 PL sections 2 and 4</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> SmPC sections 4.3 and 4.4 PL section 2</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u> Legal status: prescription only medicine</p>
3. Demyelinating disorders	<p><u>Routine risk communication:</u> SmPC sections 4.4 and 4.8 PL sections 2 and 4</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> SmPC section 4.4 PL: section 2</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u> Legal status: prescription only medicine</p>
4. Encephalitis/leukoencephalomyelitis	<p><u>Routine risk communication:</u></p>

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	<p>None proposed.</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <p>None.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>None.</p> <p>Legal status: prescription only medicine</p>
<p>5. Progressive multifocal leukoencephalopathy [PML]</p>	<p><u>Routine risk communication:</u></p> <p>None proposed.</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <p>None.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>None.</p> <p>Legal status: prescription only medicine</p>
<p>6. Impaired growth and development of juvenile subjects</p>	<p><u>Routine risk communication:</u></p> <p>None proposed.</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <p>None.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>None.</p> <p>Legal status: prescription only medicine</p>

**V.2 Additional Risk Minimisation Measures**

In line with the reference biologics Enbrel (etanercept), this medicine has additional risk minimisation measures of "Patient Card" for the important identified risk of Serious infections (including opportunistic infections, tuberculosis, Legionella, Listeria, and parasitic infections).

**Patient Card (PC)**

Objectives: To educate patients and prescribers about important safety information associated with the use of Fubelv such as serious infections (including opportunistic infections, TB, Legionella, Listeria, parasitic infection). In particular, the Patient Card is designed to ensure that information regarding the patient's current therapy and the important risks for Fubelv is held by the patient at all times and is shown to the relevant HCP as appropriate.

Rationale for the additional risk minimisation activity:

Fubelv is a biosimilar medicinal product to Enbrel. As a biosimilar, Fubelv has the same risks and hence needs to follow the same risk minimisation measures as the reference medicinal product. In order to manage the important risks, the company has developed PC aligned with what is currently in place for Enbrel. Details of the additional risk minimisation measures are included in [Annex 6](#).

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Target audience and planned distribution path:

Appropriate method of distribution and target group will be agreed with the national competent authorities prior to launch.

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

The company will monitor effectiveness of risk minimisation measures by routine pharmacovigilance activities during PSUR preparation (as per the EURD list), signal detection activity and medical review, as per internal procedures. The incidence of adverse reactions will be compared with those described in the SmPC. If there is an increased incidence of adverse reactions or if the reports are different in seriousness, severity, or outcome to that described in the SmPC, labelling changes or risk minimisation will be considered. Additionally, effectiveness of additional RMMs will be evaluated on annual basis after MA approval.

**V.3 Summary Table of Pharmacovigilance and Risk Minimisation Activities by Safety Concern**

**Table 16: Part V.3 - Summary table of pharmacovigilance activities and risk minimisation activities by safety concern**

<b>Safety Concern</b>	<b>Risk Minimisation Measures</b>	<b>Pharmacovigilance Activities</b>
Malignancy (including lymphoma and leukaemia)	<p><u>Routine risk minimisation measures:</u></p> <p>SmPC sections 4.4 and 4.8</p> <p>PL sections 2 and 4</p> <p>Legal status: prescription only medicine</p> <p><u>Additional risk minimisation measures:</u></p> <p>None</p>	<p><b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b></p> <p><i>AE Follow-up questionnaire form for Malignancy, Mycosis fungoides and Lymphoma (Annex 4)</i></p> <p><b>Additional pharmacovigilance activities:</b></p> <p>None</p>
Serious infections (including opportunistic infections, tuberculosis, Legionella, Listeria, and parasitic infections)	<p><u>Routine risk minimisation measures</u></p> <p>SmPC sections 4.3, 4.4 and 4.8.</p> <p>PL sections 2 and 4</p> <p>Legal status: prescription only medicine</p> <p><u>Additional risk minimisation measures</u></p> <p>Patient Card</p>	<p><b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b></p> <p>None</p> <p><b>Additional pharmacovigilance activities:</b></p> <p>None</p>
Demyelinating disorders	<p><u>Routine risk minimisation measures</u></p> <p>SmPC sections 4.4 and 4.8</p> <p>PL sections 2 and 4</p>	<p><b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b></p> <p><i>AE Follow-up questionnaire form for ALS, Demyelination</i></p>

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	<p>Legal status: prescription only medicine</p> <p><u>Additional risk minimisation measures</u></p> <p>None</p>	<p><i>and Guillain-Barré Syndrome (<b>Annex 4</b>)</i></p> <p><b>Additional pharmacovigilance activities:</b></p> <p>None</p>
<p>Encephalitis/leukoencephalomyelitis</p>	<p><u>Routine risk minimisation measures:</u></p> <p>None proposed.</p> <p><u>Additional risk minimisation measures:</u></p> <p>None proposed.</p>	<p><b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b></p> <p>None</p> <p><b>Additional pharmacovigilance activities:</b></p> <p>None</p>
<p>Progressive multifocal leukoencephalopathy [PML]</p>	<p><u>Routine risk minimisation measures:</u></p> <p>None proposed.</p> <p><u>Additional risk minimisation measures:</u></p> <p>None proposed.</p>	<p><b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b></p> <p><i>AE Follow-up questionnaire form for PML (<b>Annex 4</b>)</i></p> <p><b>Additional pharmacovigilance activities:</b></p> <p>None</p>
<p>Impaired growth and development of juvenile subjects</p>	<p><u>Routine risk minimisation measures:</u></p> <p>None proposed.</p> <p><u>Additional risk minimisation measures:</u></p> <p>None proposed.</p>	<p><b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b></p> <p><i>AE Follow-up questionnaire form for Juvenile idiopathic arthritis subtype (<b>Annex 4</b>)</i></p> <p><b>Additional pharmacovigilance activities:</b></p> <p>None</p>

## **Part VI: Summary of the risk management plan**

### **Summary of Risk Management Plan for Fubelv<sup>®</sup> (etanercept)**

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

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

This summary of the RMP for Fubelv should be read in the context of all the 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 Fubelv 's RMP.

#### **I. The medicine and what it is used for.**

Fubelv is authorised for

1. Treatment of rheumatoid arthritis (a disease-causing inflammation of the joints) in adults, used with another medicine, methotrexate, or alone.
2. Treatment of certain forms of juvenile idiopathic arthritis (diseases causing inflammation in the joints, with first appearance in childhood or adolescence).
3. Treatment of plaque psoriasis (a disease causing red, scaly patches on the skin) in adults and children.
4. Treatment of psoriatic arthritis (psoriasis with inflammation of the joints) in adults and adolescents.
5. Treatment of ankylosing spondylitis (a disease-causing inflammation of the joints of the spine) in adults.
6. Treatment of axial spondyloarthritis (a chronic inflammatory disease of the spine) in adults when there are no abnormalities seen on x-ray.

It contains etanercept as the active substance, and it is administered subcutaneously.

Further information about the evaluation of Fubelv's benefits can be found in Fubelv's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's [webpage: Fubelv | European Medicines Agency \(EMA\)](#)

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

Important risks of Fubelv, together with measures to minimise such 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 package leaflet 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 public (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

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In the case of Fubelv®, these routine 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 regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Fubelv is not yet available, it is listed under 'missing information' below.

**II.A List of important risks and missing information**

Important risks of Fubelv® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered to patients. 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 Fubelv®. 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/use in special patient populations etc.).

**Table 17: Part VI.1 - Summary of safety concerns**

<b>List of Important Risks and Missing Information</b>	
Important Identified Risks	<ul style="list-style-type: none"> <li>• Malignancy (including lymphoma and leukemia)</li> <li>• Serious and opportunistic infections (including tuberculosis, Legionella, Listeria and parasitic infections)</li> <li>• Demyelinating disorders</li> </ul>
Important Potential Risks	<ul style="list-style-type: none"> <li>• Encephalitis/ leukoencephalomyelitis</li> <li>• Progressive multifocal leukoencephalopathy [PML]</li> <li>• Impaired growth and development of juvenile subjects</li> </ul>
Missing Information	<ul style="list-style-type: none"> <li>• None</li> </ul>

**II.B. Summary of Important Risks**

**Table 18: Part VI.2 - Important Identified Risk: Malignancy (including lymphoma and leukaemia)**

<b>Evidence for Linking the Risk to the Medicine</b>	<p>Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been received in the post-marketing period. Based on current knowledge, a possible risk for the development of lymphomas, leukaemia or other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded. Melanoma and nonmelanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including etanercept. Post-marketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with etanercept. Analysis of the risk attributable to etanercept of relatively rare events like malignancy can be assessed by comparing the rates observed in the two phase 3 studies to those of an appropriate historical population. The observed number of extracutaneous cancers in the etanercept</p>
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	psoriasis database (10 extracutaneous malignancies/1038.7 patient-years = 1.0 per 100 patient-years) is not significantly different from the expected rate based on calculations using the general population database from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database (0.5 per 100 patient-years; 95% confidence interval [CI] = 0.2-1.1). The SEER database does not include non-melanoma skin cancers.
<b>Risk Factors and Risk Groups</b>	Patients with RA have a 10 % increase in overall malignancy risk compared with the general population. Furthermore, the standardized incidence ratio (SIR) estimates for patients with RA continued to show an increased risk of lymphoma and lung cancer as previously observed. Overall, SIR estimates for colorectal and breast cancers continued to show a decrease in risk, whereas cervical cancer, prostate cancer and melanoma appeared to show no consistent trend in risk among patients with RA compared with the general population ( <b>Simon et al, 2015</b> ) [2]. Several studies have confirmed that the risk of malignancy in psoriasis patients exceeds that in the normal population, and standardized incidence ratios of 1.78 (95% CI 1.32-2.40), 1.3 (95% CI 1.2-1.4), 1.37 (95% CI 1.28-1.47), and 1.35 (95% CI 1.22-1.49) have been reported.
<b>Risk Minimisation Measures</b>	<p><u>Routine risk minimization measures</u></p> <p>SmPC sections 4.4 and 4.8</p> <p>PL sections 2 and 4</p> <p>Legal status: prescription only medicine</p> <p><u>Additional risk minimisation measures</u></p> <p>None</p>
<b>Additional Pharmacovigilance activities</b>	None

**Table 19: Part VI.3 - Important Identified Risk: Serious and opportunistic infections (including tuberculosis, Legionella, Listeria and parasitic infections)**

<b>Evidence for Linking the Risk to the Medicine</b>	Rates of infections (the most frequently reported adverse event) were related to the duration of treatment. The most serious infections that have been reported with medicinal products containing etanercept are invasive fungal infections listeriosis and legionellosis, active tuberculosis, including miliary tuberculosis and tuberculosis with extra-pulmonary location. Upper respiratory tract infections were the most commonly reported type of infection. Increased cough and respiratory disorders (“colds”) were found to be significantly more frequent (p<0.05) in the high dose group compared to placebo and to the mid dose group. A trend (p< 0.10) toward association of fever with etanercept treatment overall and with high dose treatment as compared to placebo was noted. The majority of fevers were associated with infections or other inflammatory conditions. In the sepsis clinical trial, 108 patients with documented sepsis were treated with etanercept and 33 patients received placebo. In this study, the
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	<p>patient group was severely immuno-compromised. A higher mortality was observed in the etanercept -treated than in the placebo-treated group when the infection was caused by gram-positive or unknown microbes, and the mortality rate was raised in the groups treated with high doses of etanercept. The increased mortality observed with increasing dose could not be explained by imbalances at enrolment. Mortality was not related to an identifiable direct toxicity of etanercept.</p>
<b>Risk Factors and Risk Groups</b>	<p>Standard-dose and high-dose biological drugs (with or without traditional disease-modifying anti-rheumatic drugs [DMARDs]) have been shown to be associated with a statistically significant increase in serious infections in methotrexate-naïve rheumatoid arthritis patients compared with traditional DMARDs; the absolute risk increase of serious infections with biologic therapy was identified as 6 per 1000 for standard-dose biologic and 17 per 1000 for high-dose biologic therapy <b>(Singh et al, 2015)</b> [3].</p> <p>Patient on concomitant treatment with other immunosuppressants are at additional risk.</p>
<b>Risk Minimisation Measures</b>	<p><u>Routine risk minimisation measures</u></p> <p>SmPC sections 4.3, 4.4 and 4.8</p> <p>PL sections 2 and 4</p> <p>Legal status: prescription only medicine</p> <p><u>Additional risk minimisation measures</u></p> <p>Patient Card</p>
<b>Additional Pharmacovigilance activities</b>	<p>None</p>

**Table 20: Part VI.4 - Important Identified Risk: Demyelinating disorders**

<b>Evidence for Linking the Risk to the Medicine</b>	<p>There have been rare reports of CNS demyelinating disorders in patients treated with etanercept. Additionally, there have been very rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy). Although no clinical trials have been performed evaluating etanercept therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity.</p>
<b>Risk Factors and Risk Groups</b>	<p>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. Risk factors for GBS include male sex, prior infection (e.g. Campylobacter jejuni, Epstein Barr virus, cytomegalovirus, mycoplasma, HIV, and more recently Zika virus <b>(Blazquez &amp; Saiz 2016)</b> [4], vaccines, malignancies (e.g. lymphomas, especially Hodgkin's disease) <b>(Ansar &amp; Valadi 2015)</b> [5].</p>

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<b>Risk Minimisation Measures</b>	<u>Routine risk minimisation measures</u> SmPC section 4.4 and 4.8 PL section 2 and 4 <u>Legal status: prescription only medicine</u> <u>Additional risk minimisation measures</u> None
<b>Additional Pharmacovigilance activities</b>	None

**Table 21: Part VI.7 - Important Potential Risk: Encephalitis/ leukoencephalomyelitis**

<b>Evidence for Linking the Risk to the Medicine</b>	Currently available data is not sufficient. The impact of long-term treatment with etanercept on the development of immune mediated reaction is unknown.
<b>Risk Factors and Risk Groups</b>	Currently available data could not identify specific risk factor for risk group.
<b>Risk Minimisation Measures</b>	<u>Routine risk minimisation measures</u> None proposed. Legal status: prescription-only medicine <u>Additional risk minimisation measures</u> None proposed.
<b>Additional Pharmacovigilance activities</b>	None

**Table 22: Part VI.8 - Important Potential Risk: Progressive Multifocal Leukoencephalopathy [PML]**

<b>Evidence for Linking the Risk to the Medicine</b>	Currently available data is not sufficient.
<b>Risk Factors and Risk Groups</b>	PML primarily affects individuals with chronically and severely suppressed immune systems and is associated primarily with HIV patients, haematological malignancies, or relapsing–remitting multiple sclerosis patients treated with natalizumab. PML is also associated with other conditions such as organ transplantation, solid malignancies, sarcoidosis, autoimmune disorders (e.g. lupus, RA), and congenital immune deficiencies; these populations individually contribute a relatively small number of cases and together account for less than 10% of all reported PML cases ( <b>Pavlovic et al, 2015</b> ) <sup>[6]</sup> .
<b>Risk Minimisation Measures</b>	<u>Routine risk minimisation measures</u> None proposed.

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	Legal status: prescription-only medicine <u>Additional risk minimisation measures</u> None proposed.
<b>Additional Pharmacovigilance activities</b>	None

**Table 23: Part VI.9 - Important Potential Risk: Impaired growth and development of juvenile subjects**

<b>Evidence for Linking the Risk to the Medicine</b>	Currently available data is not sufficient.
<b>Risk Factors and Risk Groups</b>	Currently available data could not identify specific risk factor for risk group.
<b>Risk Minimisation Measures</b>	<u>Routine risk minimisation measures</u> None proposed. Legal status: prescription-only medicine <u>Additional risk minimisation measures</u> None proposed.
<b>Additional Pharmacovigilance activities</b>	None

## **II.C. Post-authorisation development plan**

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

There are no studies which are condition to marketing authorisation or specific obligation of Fubelv.

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

Not applicable

## **Part VII: Annexes**

### **List of Annexes**

Annex 4 - Specific Adverse Drug Reaction follow-up forms

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

***Annex 4 - Specific adverse drug reaction follow-up forms***

**Table of Contents**

**Follow-up forms**

Annex 4a: Targeted follow-up questionnaire for Amyotrophic Lateral Sclerosis, Demyelination, and Guillain- Barré Syndrome

Annex 4b: Targeted follow-up questionnaire for Lymphoma.

Annex 4c: Targeted follow-up questionnaire for Mycosis Fungoides

Annex 4d: Targeted follow-up questionnaire for Progressive Multifocal Leukoencephalopathy

Annex 4e: Targeted follow-up questionnaire for Juvenile idiopathic arthritis subtype.

Annex 4f: Targeted follow-up questionnaire for Malignancy.

Annex 4g: Targeted follow-up questionnaire for Adverse events in paediatric patients.

**Note:** The above questionnaires are utilized in conjunction with standard case follow-up procedures to obtain complete case information.

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**
**To be Pre-Filled by the Pharmacovigilance Department**

Local Reference No		Safety Id No	
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**Part -I - To be filled out by Patient/Reporter**

Please fill out the Questionnaire as complete as possible. First check if personal information below is prefilled correct and complete.

Report date	__/__/____	Gender	
Age	Years      Months	Race	
Occupation (please specify)		Duration (Years)	

Please tick the appropriate box (yes/no) for each question and add comments relevant to the option if any in the last column, including the duration till the date of this report and nature of the symptoms.

a. Medical History				
		Yes	No	Additional information
1	Any concurrent or history of infections especially gastrointestinal or respiratory tract infections			
2	Have you been diagnosed with any chronic immunodeficiency disorders if so, please specify the disorders			
3	Any illness after vaccinations, if so please specify the symptoms experienced			
4	History of any surgery or surgical procedures undergone			
5	History of diabetes or thyroid disorders			
6	Any history of family members (parents or siblings) diagnosed/treated for any debilitating neurological disorders, please specify the diagnosis if any			
7	History of head injury affecting consciousness			

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

8	Do you have habit of smoking^			
9	Have you been ever diagnosed with precancerous or cancerous conditions since childhood			

Please tick the appropriate box (yes/no) for each question and add comments relevant to the option if any including duration and nature of the symptoms in the last column.

<b>b. Present complaints</b>					
		Yes	No	Duration	Start date
1	Any numbness or Tingling or pricking sensation				--/---/----
2	Pain (generalized or local)				--/---/----
3	Generalized weakness				--/---/----
4	Difficulty in breathing or feeling chest tightness while breathing				--/---/----
5	Any change in speech (i.e slurred speech, difficulty in speaking)				--/---/----
6	Trouble swallowing or cramping or button the shirt or turn a key. Difficulty in chewing or muscle stiffness				--/---/----
7	Do you feel drowsy or sleepy even during daytime				--/---/----
8	Loss of touch or pain sensation				--/---/----
9	Do you have blurred or double vision				--/---/----
10	Is there any eye irritation or pain and sensitive to light				--/---/----

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

11	Paralysis of any part of body especially legs, arms, or muscles in the face				-- / -- / --
12	Trouble swallowing or cramping or button the shirt or turn a key. Difficulty in chewing, muscle stiffness				-- / -- / --
13	Stumble or frequent fall than usual, slurred or nasal speech				-- / -- / --
14	Any gait disturbance				-- / -- / --
15	Have you noticed any weight loss				-- / -- / --
16	Do you have fever with chills and headache				-- / -- / --

Additional information on any of the sections under b. present complaints should be detailed in below table with respective serial number indexed above.

No.	Additional information

If you are the Reporter/Patient of the Report, please indicate below if treating Physician can be contacted, if yes, please indicate Contact details.

Consent to contact treating physician or Healthcare professional	Yes p    No p
Contact details of Treating physician or Healthcare professional	
Contact Phone:	

**Please return the questionnaire to: E-Mail: [drugsafety@biocon.com](mailto:drugsafety@biocon.com)**

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

**Post: Department, Street, Town, Country or hand it to your treating Physician, that part II can be filled out accordingly.**

**Part -II To be filled out by treating Physician**

Adverse events	Serious <sup>A</sup>	Severity <sup>B</sup>	Onset date	Outcome <sup>C</sup>	End date <sup>D</sup> (if applicable)	Related to drug <sup>E</sup>
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
<sup>A</sup> Seriousness 1.Non-serious 2.Medically significant 3.Hospitalization/ prolonged 4.Permanent disability/incapacity 5. Congenital anomaly 6. Life-threatening 7. Death		<sup>B</sup> Severity 1.Mild 2.Moderate 3. Severe		<sup>C</sup> Outcome 1.Recovered 2. Recovering 3. Not recovered 4.Recovered with sequelae 5. Death 6.Unknown	<sup>D</sup> Please complete only if outcome option is 1 recovered.	<sup>E</sup> Related N No Y Yes (please specify the serial number of the suspect drugs from above box, if related to suspect drug 1 and not related to suspect drug 2, enter as Y 1, N 2)

**a. Brighton's diagnostic criteria for GBS<sup>#</sup>**

Clinical finding	Level of diagnostic certainty
Bilateral and flaccid weakness of limbs	
Decreased or absent deep tendon reflexes in weak limbs	
Monophasic course and time between onset-nadir 12 h to 28 days	

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

CSF cell count <50/μl	
CSF protein concentration > normal value	
NCS findings consistent with one of the subtypes of GBS	
Absence of alternative diagnosis for weakness	

# please complete the section a. if any of the symptoms above mentioned were documented in this patient's history and GBS is diagnosed (level 1 to 4 decreasing certainty level. i.e. Level 1 is the highest level of diagnostic certainty)

b. Diagnostic Investigations	
Tests	Results
Electromyography (EMG)	
Nerve conduction study (NCS)	
Cerebrospinal fluid (CSF) analysis	Protein level _____ mg/L Glucose _____ mg/dL WBC _____ RBC _____
Muscle biopsy	
Antibody tests	
Others (urinalysis for renal function and heavy metals if performed)	

Please specify the diagnostic test to ensure the confirmatory diagnosis furnished above

c. Hematology	
Tests	Results (units)

Please attach the haematology profile performed before and after Etanercept treatment start date  
 \$ Please specify if the demyelinating disorder was diagnosed (i.e. transverse myelitis or multiple sclerosis)

d. Surgical intervention (if applicable)	
Surgery underwent	
Date of surgery	__/__/__
Any recurrence after this	

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

 surgery.  
 If yes, please provide

**e. Medical intervention (if applicable)**

Treatment medications	Indication	Start date	Stop date
		--/ /--	--/ /--
		--/ /--	--/ /--
		--/ /--	--/ /--
		--/ /--	--/ /--
		--/ /--	--/ /--

Physical examination Findings <i>(with specific body system involved)</i>	
Confirmed diagnosis	
If not confirmed please provide provisional diagnosis	
Date of diagnosis	

**Etanercept Therapy**

Start date	End date	Dose	Route	Indication	Action taken
--/ /--	--/ /--				

**Other Suspect/Concomitant Medications**

Medications <sup>\$</sup>	Start date	End date	Dose	Route	Indication	Action taken
	--/ /--	--/ /--				



**TARGETED FOLLOW UP FORM**

**BBL Case No.:**

	--/---/----	--/---/----				
	--/---/----	--/---/----				
	--/---/----	--/---/----				
	--/---/----	--/---/----				
	--/---/----	--/---/----				

<i>Treating Physician or HCP Name</i>		<i>Date of report</i>	--/---/----
<i>Treating Physician or HCP Signature</i>		<i>Dispatch Date</i>	--/---/----

**Please return the questionnaire to: E-Mail: [drugsafety@biocon.com](mailto:drugsafety@biocon.com)**

**Post: Department, Street, Town, Country or hand it to your treating Physician, that part II can be filled out accordingly.**

**Reporter's Details:**

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: \_\_\_\_\_ Sign \_\_\_\_\_

Occupation: \_\_\_\_\_ Date: \_\_\_\_\_

Biocon Biologics is committed to holding patient's and reporter's personal data in strict confidence. Personal data, here, means any information by which a person is, directly or



<b>TARGETED FOLLOW UP FORM</b>		
<b>BBL Case No.:</b>		

indirectly, identified or identifiable, which includes, but is not limited, to name, address, contact number, email address, genetic data and data concerning health. Biocon Biologics strictly adheres to applicable data privacy and data integrity laws, including, but not limited to, General Data Protection Regulations [EU] 2016/679 [“GDPR”] or its equivalent, as amended from time to time.

**Additional Information:**

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**TARGETED FOLLOW UP FORM**

**BBL Case No.:**

**To be Pre-Filled by the Pharmacovigilance Department**

Local Reference No		Safety Id No	
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**Part -I - To be filled out by Patient/Reporter**

Please fill out the Questionnaire as complete as possible. First check if personal information below is prefilled correct and complete.

Report date	_/_/____/____	Gender	
Age	Years      Months	Race	
Occupation (please specify)		Duration (Years)	

Please tick the appropriate box (yes/no) for each question and add comments relevant to the option if any in the last column, including the duration till the date of this report and nature of the symptoms.

a. Medical History				
		Yes	No	Additional information
1	Pre-existing diagnosed lymphoma in any part of the body			
2	Any family members suffered from similar ailment			
3	Any history of family members (parents or siblings) diagnosed/treated lymphoma			
4	Any chronic therapy with hormones, steroids or medication			
5	Menstrual history- any change in menstruating period, amount of flow ( <i>for female patients only</i> )			
6	Underwent surgery for any ailment, if so please specify the diagnosis and treatment			
7	Exposure to radiations especially nuclear radiation/ chemical exposure			

Please tick the appropriate box (yes/no) for each question and add comments relevant to the option if any in the last column, including the duration till the date of this report and nature of the symptoms

b. Present complaints					
		Yes	No	Duration	Start date
1	Feeling weak or tired without any exertion				_/_/____/____



**TARGETED FOLLOW UP FORM**

**BBL Case No.:**

2	Sudden weight loss or gain without any reason				--/---/---
3	Any skin changes either with a new mole or change is shape and size of exiting mole				--/---/---
4	Any skin changes only sun exposed areas of the body				--/---/---
5	Sore/Ulcer that was not healing				--/---/---
6	Any change in bowel or bladder habits				--/---/---
7	Persistent hoarseness or change in voice or cough				--/---/---
8	Breast changes in size or shape; change in texture of skin over breast				--/---/---
9	Any thickness or swelling in any part body for long duration				--/---/---
10	Any unusual discharge (i.e. nasal, ear, urethra)				--/---/---
11	Loss of appetite				--/---/---
12	Problems in eating- any discomfort, swallowing difficulty				--/---/---
13	Abdominal pain for chronic period				--/---/---
14	If any pre-existing cancerous condition present at start of Etanercept therapy, whether increase in tumor size or any pre-existing symptoms worsened after starting Etanercept therapy				--/---/---

Additional information on any of the sections under b. present complaints should be detailed in below table with respective serial number indexed above

No.	Additional information

If you are the Reporter/Patient of the Report, please indicate below if treating Physician can be contacted, if yes, please indicate Contact details.

Consent to contact treating physician or Healthcare professional	Yes <input type="checkbox"/> No <input type="checkbox"/>
Contact details of Treating physician or Healthcare professional	
Contact Phone:	



**TARGETED FOLLOW UP FORM**

**BBL Case No.:**

Please return the questionnaire to: E-Mail: [drugsafety@biocon.com](mailto:drugsafety@biocon.com)

**Post: Department, Street, Town, Country or hand it to your treating Physician, that part II can be filled out accordingly.**

**Part -II To be filled out by treating Physician**

Adverse events	Serious <sup>A</sup>	Severity <sup>B</sup>	Onset date	Outcome <sup>C</sup>	End date <sup>D</sup> (if applicable)	Related to drug <sup>E</sup>
			_ / _ / _ _		_ / _ / _ _	
			_ / _ / _ _		_ / _ / _ _	
			_ / _ / _ _		_ / _ / _ _	
			_ / _ / _ _		_ / _ / _ _	
			_ / _ / _ _		_ / _ / _ _	
			_ / _ / _ _		_ / _ / _ _	
<b><sup>A</sup>Seriousness</b> 1.Non-serious 2.Medically significant 3.Hospitalization/ prolonged 4.Permanent disability/incapacity 5. Congenital anomaly 6. Life-threatening 7. Death		<b><sup>B</sup>Severity</b> 1.Mild 2.Moderate 3. Severe		<b><sup>C</sup>Outcome</b> 1.Recovered 2. Recovering 3.Not recovered 4.Recovered with sequelae 5. Death 6.Unknown	<b><sup>D</sup></b> Please complete only if outcome option is 1 recovered.	<b><sup>E</sup>Related</b> N No Y Yes (please specify the serial number of the suspect drugs from above box, if related to suspect drug 1 and not related to suspect drug 2, enter as Y 1, N 2)

a. Diagnostic Investigations	
Tests	Results

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**


Please specify the diagnostic test to ensure the confirmatory diagnosis furnished above

b. Hematology	
Tests	Results (units)

Please attach the haematology profile performed before and after Etanercept treatment start date

<b>Physical examination</b>	Findings <i>(with specific body system involved)</i> Lymph node involved: _____ <i>(please specify the nodes)</i> Nature of swelling include size _____ Other systemic involvement _____ Metastases if any: _____ <i>(please specify the sites involved)</i>
<b>Confirmed diagnosis</b> <i>(please confirm if malignant neoplasm progression is diagnosed)</i>	
<b>If not confirmed please provide provisional diagnosis</b>	
<b>Date of diagnosis</b>	

c. Staging of Lymphoma

*Please specify the staging classification followed*

d. Surgical intervention (if applicable)	
Surgery underwent	



**TARGETED FOLLOW UP FORM**

**BBL Case No.:**


Date of surgery	--/ /--
Any recurrence after this surgery. If yes, please provide	

e. Medical intervention (if applicable)	
Chemotherapy Regimen	<i>For each cycle, chemotherapeutic drugs administered</i>
	1
	2
	3
	4
	5
Start date	--/ /--
End date If therapy discontinued while treatment with Etanercept	--/ /--
Number of cycles completed	

Etanercept Therapy					
Start date	End date	Dose	Route	Indication	Action taken
--/ /--	--/ /--				

Other Suspect/Concomitant Medications						
Medications <sup>§</sup>	Start date	End date	Dose	Route	Indication	Action taken
	--/ /--	--/ /--				
	--/ /--	--/ /--				
	--/ /--	--/ /--				
	--/ /--	--/ /--				
	--/ /--	--/ /--				
	--/ /--	--/ /--				

Treating Physician or HCP Name		Date of report	--/ /--
Treating Physician or		Dispatch Date	

		
<b>TARGETED FOLLOW UP FORM</b>		
<b>BBL Case No.:</b>		

<i>HCP Signature</i>			_ _ / _ _ / _ _ _ _
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**Please return the questionnaire to: E-Mail: [drugsafety@biocon.com](mailto:drugsafety@biocon.com)**

**Post: Department, Street, Town, Country or hand it to your treating Physician, that part II can be filled out accordingly.**

**Reporter’s Details:**

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: \_\_\_\_\_ Sign \_\_\_\_\_

Occupation: \_\_\_\_\_ Date: \_\_\_\_\_

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**Additional Information:**

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**TARGETED FOLLOW UP FORM**
**BBL Case No.:**
**To be Pre-Filled by the Pharmacovigilance Department**

Local Reference No		Safety Id No	
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**Part - I - To be filled out by Patient/Reporter**

Please fill out the Questionnaire as complete as possible. First check if personal information below is prefilled correct and complete.

Report date	--/--/----	Gender	
Age	Years Months	Race	
Occupation (please specify)		Duration (Years)	

Please tick the appropriate box (yes/no) for each question and add comments relevant to the option if any in the last column, including the duration till the date of this report and nature of the symptoms.

a. Medical History				
		Yes	No	Additional information
1	Pre-existing diagnosed Lymphoma in any part of the body			
2	Any family members suffered from similar ailment			
3	Any history of family members (parents or siblings) diagnosed/treated lymphoma			
4	Any chronic therapy with hormones, steroids or medication			
5	Menstrual history- any change in menstruating period, amount of flow ( <i>for female patients only</i> )			
6	Underwent surgery for any ailment, if so please specify the diagnosis and treatment			
7	Exposure to radiations especially nuclear radiation/ chemical exposure			

Please tick the appropriate box (yes/no) for each question and add comments relevant to the option if any including duration and nature of the symptoms in the last column.

b. Present complaints					
		Yes	No	Duration	Start date
1	Feeling weak or tired without any exertion				--/--/----
2	Sudden weight loss or gain without any reason				--/--/----

**TARGETED FOLLOW UP FORM**

**BBL Case No.:**

3	Any skin changes either with a new mole or change in shape and size of existing mole				--/---/-----
4	Any skin changes only sun exposed areas of the body				--/---/-----
5	Sore/Ulcer that was not healing				--/---/-----
6	Any change in bowel or bladder habits				--/---/-----
7	Persistent hoarseness or change in voice or cough				--/---/-----
8	Breast changes in size or shape; change in texture of skin over breast				--/---/-----
9	Any thickness or swelling in any part body for long duration				--/---/-----
10	Any unusual discharge (i.e. nasal, ear, urethra)				--/---/-----
11	Loss of appetite				--/---/-----
12	Problems in eating- any discomfort, swallowing difficulty				--/---/-----
13	Abdominal pain for chronic period				--/---/-----

Additional information on any of the sections under b. present complaints should be detailed in below table with respective serial number indexed above.

No.	Additional information

If you are the Reporter/Patient of the Report, please indicate below if treating Physician can be contacted, if yes, please indicate Contact details.

Consent to contact treating physician or Healthcare professional	Yes <input type="checkbox"/> No <input type="checkbox"/>
Contact details of Treating physician or Healthcare professional	
Contact Phone:	

**Please return the questionnaire to: E-Mail: [drugsafety@biocon.com](mailto:drugsafety@biocon.com)**

**Post: Department, Street, Town, Country or hand it to your treating Physician, that part II can be filled out accordingly.**

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**
**Part II To be filled out by treating Physician**

Adverse events	Serious <sup>A</sup>	Severity <sup>B</sup>	Onset date	Outcome <sup>C</sup>	End date <sup>D</sup> (if applicable)	Related to drug <sup>E</sup>
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
<b><sup>A</sup>Seriousness</b> 1.Non-serious 2.Medically significant 3.Hospitalization/ prolonged 4.Permanent disability/incapacity 5. Congenital anomaly 6. Life-threatening 7. Death		<b><sup>B</sup>Severity</b> 1.Mild 2.Moderate 3. Severe		<b><sup>C</sup>Outcome</b> 1.Recovered 2. Recovering 3.Not recovered 4.Recovered with sequelae 5. Death 6.Unknown	<b><sup>D</sup></b> Please complete only if outcome option is 1 recovered.	<b><sup>E</sup>Related</b> N No Y Yes (please specify the serial number of the suspect drugs from above box, if related to suspect drug 1 and not related to suspect drug 2, enter as Y 1, N 2)

<b>Physical examination Findings</b> <i>(with specific body system involved)</i>	Systemic involvement _____  Metastases if any: _____ <i>(please specify the sites involved)</i>
<b>Confirmed diagnosis</b> <i>(please confirm if malignant)</i>	

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

<i>neoplasm progression is diagnosed)</i>	
If not confirmed please provide provisional diagnosis	
Date of diagnosis	

<b>a. Diagnostic Investigations</b>	
Tests	Results

*Please specify the diagnostic test to ensure the confirmatory diagnosis furnished above*

<b>b. Hematology</b>	
Tests	Results (units)

*Please attach the haematology profile performed before and after Etanercept treatment start date*

<b>c. Staging of Lymphoma</b>

*Please specify the grading classification followed*
*Please specify the staging classification followed*

<b>d. Surgical intervention (if applicable)</b>	
Surgery underwent	
Date of surgery	--/---/----
Any recurrence after this surgery. If yes, please provide	

<b>e. Medical intervention (if applicable)</b>	
Chemotherapy Regimen	<i>For each cycle, chemotherapeutic drugs administered</i>
	1
	2
	3
	4
	5
Start date	--/---/----
End date If therapy discontinued while treatment with Etanercept	--/---/----



**TARGETED FOLLOW UP FORM**

**BBL Case No.:**

Number of cycles completed

**Etanercept Therapy**

Start date	End date	Dose	Route	Indication	Action taken
--/--/----	--/--/----				

**Other Suspect/Concomitant Medications**

Medications <sup>§</sup>	Start date	End date	Dose	Route	Indication	Action taken
	--/--/----	--/--/----				
	--/--/----	--/--/----				
	--/--/----	--/--/----				
	--/--/----	--/--/----				
	--/--/----	--/--/----				
	--/--/----	--/--/----				

*Treating Physician or HCP Name*

*Date of report*

--/--/----

*Treating Physician or HCP Signature*

*Dispatch Date*

--/--/----

**Please return the questionnaire to: E-Mail: [drugsafety@biocon.com](mailto:drugsafety@biocon.com)**

**Post: Department, Street, Town, Country or hand it to your treating Physician, that part II can be filled out accordingly.**

**Reporter's Details:**

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.




**TARGETED FOLLOW UP FORM**

**BBL Case No.:**

Name:

Sign

Occupation:

Date:

Biocon Biologics is committed to holding patient’s and reporter’s personal data in strict confidence. Personal data, here, means any information by which a person is, directly or indirectly, identified or identifiable, which includes, but is not limited, to name, address, contact number, email address, genetic data and data concerning health. Biocon Biologics strictly adheres to applicable data privacy and data integrity laws, including, but not limited to, General Data Protection Regulations [EU] 2016/679 [“GDPR”] or its equivalent, as amended from time to time.

**Additional Information:**

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**TARGETED FOLLOW UP FORM**

**BBL Case No.:**

**To be Pre-Filled by the Pharmacovigilance Department**

Local Reference No		Safety Id No	
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**Part -I - To be filled out by Patient/Reporter**

Please fill out the Questionnaire as complete as possible. First check if personal information below is prefilled correct and complete.

Report date	--/--/----	Gender	
Age	Years      Months	Race	
Occupation (please specify)		Duration (Years)	

Please tick the appropriate box (yes/no) for each question and add comments relevant to the option if any in the last column, including the duration till the date of this report and nature of the symptoms.

a. Medical History				
		Yes	No	Additional information
1	Any pre-existing or ongoing viral infections especially Polyoma or JC virus infections			
2	Have you been diagnosed with any chronic immunodeficiency disorders if so, please specify the disorders			
3	History of recurrent or prolonged hospitalization for any chronic infectious or non-infectious conditions (please specify)			
4	History of any organ transplantation			
5	Are you taking any medications including any form of corticosteroids for longer duration (>6 months, please specify drugs)*			
6	Have you been ever diagnosed with precancerous or cancerous conditions since childhood			

*\*please detail the medications in the section e. past medication in page 3.*

Please tick the appropriate box (yes/no) for each question and add comments relevant to the option if any including duration and nature of the symptoms in the last column.

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

b. Present complaints					
		Yes	No	Duration	Start date
1	Clumsiness or loss of coordination				--/---/---
2	Difficulty in walking				--/---/---
3	Facial drooping				--/---/---
4	Any changes in vision including vision loss				--/---/---
5	Personality changes				--/---/---
6	Generalized weakness and getting worse				--/---/---
7	Trouble in speaking				--/---/---
8	Any difficulty in remembering the incidents that recently happened				--/---/---
9	Any delay in responding or delay in action due to thinking ability				--/---/---
10	Was there any frequent fall without dizziness				--/---/---

Additional information on any of the sections under b. present complaints should be detailed in below table with respective serial number indexed above.

No.	Additional information

If you are the Reporter/Patient of the Report, please indicate below if treating Physician can be contacted, if yes, please indicate Contact details.

Consent to contact treating physician or Healthcare professional	Yes <input type="checkbox"/> No <input type="checkbox"/>
Contact details of Treating physician or Healthcare professional	

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

Contact Phone:

 Please return the questionnaire to: E-Mail: [drugsafety@biocon.com](mailto:drugsafety@biocon.com)

Post: Department, Street, Town, Country or hand it to your treating Physician, that part II can be filled out accordingly.

**Part -II To be filled out by treating Physician**

Adverse events	Serious <sup>A</sup>	Severity <sup>B</sup>	Onset date	Outcome <sup>C</sup>	End date <sup>D</sup> (if applicable)	Related to drug <sup>E</sup>
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
<sup>A</sup> Seriousness 1.Non-serious 2.Medically significant 3.Hospitalization/ prolonged 4.Permanent disability/incapacity 5. Congenital anomaly 6. Life-threatening 7. Death		<sup>B</sup> Severity 1.Mild 2.Moderate 3. Severe		<sup>C</sup> Outcome 1.Recovered 2. Recovering 3.Not recovered 4.Recovered with sequelae 5. Death 6.Unknown	<sup>D</sup> Please complete only if outcome option is 1 recovered.	<sup>E</sup> Related N No Y Yes (please specify the serial number of the suspect drugs from above box, if related to suspect drug 1 and not related to suspect drug 2, enter as Y 1, N 2)
<b>Description of adverse experience</b>						

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

a. Diagnostic Investigations	
Tests	Results
MRI	
CT scan Brain	
Brain Biopsy	
Cerebrospinal fluid (CSF) analysis	
Other	

Please specify the diagnostic test to ensure the confirmatory/ provisional diagnosis furnished above

b. Hematology	
Tests	Results (units)
JC virus antibody test	

Please attach the haematology profile performed before and after Etanercept treatment start date

c. Past surgical intervention (if applicable)	
Surgery underwent	
Date of surgery	__/__/__
Any recurrence after this surgery. If yes, please provide	

d. Medical intervention (if applicable)			
Treatment medications	Indication	Start date	Stop date
		__/__/__	__/__/__
		__/__/__	__/__/__
		__/__/__	__/__/__
		__/__/__	__/__/__
		__/__/__	__/__/__

e. Past medications (if applicable)						
Medicatio	Start date	End date	Dose	Route	Indication	Action taken

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

ns <sup>5</sup>						
	--/---/----	--/---/----				
	--/---/----	--/---/----				
	--/---/----	--/---/----				
	--/---/----	--/---/----				
	--/---/----	--/---/----				

**Etanercept Therapy**

Start date	End date	Dose	Route	Indication	Action taken
--/---/----	--/---/----				

**Other Suspect/Concomitant Medications**

Medications <sup>5</sup>	Start date	End date	Dose	Route	Indication	Action taken
	--/---/----	--/---/----				
	--/---/----	--/---/----				
	--/---/----	--/---/----				
	--/---/----	--/---/----				
	--/---/----	--/---/----				
	--/---/----	--/---/----				

<i>Treating Physician or HCP Name</i>		<i>Date of report</i>	--/---/----
<i>Treating Physician or HCP Signature</i>		<i>Dispatch Date</i>	--/---/----

**Please return the questionnaire to: E-Mail: [drugsafety@biocon.com](mailto:drugsafety@biocon.com)**

**Post: Department, Street, Town, Country or hand it to your treating Physician, that part II can be filled out accordingly.**



<b>TARGETED FOLLOW UP FORM</b>		
<b>BBL Case No.:</b>		

**Reporter’s Details:**

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: Sign

Occupation: Date:

Biocon Biologics is committed to holding patient’s and reporter’s personal data in strict confidence. Personal data, here, means any information by which a person is, directly or indirectly, identified or identifiable, which includes, but is not limited, to name, address, contact number, email address, genetic data and data concerning health. Biocon Biologics strictly adheres to applicable data privacy and data integrity laws, including, but not limited to, General Data Protection Regulations [EU] 2016/679 [“GDPR”] or its equivalent, as amended from time to time.

**Additional Information:**

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**TARGETED FOLLOW UP FORM**

**BBL Case No.:**

**To be Pre-Filled by the Pharmacovigilance Department**

Local Reference No		Safety Id No	
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**Part -I - To be filled out by Patient/Reporter**

Please fill out the Questionnaire as complete as possible. First check if personal information below is prefilled correct and complete.

Report date	--/--/----	Gender	
Age	Years      Months	Race	
Occupation (please specify)		Duration (Years)	

Please tick the appropriate box (yes/no) for each question and add comments relevant to the option if any in the last column, including the duration till the date of this report and nature of the symptoms.

a. Medical History				
		Yes	No	Additional information
1	Any family members (parent or sibling) suffered from chronic joint pain, swelling of joint			
2	History of recurrent or prolonged hospitalization for any chronic infectious or non-infectious conditions (please specify)			
3	Ever diagnosed with bone or joint or skin related conditions which extended more than 6 months for which medications taken			
4	Are you taking any medications for longer duration (>6 months, please specify drugs)			
5	Have you undergone any surgery for any medical condition			
6	Menstrual history- any change in menstruating period, amount of flow ( <i>for female patients only</i> )			

Please tick the appropriate box (yes/no) for each question and add comments relevant to the option if any including duration and nature of the symptoms in the last column.

b. Present complaints					
		Yes	No	Duration	Start date

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

1	Joints that are warm to the touch				--/-----
2	Swelling and tenderness at joints				--/-----
3	Facial drooping				--/-----
4	Fever				--/-----
5	Rash				--/-----
6	Limping				--/-----
7	Pain (often worse following sleep or inactivity)				--/-----
8	Inability to bend or straighten joints completely				--/-----
9	Decreased physical activity				--/-----
10	Fatigue				--/-----
11	Swollen lymph nodes				--/-----
12	Reduced appetite				--/-----
13	Weight loss				--/-----
14	Please confirm if any of the above complaints were existing before start of Etanercept therapy				--/-----
15	Any change in nature or severity of the above complaints after starting Etanercept therapy				--/-----

Additional information on any of the sections under b. present complaints should be detailed in below table with respective serial number indexed above.

No.	Additional information



**TARGETED FOLLOW UP FORM**

**BBL Case No.:**


If you are the Reporter/Patient of the Report, please indicate below if treating Physician can be contacted, if yes, please indicate Contact details.

No.	Additional information
Parent's consent to contact treating physician or Healthcare professional	Yes <input type="checkbox"/> No <input type="checkbox"/>
Contact details of Treating physician or Healthcare professional	
Contact Phone:	

**Please return the questionnaire to: E-Mail: [drugsafety@biocon.com](mailto:drugsafety@biocon.com)**

**Post: Department, Street, Town, Country or hand it to your treating Physician, that part II can be filled out accordingly.**

**Part -II To be filled out by treating Physician**

Adverse events	Serious <sup>A</sup>	Severity <sup>B</sup>	Onset date	Outcome <sup>C</sup>	End date <sup>D</sup> (if applicable)	Related to drug <sup>E</sup>
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

<b><sup>A</sup>Seriousness</b> 1.Non-serious 2.Medically significant 3.Hospitalization/ prolonged 4.Permanent disability/incapacity 5. Congenital anomaly 6. Life-threatening 7. Death	<b><sup>B</sup>Severity</b> 1.Mild 2.Moderate 3. Severe		<b><sup>C</sup>Outcome</b> 1.Recovered 2. Recovering 3.Not recovered 4.Recovered with sequelae 5. Death 6.Unknown	<b><sup>D</sup>Please complete only if outcome option is 1 recovered.</b>	<b><sup>E</sup>Related</b> N No Y Yes (please specify the serial number of the suspect drugs from above box, if related to suspect drug 1 and not related to suspect drug 2, enter as Y 1, N 2)
---	--	--	---	---	--

Clinical Findings	
Body temperature	_____ F
Bone and Joint Involvement	
Number of joints affected	_____ <i>please specify joints</i>
Pain or tenderness	Yes <input type="checkbox"/> No <input type="checkbox"/> Nature of pain or tenderness _____
Skin involvement	
Rash type _____ <i>(please specify the nature of rash)</i>	
Area involvement _____ <i>(please specify the portion of body surface affected. i.e. front half of the body excluding limbs)</i>	
Systemic involvement	
Lymph nodes	Enlarged Yes <input type="checkbox"/> No <input type="checkbox"/> <i>please specify</i> _____
Other Systemic changes	

a. Diagnostic Investigations	
Tests	Results
MRI	
CT scan Brain	
Brain Biopsy	
Rheumatoid factor	
Biochemical test (including uric acid)	
Other serology tests (CRP)	

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

Please specify the diagnostic test to ensure the confirmatory/ provisional diagnosis furnished above

b. Hematology	
Tests	Results (units)

Please attach the haematology profile performed before and after Etanercept treatment start date

c. Surgical intervention (if applicable)	
Surgery underwent	
Date of surgery	__/__/__
Any recurrence after this surgery. If yes, please provide	

d. Medical intervention (if applicable)	
Chemotherapy Regimen	<i>For each cycle, chemotherapeutic drugs administered</i>
	1
	2
	3
	4
	5
Start date	__/__/__
End date If therapy discontinued while treatment with Etanercept	__/__/__
Number of cycles completed	

Confirmed diagnosis <i>(please specify the sub type of JRA with classification followed)</i>	
If not confirmed please provide provisional diagnosis	
Date of diagnosis	

Etanercept Therapy					
Start date	End date	Dose	Route	Indication	Action taken



**TARGETED FOLLOW UP FORM**

**BBL Case No.:**

_/_/____	_/_/____				
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Other Suspect/Concomitant Medications						
Medications <sup>§</sup>	Start date	End date	Dose	Route	Indication	Action taken
	_/_/____	_/_/____				
	_/_/____	_/_/____				
	_/_/____	_/_/____				
	_/_/____	_/_/____				
	_/_/____	_/_/____				
	_/_/____	_/_/____				

§ Please append (S) for suspect and (C) for concomitant adjacent to product name

Treating Physician Name	
Treating Physician Signature	
Date	_/_/____
Dispatch Date	_/_/____

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**Post: Department, Street, Town, Country or hand it to your treating Physician, that part II can be filled out accordingly.**

**Reporter's Details:**



**TARGETED FOLLOW UP FORM**

**BBL Case No.:**

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name:

Sign

Occupation:

Date:

Biocon Biologics is committed to holding patient’s and reporter’s personal data in strict confidence. Personal data, here, means any information by which a person is, directly or indirectly, identified or identifiable, which includes, but is not limited, to name, address, contact number, email address, genetic data and data concerning health. Biocon Biologics strictly adheres to applicable data privacy and data integrity laws, including, but not limited to, General Data Protection Regulations [EU] 2016/679 [“GDPR”] or its equivalent, as amended from time to time.

**Additional Information:** \_\_\_\_\_

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**TARGETED FOLLOW UP FORM**

**BBL Case No.:**

**To be Pre-Filled by the Pharmacovigilance Department**

Local Reference No		Safety Id No	
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**Part -I - To be filled out by Patient/Reporter**

Please fill out the Questionnaire as complete as possible. First check if personal information below is prefilled correct and complete.

Report date	--/---/----	Gender	
Age	Years      Months	Race	
Occupation (please specify)		Duration (Years)	

Please tick the appropriate box (yes/no) for each question and add comments relevant to the option if any in the last column, including the duration till the date of this report and nature of the symptoms.

a. Medical History				
		Yes	No	Additional information
1	Pre-existing diagnosed carcinoma in any part of the body			
2	Any family members suffered from similar ailment			
3	Any history of family members (parents or siblings) diagnosed/treated cancer			
4	Any chronic therapy with hormones, steroids or medication			
5	Have you been ever diagnosed with precancerous or cancerous conditions since childhood			
6	Menstrual history- any change in menstruating period, amount of flow ( <i>for female patients only</i> )			
7	Underwent surgery for any ailment, if so please specify the diagnosis and treatment			
8	Tobacco use in any form ( I.e chewing, smoking)			

Please tick the appropriate box (yes/no) for each question and add comments relevant to the option if any including duration and nature of the symptoms in the last column.

b. Present complaints					
		Yes	No	Duration	Start date
1	Feeling weak or tired without any exertion				--/---/----
2	Sudden weight loss or gain without any reason				--/---/----
3	Any skin changes either with a new mole or change in shape and size of existing mole				--/---/----
4	Any skin changes only sun exposed areas of the				--/---/----

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

	body				
5	Sore/Ulcer that was not healing				--/---/---
6	Any change in bowel or bladder habits				--/---/---
7	Persistent hoarseness or change in voice or cough				--/---/---
8	Breast changes in size or shape; change in texture of skin over breast				--/---/---
9	Any thickness or swelling in any part body for long duration				--/---/---
10	Any unusual discharge (i.e. nasal, ear, urethra)				--/---/---
11	Loss of appetite				--/---/---
12	Problems in eating- any discomfort, swallowing difficulty				--/---/---
13	Abdominal pain for chronic period				--/---/---

Additional information on any of the sections under b. present complaints should be detailed in below table with respective serial number indexed above.

No.	Additional information

If you are the Reporter/Patient of the Report, please indicate below if treating Physician can be contacted, if yes, please indicate Contact details.

Consent to contact treating physician or Healthcare professional	Yes <input type="checkbox"/> No <input type="checkbox"/>
Contact details of Treating physician or Healthcare professional	
Contact Phone:	

Please return the questionnaire to: E-Mail: [drugsafety@biocon.com](mailto:drugsafety@biocon.com)

Post: Department, Street, Town, Country or hand it to your treating Physician, that part II can be filled out accordingly.

**Part -II To be filled out by treating Physician**

Adverse events	Serious <sup>A</sup>	Severity <sup>B</sup>	Onset date	Outcome <sup>C</sup>	End date <sup>D</sup> (if applicable)	Related to drug <sup>E</sup>
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**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
<b><sup>A</sup>Seriousness</b> 1.Non-serious 2.Medically significant 3.Hospitalization/ prolonged 4.Permanent disability/incapacity 5. Congenital anomaly 6. Life-threatening 7. Death	<b><sup>B</sup>Severity</b> 1.Mild 2.Moderate 3. Severe			<b><sup>C</sup>Outcome</b> 1.Recovered 2. Recovering 3.Not recovered 4.Recovered with sequelae 5. Death 6.Unknown	<b><sup>D</sup>Please complete only if the outcome option is 1 recovered.</b>	<b><sup>E</sup>Related</b> N No Y Yes (please specify the serial number of the suspect drugs from above box, if related to suspect drug 1 and not related to suspect drug 2, enter as Y 1, N 2)

Physical examination Findings <i>(with specific body system involved)</i>	Tumor site : _____ <i>(please specify the system involved)</i>  Tumor size: _____  Any metastases _____ <i>(please specify the sites involved)</i>  Other systemic involvement _____
Confirmed diagnosis <i>(please confirm if malignant neoplasm progression is diagnosed)</i>	
If not confirmed please provide provisional diagnosis	
Date of diagnosis	

<b>a. Diagnostic Investigations</b>
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**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

Tests	Results

Please specify the diagnostic test to ensure the confirmatory diagnosis furnished above

<b>b. Haematology</b>	
Tests	Results (units)

Please attach the haematology profile performed before and after Etanercept treatment start date

<b>c. Grading of carcinoma</b>

*Please specify the grading classification followed*

<b>d. TNM staging of carcinoma/other</b>

*Please specify the staging classification followed*

<b>e. Surgical intervention (if applicable)</b>	
Surgery underwent	
Date of surgery	__/__/__
Any recurrence after this surgery. If yes, please provide	

<b>f. Medical intervention (if applicable)</b>		
Chemotherapy Regimen		<i>For each cycle, chemotherapeutic drugs administered</i>
	1	
	2	
	3	
	4	
5		
Start date	__/__/__	
End date	__/__/__	

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

If therapy discontinued while treatment with Etanercept

Number of cycles completed

Etanercept Therapy						
Start date	End date	Dose	Route	Indication	Action taken	
--/---/----	--/---/----					

Other Suspect/Concomitant Medications						
Medications <sup>s</sup>	Start date	End date	Dose	Route	Indication	Action taken
	--/---/----	--/---/----				
	--/---/----	--/---/----				
	--/---/----	--/---/----				
	--/---/----	--/---/----				
	--/---/----	--/---/----				
	--/---/----	--/---/----				

<i>Treating Physician or HCP Name</i>		<i>Date of report</i>	--/---/----
<i>Treating Physician or HCP Signature</i>		<i>Dispatch Date</i>	--/---/----

Please return the questionnaire to: E-Mail: [drugsafety@biocon.com](mailto:drugsafety@biocon.com)

Post: Department, Street, Town, Country or hand it to your treating Physician, that part II can be filled out accordingly.

**Reporter's Details:**



**TARGETED FOLLOW UP FORM**

**BBL Case No.:**

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: \_\_\_\_\_ Sign \_\_\_\_\_

Occupation: \_\_\_\_\_ Date: \_\_\_\_\_

Biocon Biologics is committed to holding patient’s and reporter’s personal data in strict confidence. Personal data, here, means any information by which a person is, directly or indirectly, identified or identifiable, which includes, but is not limited, to name, address, contact number, email address, genetic data and data concerning health. Biocon Biologics strictly adheres to applicable data privacy and data integrity laws, including, but not limited to, General Data Protection Regulations [EU] 2016/679 [“GDPR”] or its equivalent, as amended from time to time.

**Additional Information:**

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**TARGETED FOLLOW UP FORM**
**BBL Case No.:**
**To be Pre-Filled by the Pharmacovigilance Department**

Local Reference No		Safety Id No	
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**Part -I - To be filled out by Patient/Reporter**

Please fill out the Questionnaire as complete as possible. First check if personal information below is prefilled correct and complete.

Report date	--/---/----	Gender	
Age	Years Months	Race	
Occupation (please specify)		Duration (Years)	

Please tick the appropriate box (yes/no) for each question and add comments relevant to the option if any in the last column, including the duration till the date of this report and nature of the symptoms.

a. Medical History				
		Yes	No	Additional information
1	History of any recurrent respiratory infections (e. g. Cough, cold, fever, wheezing, cry)			
2	History of any recurrent gastrointestinal disorders (e. g. Loose motions or diarrhea, nausea, vomiting, fever, abdominal colic, cry)			
3	History of any recurrent urinary tract disorders (e. g. Swelling over face or feet or over the body, difficulty in micturition or voiding of urine, fever, cry )			
4	History of any recurrent Hepatobiliary disorders (e. g. yellowish discoloration of urine or sclera, discoloration of stools, fever, cry)			
5	History of any recurrent Cardiac disorders (e. g. difficulty in breathing, discoloration of nails or body, swelling over legs or body, coughing of blood, chest discomfort or chest pain )			
6	History of exclusive breast feeding			
7	History of onset of top feeding or weaning from breast feeding (please specify top feeding items)			
8	History of recent or previous vaccination or immunization followed by any adverse experiences			

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

9	History of recent or past phototherapy			
10	History of weakness in any part of body (especially arm, legs, facial muscles)			
11	History of any surgery or surgical procedures since birth			
12	History of recurrent or prolonged hospitalization for any chronic infectious or non-infectious conditions (please specify)			
13	Menstrual history- onset of menarche, any change in menstruating period, amount of flow ( <i>if applicable</i> )			

Please tick the appropriate box (yes/no) for each question and add comments relevant to the option if any including duration and nature of the symptoms in the last column.

Past medication history (if applicable)				
Medication name	Indication	Route	Start date	Stop date
			--/ /--	--/ /--
			--/ /--	--/ /--
			--/ /--	--/ /--
			--/ /--	--/ /--
			--/ /--	--/ /--

b. Present complaints					
		Yes	No	Duration	Start date
1	Recurrent cough or cold				--/ /--
2	Wheezing				--/ /--
3	Fever				--/ /--
4	Irritable with cry				--/ /--
5	Loose motions or watery stools				--/ /--

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

6	Nausea				--/---/---
7	Vomiting				--/---/---
8	Abdominal colic				--/---/---
9	Coughing of blood				--/---/---
10	Chest discomfort or Chest pain				--/---/---
11	Increase in heart rate				--/---/---
12	Weakness in any part of body (especially arm, legs, facial muscles)				--/---/---
13	Changes in urination habits				--/---/---
14	Any changes in food intake (i.e. appetite)				--/---/---
15	Edema localized or generalized				--/---/---
16	Weight gain ( <i>please specify the change in weight with duration</i> )				--/---/---
17	Generalized weakness				--/---/---

Additional information on any of the sections under b. present complaints should be detailed in below table with respective serial number indexed above.

No.	Additional information

If you are the Reporter/Patient of the Report, please indicate below if treating Physician can be contacted, if yes, please indicate Contact details.

Parent's consent to contact treating physician or Healthcare professional	Yes <input type="checkbox"/> No <input type="checkbox"/>
---	--

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

Contact details of Treating physician or Healthcare professional

Contact Phone:

Please return the questionnaire to: E-Mail: [drugsafety@biocon.com](mailto:drugsafety@biocon.com)

Post: Department, Street, Town, Country or hand it to your treating Physician, that part II can be filled out accordingly.

**Part -II To be filled out by treating Physician**

Adverse events	Serious <sup>A</sup>	Severity <sup>B</sup>	Onset date	Outcome <sup>C</sup>	End date <sup>D</sup> (if applicable)	Related to drug <sup>E</sup>
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
			--/---/----		--/---/----	
<b><sup>A</sup>Seriousness</b> 1.Non-serious 2.Medically significant 3.Hospitalization/ prolonged 4.Permanent disability/incapacity 5. Congenital anomaly 6. Life-threatening 7. Death		<b><sup>B</sup>Severity</b> 1.Mild 2.Moderate 3. Severe		<b><sup>C</sup>Outcome</b> 1.Recovered 2. Recovering 3.Not recovered 4.Recovered with sequelae 5. Death 6.Unknown	<sup>D</sup> Please complete only if the outcome option is 1 recovered.	<b><sup>E</sup>Related</b> N No Y Yes (please specify the serial number of the suspect drugs from above box, if related to suspect drug 1 and not related to suspect drug 2, enter as Y 1, N 2)

**Clinical Findings**

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

Body temperature	_____ F
Pulse rate	_____
Blood pressure	_____ mm Hg _____
Respiratory System	Breath sounds _____ Respiratory rate _____
Cardiac system	Heart sounds _____ (if any abnormality, please specify) Murmur _____ (if any abnormality, please specify) Other findings _____
Nervous system	Deep tendon reflexes _____ (if significant) Tone of muscles _____ (if significant)
Gastrointestinal system	Abdominal tenderness _____
<b>Skin involvement</b>	
Rash type _____ (please specify the nature of rash)	
Area involvement _____ (please specify the portion of body surface affected. i.e. front half of the body excluding limbs)	
<b>Systemic involvement</b>	
Lymph nodes	Enlarged Yes <input type="checkbox"/> No <input type="checkbox"/> please specify _____
Other Systemic changes	

a. Diagnostic Investigations	
Tests	Results

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**


Please specify the diagnostic test to ensure the confirmatory/ provisional diagnosis furnished above

b. Hematology	
Tests	Results (units)

Please attach the haematology profile performed before and after Etanercept treatment start date

c. Surgical intervention (if applicable)	
Surgery underwent	
Date of surgery	--/--/----

d. Medical intervention (if applicable)			
Treatment medications	Indication	Start date	Stop date
		--/--/----	--/--/----
		--/--/----	--/--/----
		--/--/----	--/--/----
		--/--/----	--/--/----
		--/--/----	--/--/----

Etanercept Therapy						
Start date	End date	Dose	Route	Indication	Action taken	
--/--/----	--/--/----					
Other Suspect/Concomitant Medications						
Medications <sup>\$</sup>	Start date	End date	Dose	Route	Indication	Action taken
	--/--/----	--/--/----				

**TARGETED FOLLOW UP FORM**
**BBL Case No.:**

	—	—				
	--/---/---	--/---/---				
	—	—				
	--/---/---	--/---/---				
	—	—				
	--/---/---	--/---/---				
	—	—				

§ Please append (S) for suspect and (C) for concomitant adjacent to product name

Treating Physician Name	
Treating Physician Signature	
Date	--/---/---
Dispatch Date	--/---/---

**Please return the questionnaire to: E-Mail: [drugsafety@biocon.com](mailto:drugsafety@biocon.com)**
**Post: Department, Street, Town, Country or hand it to your treating Physician, that part II can be filled out accordingly.**
**Reporter's Details:**

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: \_\_\_\_\_ Sign \_\_\_\_\_

Occupation: \_\_\_\_\_ Date: \_\_\_\_\_



<b>TARGETED FOLLOW UP FORM</b>		
<b>BBL Case No.:</b>		

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**Additional Information:**

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Etanercept

***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 these safety concern and when to seek attention from a healthcare professional.
- Contact details of the etanercept prescriber