EU Risk Management Plan (RMP) for EKSUNBI (Ustekinumab)

RMP version to be assessed as part of this application:

RMP Version number: 2.0

Data lock point for this RMP: Nov 22, 2024

Date of final sign off: Nov 25, 2024

Rationale for submitting an updated RMP:

Update to be in line with the reference product's RMP and update based on safety update of the product information.

Summary of significant changes in this RMP:

<Safety specification>

- Removed 'Exposure during pregnancy' from important potential risk
- Replaced "non-melanoma skin cancer" with "skin cancer" in Part II: Module SVII.3.1

<Risk minimisation measures>

- Deleted routine risk minimisation measures for the removed safety concern
- Replaced "non-melanoma skin cancer" with "skin cancer" from routine risk minimisation measures in Part V.1.

Other RMP versions under evaluation: None.

Details of the currently approved RMP:

Version number: 1.0

Approved with procedure: EMEA/H/C/006448/0000

Date of approval (opinion date): Jul 25, 2024 (CHMP opinion date)

EU QPPV name: John Hart

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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

Signature: N/A

Date: N/A

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LIST OF ABBREVIATIONS

ATC	anatomical therapeutic chemical classification
BP	blood pressure
CI	confidence interval
DNA	deoxyribonucleic acid
EC	European Commission
eCTD	electronic Common Technical Document
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
HIV	human immunodeficiency virus
IL	interleukin
INN	international non-proprietary name
MAC	*Mycobacterium avium* / *Mycobacterium intracellulare* complex
NK	natural killer
NTM	non-tuberculosis mycobacterial
PUVA	psoralen and ultraviolet A
PL	package leaflet
PSUR	Periodic Safety Update Report
OR	odds ratio
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
SD	standard deviation
SmPC	summary of product characteristics
Th1	T helper 1
Th17	T helper 17
TNFα	tumour necrosis factor alpha
ULN	upper limit of normal
US	United States

Part I: Product(s) overview

Table Part I.1: Product(s) overview

Active substance(s) (INN or common name)	Ustekinumab
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, interleukin inhibitors (L04AC05)
Marketing Authorisation Applicant	Samsung Bioepis NL B.V. (the Netherlands)
Medicinal products to which this RMP refers	3
Invented name(s) in the EEA	EKSUNBI
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Ustekinumab is a fully human IgG1κ monoclonal antibody to interleukin (IL)-12/23.
	Summary of mode of action: Ustekinumab binds with specificity to the shared p40 protein subunit of human cytokines IL-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines participate in immune functions; IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype, IL-23 induces the T helper 17 (Th17) pathway. However, abnormal regulation of IL-12 and IL-23 has been associated with immune mediated diseases, such as psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis. By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis

Table Part I.1: Product(s) overview

	through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.
	Important information about its composition: Ustekinumab is produced in Chinese hamster ovary cells by recombinant DNA technology.
Hyperlink to the Product Information	Product Information
Indication(s) in the EEA	**Current:** EKSUNBI is indicated for the treatment of: • moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate or psoralen and ultraviolet A (PUVA) • moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies • active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug therapy has been inadequate • moderately to severely active Crohn's disease in adults who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies • moderately to severely active ulcerative colitis in adults who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies. **Proposed:** Not applicable
Dosage in the EEA	**Current:** <u>Plaque psoriasis</u>

Table Part I.1: Product(s) overview

The recommended dose for EKSUNBI is an initial dose of 45 mg administered subcutaneously, followed by 45 mg dose 4 weeks later, and then every 12 weeks thereafter.

Paediatric plaque psoriasis

The recommended dose of EKSUNBI for the paediatric population with a body weight over 60 kg is shown below (Table A). EKSUNBI should be administered at Weeks 0 and 4, then every 12 weeks thereafter.

Table A: Recommended dose of ustekinumab for paediatric psoriasis

Body weight at the time of dosing	Recommended Dose
≥ 60-≤ 100 kg	45 mg
> 100 kg	90 mg

There is no dosage form for EKSUNBI that allows weight-based dosing for paediatric patients below 60 kg

Patients weighing less than 60 kg should be accurately dosed on a mg/kg basis using another ustekinumab product, 45 mg solution for injection in vials offering weight-based dosing instead. Only the patients weighing 60 kg or more may be dosed using an EKSUNBI fixed-dose pre-filled syringe.

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment

Psoriatic arthritis

The recommended posology of EKSUNBI is an initial dose of 45 mg administered subcutaneously, followed by 45 mg dose 4 weeks later, and then every 12 weeks thereafter.

Crohn's disease / Ulcerative colitis

The recommended posology of EKSUNBI is an initial, single intravenous dose based on body weight. The infusion solution should be composed of the number of vials of EKSUNBI 130 mg as specified in Table B.

Table B: Initial intravenous dosing of EKSUNBI

Table Part I.1: Product(s) overview

<table>
<tr><td></td><td>
<table>
<tr><th>Body weight of patient at the time of dosing</th><th>Recommended dose*</th><th>Number of 130 mg EKSUNBI vials</th></tr>
<tr><td>≤ 55 kg</td><td>260 mg</td><td>2</td></tr>
<tr><td>> 55 kg to ≤ 85 kg</td><td>390 mg</td><td>3</td></tr>
<tr><td>> 85 kg</td><td>520 mg</td><td>4</td></tr>
</table>
* Approximately 6 mg/kg

The first subcutaneous administration of 90 mg EKSUNBI should take place at week 8 after the intravenous dose. After this, dosing every 12 weeks is recommended.

Patients who have not shown adequate response at 8 weeks after the first subcutaneous dose, may receive a second subcutaneous dose at this time.

Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks.

Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment.

Proposed: Not applicable</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>Current:
<u>Solution for injection in pre-filled syringe</u>

Each EKSUNBI 45 mg pre-filled syringe contains 45 mg ustekinumab in 0.5 mL.

Each EKSUNBI 90 mg pre-filled syringe contains 90 mg ustekinumab in 1 mL.

<u>Concentrate for solution for infusion in a vial</u>

Each vial contains 130 mg ustekinumab in 26 mL (5 mg/mL).

Proposed: Not applicable.</td></tr>
</table>

Table Part I.1: Product(s) overview

Is/will the product be subject to additional monitoring in the EU?	Yes

ATC = anatomical therapeutic chemical classification; DNA = deoxyribonucleic acid; EEA = European Economic Area; EU = European Union; IL = interleukin; INN = international non-proprietary name; PUVA = psoralen and ultraviolet A; Th = T helper; TNFα = tumour necrosis factor alpha.

Part II: Safety specification

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

Based on the Guideline on good pharmacovigilance practices Module V – Risk management systems (Rev. 2), this module is not applicable for the medicinal product(s) seeking a marketing authorisation according to Article 10(4) of Directive 2001/83/EC, as amended.

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

Samsung Bioepis developed EKSUNBI as a similar biological medicinal product to the reference product STELARA (ustekinumab). A series of *in vitro* pharmacodynamics studies were performed between EKSUNBI and STELARA (EU-sourced), and data from the comparative structural analyses, physicochemical analyses, as well as *in vitro* non-clinical studies and functional assays, demonstrated similarity between the two products. No noted differences were observed in the biological activity between EKSUNBI and EU-sourced STELARA, and following a stepwise and risk-based approach, *in vivo* animal studies were not deemed necessary for the development of EKSUNBI.

No safety pharmacology, single- or repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and development toxicity, local tolerance, or other toxicity studies were conducted, in accordance with the endorsement received by the European Medicines Agency (EMA) during scientific advice and follow-up scientific advice (EMA/CHMP/SAWP/791150/2017; EMA/CHMP/SAWP/493969/2019).

A detailed description of the non-clinical development programme for EKSUNBI is provided in the eCTD Module 2.4 (Non-clinical Overview).

The non-clinical programmes for EKSUNBI and STELARA did not identify any drug attributable adverse toxicity findings, and the toxicity profile of EKSUNBI is not expected to differ from that of the reference product.

Part II: Module SIII - Clinical trial exposure

The clinical development programme for EKSUNBI consists of a completed Phase I study in healthy subjects (SB17-1001) and a completed Phase III study in subjects with moderate to severe plaque psoriasis (SB17-3001).

Study SB17-1001 was a randomised, double-blind, three-arm, parallel group, single-dose study to compare the pharmacokinetics, safety, tolerability, and immunogenicity between EKSUNBI and the reference product STELARA (EU- and United States [US]-sourced).

Study SB17-3001 was a randomised, double-blind, multicentre study to evaluate the efficacy, safety, tolerability, pharmacokinetics, and immunogenicity of EKSUNBI compared to the reference product STELARA (EU-sourced) in subjects with moderate to severe plaque psoriasis.

The subject exposure to EKSUNBI and STELARA is provided in Table SIII.1, while the subject demographic characteristics are detailed in Table SIII.2 (for study SB17-1001) and Table SIII.3 (for study SB17-3001).

A detailed description of the clinical development programme for EKSUNBI is provided in the eCTD Module 2.5 (Clinical Overview) and Module 2.7.4 (Summary of Clinical Safety).

The safety profile of ustekinumab and its positive benefit-risk balance is based solely on the data collected for the reference product STELARA[1], taking into account data collected in studies SB17-1001 and SB17-3001.

Table SIII.1: Cumulative subject exposure in the clinical trials with EKSUNBI

Clinical trial	Number of subjects			
	EKSUNBI	STELARA (EU-sourced)	STELARA (US-sourced)	Total
SB17-1001	67	67	67	201
SB17-3001	371*	254	-	503
Total	**438***	**321**	**67**	**704**

EU = European Union; US = United States.
* 122 subjects from the STELARA treatment group transitioned to EKSUNBI per protocol

Table SIII.2: Demographic characteristics from study SB17-1001 (randomised set)

Characteristics	EKSUNBI (N = 67)	STELARA (EU-sourced) (N = 67)	STELARA (US-sourced) (N = 67)	Total (N = 201)
Age (years)				
n	67	67	67	201
Mean (SD)	34.9 (10.75)	33.0 (10.16)	33.4 (10.79)	33.8 (10.55)
Median	35.0	32.0	30.0	33.0
Min, max	18, 54	18, 51	19, 55	18, 55
Gender, n (%)				
Male	41 (61.2)	42 (62.7)	41 (61.2)	124 (61.7)
Female	26 (38.8)	25 (37.3)	26 (38.8)	77 (38.3)
Race, n (%)				

Characteristics	EKSUNBI (N = 67)	STELARA (EU-sourced) (N = 67)	STELARA (US-sourced) (N = 67)	Total (N = 201)
White	56 (83.6)	56 (83.6)	58 (86.6)	170 (84.6)
Black or African American	9 (13.4)	6 (9.0)	6 (9.0)	21 (10.4)
American Indian or Alaska Native	2 (3.0)	1 (1.5)	1 (1.5)	4 (2.0)
Native Hawaiian or other Pacific Islander	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Multiple	0 (0.0)	2 (3.0)	2 (3.0)	4 (2.0)
Ethnicity, n (%)				
Hispanic or Latino	2 (3.0)	2 (3.0)	1 (1.5)	5 (2.5)
Not Hispanic or Latino	65 (97.0)	65 (97.0)	66 (98.5)	196 (97.5)

EU = European Union; max = maximum; min = minimum; n = number of subjects; SD = standard deviation; US = United States.
Note: Percentages were based on the number of subjects in the randomised set.

Table SIII.3: Demographic characteristics from study SB17-3001 (randomised set)

Characteristics	EKSUNBI (N = 249)	STELARA (EU-sourced) (N = 254)*	Total (N = 503)
Age (years)			
n	249	254	503
Mean (SD)	44.0 (13.21)	44.3 (12.42)	44.2 (12.81)
Median	43.0	44.0	43.0
Min, max	19, 77	18, 76	18, 77
Gender, n (%)			
Male	150 (60.2)	162 (63.8)	312 (62.0)
Female	99 (39.8)	92 (36.2)	191 (38.0)
Race, n (%)			
Asian	2 (0.8)	4 (1.6)	6 (1.2)
White	247 (99.2)	250 (98.4)	497 (98.8)
Ethnicity, n (%)			
Korean	2 (0.8)	4 (1.6)	6 (1.2)
Mixed	0 (0.0)	1 (0.4)	1 (0.2)
Other	247 (99.2)	249 (98.0)	496 (98.6)

EU = European Union; max = maximum; min = minimum; n = number of subjects; SD = standard deviation.
Note: Percentages were based on the number of subjects in the randomised set.
* 122 subjects from the STELARA treatment group transitioned to EKSUNBI per protocol.

Part II: Module SIV - Populations not studied in clinical trials

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

The summary of important exclusion criteria presented in this section is based on the exclusion criteria selected for the comparative Phase III study SB17-3001 in patients with moderate to severe plaque psoriasis. However, any limitations of the clinical trial population are solely based on the data available for the reference product STELARA[1].

Women of childbearing potential who were pregnant, planning to become pregnant, lactating, or not using adequate birth control, as specified in the protocol.

Reason for exclusion	These criteria were selected to minimise potential risks to pregnancy and/or foetal development.
Is it considered to be included as missing information?	No
Rationale	Non-clinical studies did not indicate direct or indirect harmful effects of ustekinumab with respect to pregnancy, embryonic/foetal development, parturition or postnatal development. It is preferable to avoid the use of ustekinumab in pregnancy.

Active or latent tuberculosis at Screening

Reason for exclusion	Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. These criteria were selected to minimise potential bias in collected data and to minimise potential risks to study participants.
Is it considered to be included as missing information?	No
Rationale	Serious infections (including mycobacterial and *Salmonella* infections) represent an important potential risk of ustekinumab (refer to Part II: Module SVII). Special precaution during therapy with ustekinumab is necessary.

History of recurrent significant infections and/or current treatment for systemic infection

Reason for exclusion	Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. These criteria were selected to minimise potential bias in collected data and to minimise potential risks to study participants. In clinical studies, serious bacterial, fungal, and viral infections were observed in patients receiving ustekinumab.

Is it considered to be included as missing information?	No
Rationale	Serious infections (including mycobacterial and *Salmonella* infections) represent an important potential risk of ustekinumab (refer to Part II: Module SVII). Special precaution during therapy with ustekinumab is necessary.

History of malignancy (except for squamous or basal cell carcinoma of the skin that had been treated and had not recurred within 3 months prior to Screening, or was surgically treated cervical carcinoma in situ) within the last 5 years prior to Screening

Reason for exclusion	These criteria were selected to minimise potential bias in collected data and to minimise potential risks to study participants.
Is it considered to be included as missing information?	No
Rationale	Malignancy represents an important potential risk of ustekinumab (refer to Part II: Module SVII). The guidance for the use of EKSUNBI in patients with a history of malignancy and in patients who continue treatment after developing malignancy while receiving EKSUNBI is provided in SmPC Section 4.4 (Special Warning and Precautions for Use). There is no ongoing or planned additional pharmacovigilance activities to investigate the use of ustekinumab in patients with concurrent malignancy or a history of malignancy.

Uncontrolled systemic disease including but not limited to uncontrolled diabetes mellitus (in the opinion of the Investigator), or uncontrolled systemic hypertension (systolic blood pressure [BP] ≥ 160 mmHg and/or diastolic BP ≥ 100 mmHg on optimal medical regimen) at Screening

Reason for exclusion	These criteria were selected to minimise potential bias in collected data and to minimise potential risks to study participants.
Is it considered to be included as missing information?	No
Rationale	The safety profile of ustekinumab is not expected to differ in these patient populations. However, special precaution during therapy with ustekinumab is necessary.

Impaired renal and hepatic function (serum creatinine ≥ 1.5 × upper limit of normal [ULN]; serum alanine aminotransferase and aspartate aminotransferase ≥ 2 × ULN) at Screening

Reason for exclusion	These criteria were selected to minimise potential bias in collected data and to minimise potential risks to study participants.
Is it considered to be included as missing information?	No
Rationale	The safety profile of ustekinumab is not expected to differ in patients with renal and hepatic impairment. Available data do not suggest a need for a dose adjustment with ustekinumab in these patients.

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 SIV.1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment	Not included in the clinical development programme or not specifically studied.
Population with relevant different ethnic origin	Refer to Table SIII.2 and Table SIII.3.
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Other	Not applicable.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

The potential for misuse for illegal purposes is considered negligible, given the mechanism of action of ustekinumab.

Part II: Module SVII - Identified and potential risks

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

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

There are currently no risks considered as not important for inclusion in the list of safety concerns in respect to this RMP.

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

The safety concerns in the RMP for the biosimilar product EKSUNBI are aligned with the safety concerns for the reference product STELARA[2], taking into account the findings from the comparative studies SB17-1001 and SB17-3001, and the potential unique characteristics of the EKSUNBI medicinal product.

Important identified risk(s): None

Important potential risk(s):

- **Serious infections (including mycobacterial and *Salmonella* infections)**

Risk-benefit impact:

There is a theoretical risk of infection or reactivation of a latent infection associated with the administration of ustekinumab pertaining to IL-12/23 inhibition[3]. Serious infections could have a marked impact on the patient's quality of life and in some cases have a fatal outcome. Considering the infrequent occurrence in clinical practice and risk minimisation measures in place, the impact of this risk on the benefit-risk balance of ustekinumab is acceptable.

- **Malignancy**

Risk-benefit impact:

There is a theoretical risk of malignancy associated with the administration of ustekinumab pertaining to IL-12/23 inhibition[3,4,5]. Malignancies could have a marked impact on the patient's quality of life and in some cases have a fatal outcome. Considering the infrequent occurrence in clinical practice and risk minimisation measures in place, the impact of this risk on the benefit-risk balance of ustekinumab is acceptable.

- **Cardiovascular events**

Risk-benefit impact:

By the inhibition of the Th17 pathway, ustekinumab may induce atherosclerotic plaque rupture and atherothrombotic events, including stroke and acute coronary syndrome[6]. Such events could have a marked impact on the patient's quality of life, and in more severe cases, have a fatal outcome. Considering the characteristics of the target population of ustekinumab and risk minimisation measures in place, the impact of this risk on the benefit-risk balance of ustekinumab is acceptable.

- **Serious depression including suicidality**

Risk-benefit impact:

Patients with moderate to severe psoriasis are at an increased risk for depressive symptoms due to the underlying condition and other risk factors[7,8]. Depression could have a marked impact on the patient's quality of life, and in more severe cases, lead to suicide. Considering the infrequent occurrence in clinical practice and risk minimisation measures in place, the impact of this risk on the benefit-risk balance of ustekinumab is acceptable.

- **Venous thromboembolism**

Risk-benefit impact:

Patients with inflammatory bowel disease are at risk of thromboembolism due to the underlying condition and other risk factors (e.g. dehydration, use of catheters, prolonged immobilisation, hospitalisation, surgical interventions, and oral contraceptive use). Venous thromboembolism events may have a marked impact on the patient's quality of life. Considering the anticipated benefits of the therapy and the risk minimisation measures in place, the impact of this risk on the benefit-risk balance of ustekinumab is acceptable.

- **Exposure during pregnancy**

Risk-benefit impact:

Ustekinumab crosses the placenta and has been detected in the serum of infants born to female patients treated with ustekinumab during pregnancy. The clinical impact of this is unknown, however, the risk of infection in infants exposed *in utero* to ustekinumab may be increased after birth[9]. Considering the characteristics of the target population of ustekinumab and the risk minimisation measures in place, the impact of this risk on benefit-risk balance of ustekinumab is acceptable.

Missing information:

- **Long-term safety in paediatric psoriasis patients 6 years and older**

Risk-benefit impact:

The safety profile of ustekinumab is not expected to differ in paediatric psoriasis patients 6 years and older, but the long-term impact of ustekinumab use in this population requires further investigation.

- **Long-term impact on growth and development in paediatric psoriasis patients 6 years and older**

Risk-benefit impact:

The safety profile of ustekinumab is not expected to differ in paediatric psoriasis patients 6 years and older, but the long-term impact of ustekinumab use in this population requires further investigation.

- **Long-term safety in adult patients with moderately to severely active Crohn's disease**

Risk-benefit impact:

The safety profile of ustekinumab is not expected to differ with long-term administration in adult patients with moderately to severely active Crohn's disease, but the long-term use of ustekinumab in this population requires further investigation.

- **Long-term safety in adult patients with moderately to severely active ulcerative colitis**

Risk-benefit impact:

The safety profile of ustekinumab is not expected to differ with long-term administration in adult patients with moderately to severely active ulcerative colitis, but the long-term use of ustekinumab in this population requires further investigation.

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

The following safety concern has been removed from the RMP:

Safety Concern	Reason for Removal from the List of Safety Concerns
Important potential risks	
Exposure during pregnancy	This risk has been removed to be in line with the most recent version of the originator RMP.

There were no new safety concerns identified from the last version to the data lock point.

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

Important identified risk: None

Important potential risk 1: Serious infections (including mycobacterial and Salmonella infections)

Potential mechanisms:

The mechanism by which ustekinumab may increase the risk of serious infections has not yet been elucidated.

In vitro and animal studies have suggested that IL-12 and IL-23 may have distinct roles in contributing to protective immune responses to bacterial infections and tumours. Thus, there is a theoretical risk of infection or reactivation of a latent infection associated with the administration of ustekinumab pertaining to IL-12/23 inhibition[3].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of ustekinumab as reflected in the Product Information and the summary of safety concerns for the reference product STELARA[1,2].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency of infections is 'common' (i.e. ≥1 in 100 to <1 in 10) for upper respiratory tract infections, nasopharyngitis, and sinusitis, and 'uncommon' (i.e. ≥1 in 1,000 to <1 in 100) for cellulitis, dental infections, herpes zoster, lower respiratory tract infection, viral upper respiratory tract infection, and vulvovaginal mycotic infection, based on the overall experience

with ustekinumab from fourteen Phase II and Phase III clinical studies, encompassing data from 6,709 patients with psoriasis and/or psoriatic arthritis, Crohn's disease, and ulcerative colitis, and the post-marketing experience[1].

In placebo-controlled studies of patients with psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis, the rates of infection or serious infection were similar between ustekinumab-treated patients and those treated with placebo. In the placebo-controlled period of these clinical trials, the rate of infection was 1.36 per patient-year of follow-up in ustekinumab-treated patients, and 1.34 in placebo-treated patients. Serious infections occurred at the rate of 0.03 per patient-year of follow-up in ustekinumab-treated patients (30 serious infections in 930 patient-years of follow-up) and 0.03 in placebo-treated patients (15 serious infections in 434 patient-years of follow-up)[1].

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis clinical trials, representing 11,581 patient-years of exposure in 6,709 patients, the median follow-up was 1.0 years; 1.1 years for psoriatic disease studies, 0.6 year for Crohn's disease studies, and 1.0 years for ulcerative colitis studies. The rate of infection was 0.91 per patient-year of follow-up in ustekinumab-treated patients, and the rate of serious infections was 0.02 per patient-year of follow-up in ustekinumab-treated patients (199 serious infections in 11,581 patient-years of follow-up) and serious infections reported included pneumonia, anal abscess, cellulitis, diverticulitis, gastroenteritis, and viral infections[1].

In clinical studies, patients with latent tuberculosis who were concurrently treated with isoniazid did not develop tuberculosis[1].

Across clinical trials in all indications for which ustekinumab is approved, analysis for serious infections in pooled data during the controlled period does not suggest an increased risk of serious infection in the overall ustekinumab-treated population[2].

No serious infections were reported in the Phase I comparative study SB17-1001, whereas one serious event of pneumonia was reported in 1 (0.4%) patient receiving STELARA in the Phase III comparative study SB17-3001.

The occurrence and management of serious infections can have significant clinical and economic impact on patients. Treatment discontinuation may be required for patients experiencing such events, which can have significant implications for the management of the disease.

Risk factors and risk groups:

Risk factors for the development of serious infections include diabetes and other comorbidities, as well as the concomitant use of steroids, anti-TNFs, other immunosuppressants, or other biologics[2].

Tuberculosis

The most common risk factors for the development of tuberculosis include conditions impairing the development of effective cell-mediated immunity to the infection (i.e. advanced age, human immunodeficiency virus [HIV] infection), alcohol abuse, malignancy, corticosteroids or other immunosuppression, connective tissue disease, renal failure, diabetes, and pregnancy[2].

A risk factor for the development of tuberculosis is exposure to tuberculosis, and patients who were born or lived in countries considered by the World Health Organization to have a high

tuberculosis burden (incidence: >300 cases/100,000 population/year) [10] or have travelled to these locations may be at higher risk. Exposure in the health care setting or in high-density institutions (i.e. prisons) may also put patients at higher risk of development of tuberculosis. The possibility of latent tuberculosis must be considered, especially in patients who have immigrated from or travelled to countries with a high prevalence of tuberculosis or had close contact with a person with active tuberculosis. In patients who are severely ill or immunocompromised, tuberculin tests may yield false negative results[2].

Non-tuberculosis mycobacterial (NTM) infections

A retrospective/prospective review performed in Australia found that significant risks for non-HIV-associated pulmonary *Mycobacterium avium*/*Mycobacterium intracellulare* complex (MAC) disease included male sex (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.0 to 4.5) and age >50 years (OR, 26.5; 95% CI, 10.9 to 67.3)[2,11]. Similarly, in a US study including 933 patients with 1 or more NTM isolates, pulmonary disease prevalence was highest in persons aged >50 years (15.5 cases per 100,000 persons)[2,12]. In addition, chronic respiratory disease, especially chronic obstructive pulmonary disease treated with inhaled corticosteroid therapy is a strong risk factor for NTM pulmonary disease. Prolonged occupational exposure to soil was an important risk factor for MAC infection in a US study[2,13].

Salmonella

Factors that could increase risk of *Salmonella* infection include activities that result in close contact with *Salmonella* (e.g. international travel, owning a pet bird or reptile) and health issues that weaken resistance to infection (e.g. stomach or bowel disorders leading to use of antacids; recent antibiotic use; inflammatory bowel disease; or impaired immunity from acquired immune deficiency syndrome, sickle cell disease, malaria, anti-rejection drugs taken after organ transplants, and corticosteroids)[2].

Preventability:

Considering the unknown mechanism for this risk, the occurrence of serious infections in patients receiving ustekinumab cannot be fully prevented. However, identifying the risk factors could allow early detection and timely intervention, thereby decreasing the potential for worsening severity and complications.

Ustekinumab is contraindicated in patients with a clinically important, active infection (e.g. active tuberculosis).

Prior to initiating treatment with ustekinumab, patients should be evaluated for tuberculosis infection, and treatment of latent tuberculosis infection should be initiated. Anti-tuberculosis therapy should also be considered prior to initiation of ustekinumab in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving ustekinumab should be monitored closely for signs and symptoms of active tuberculosis during and after treatment.

Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating this patient population with ustekinumab.

Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and ustekinumab should not be administered until the infection resolves.

Patients are instructed to report any symptoms suggestive of infection without delay.

Impact on the risk-benefit balance of the product:

Serious infections could have a marked impact on the patient's quality of life and in some cases have a fatal outcome. Considering the infrequent occurrence in clinical practice and risk minimisation measures in place, the impact of this risk on the benefit-risk balance of ustekinumab is acceptable.

Public health impact:

No impact on public health is expected.

Important potential risk 2: Malignancy

Potential mechanisms:

The mechanism by which ustekinumab may cause malignancy has not yet been elucidated.

In vitro and animal studies have suggested that IL-12 and IL-23 may have distinct roles in contributing to protective immune responses to bacterial infections and tumours. Thus, there is a theoretical risk of malignancy associated with the administration of ustekinumab pertaining to IL-12/23 inhibition[3,4,5].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of ustekinumab as reflected in the Product Information and the summary of safety concerns for the reference product STELARA[1,2].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

In the placebo-controlled period of the psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical trials with ustekinumab, the incidence of malignancies excluding non-melanoma skin cancer was 0.11 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in 929 patient-years of follow-up) compared with 0.23 for placebo-treated patients (1 patient in 434 patient-years of follow-up). The incidence of non-melanoma skin cancer was 0.43 per 100 patient-years of follow-up for ustekinumab-treated patients (4 patients in 929 patient-years of follow-up) compared to 0.46 for placebo-treated patients (2 patients in 433 patient-years of follow-up)[1].

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical trials, representing 11,561 patient-years of exposure in 6,709 patients, the median follow-up was 1.0 years; 1.1 years for psoriatic disease studies, 0.6 year for Crohn's disease studies, and 1.0 years for ulcerative colitis studies. Malignancies excluding non-melanoma skin cancers were reported in 62 patients in 11,561 patient-years of follow-up (incidence of 0.54 per 100 patient-years of follow-up for ustekinumab-treated patients). The incidence of malignancies reported in ustekinumab-treated patients was comparable to the incidence expected in the general population (standardised incidence ratio = 0.93 [95% CI: 0.71, 1.20], adjusted for age, gender, and race). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, colorectal, melanoma and breast cancers. The incidence of non-melanoma skin cancer was 0.49 per 100 patient-years of follow-up for

ustekinumab-treated patients (56 patients in 11,545 patient-years of follow-up). The ratio of patients with basal versus squamous cell skin cancers (3:1) was comparable with the ratio expected in the general population[1].

No malignancies occurred in the Phase I comparative study SB17-1001, whereas an event of prostate cancer was reported in 1 (0.2%) patient receiving STELARA in the Phase III comparative study SB17-3001, leading to permanent treatment discontinuation.

The occurrence and management of malignancies can have significant clinical and economic impact on patients. Permanent treatment discontinuation may be required for patients experiencing such events, which can have significant implications for the management of the disease.

Risk factors and risk groups:

Among patients with psoriasis, increased risk of solid cancers appears to be related to alcohol drinking and cigarette smoking. In addition, exposure to PUVA and immunosuppressants, including cyclosporin and possibly methotrexate, has been associated with squamous cell carcinoma in patients with psoriasis. General risk factors for malignancy include increasing age, lifestyle factors (such as use of alcohol and tobacco and obesity), family history of cancer, and certain environmental exposures[2].

Risk factors for the development of malignancy can differ by cancer site. However, in general, factors that can increase risk of malignancies in patients with inflammatory bowel disease include smoking, ongoing inflammation, and carcinogenic effects of immunosuppressive drugs[2].

Preventability:

Considering the unknown mechanism for this risk, the occurrence of malignancies in patients receiving ustekinumab cannot be fully prevented. However, identifying the risk factors could allow early detection and timely intervention, thereby decreasing the potential for worsening severity and complications.

All patients, in particular those above 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of skin cancer.

Impact on the risk-benefit balance of the product:

Malignancies could have a marked impact on the patient's quality of life and in some cases have a fatal outcome. Considering the infrequent occurrence in clinical practice and risk minimisation measures in place, the impact of this risk on the benefit-risk balance of ustekinumab is acceptable.

Public health impact:

No impact on public health is expected.

Important potential risk 3: Cardiovascular events

Potential mechanisms:

The mechanism by which ustekinumab may cause cardiovascular events has not yet been elucidated.

It is hypothesised that, by the inhibition of the Th17 pathway, ustekinumab may induce atherosclerotic plaque rupture and atherothrombotic events, including stroke and acute coronary syndrome[6].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of ustekinumab as reflected in the Product Information and the summary of safety concerns for the reference product STELARA[1,2].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency of cardiovascular events in patients receiving ustekinumab has not yet been established.

No cardiovascular events occurred in the Phase I comparative study SB17-1001.

One event of acute myocardial infarction was reported in a patient in the EKSUNBI treatment group, and one event of atrial fibrillation was reported in a patient in the STELARA treatment group in the Phase III comparative study SB17-3001.

A numeric imbalance in rates of investigator-reported major adverse cardiovascular events was observed between ustekinumab- and placebo-treated subjects in controlled clinical trials in psoriasis. However, such events were comparable with expected rates in either the general population or in the psoriasis population, and comparable to rates in trials of other biologics[2].

Through approximately 5 years of follow-up in Crohn's disease clinical trials and approximately 2 years of follow-up in ulcerative colitis clinical trials, the incidence of serious major adverse cardiovascular events was low in ustekinumab-treated subjects and placebo-treated subjects, with no consistent evidence that ustekinumab increases cardiovascular risk[2].

Patients with psoriasis are at an increased risk of cardiovascular events due to the underlying disease. A systematic review and meta-analysis of observational studies examining the cardiovascular risk in 201,239 patients with mild psoriasis and 17,415 patients with severe psoriasis showed an estimated excess of 11,500 major adverse cardiovascular events each year[14] .

The relative risk of myocardial infarction increases with increasing psoriasis severity, with a 3-fold increase in the risk of myocardial infarction for male patients with psoriasis at the age of 30 years. This risk was observed in all age groups, although it decreased with age. Other studies confirmed an increase in cardiovascular disease, peripheral vascular disease, stroke, and overall mortality, and also showed a correlation between the risk of cardiovascular morbidity and psoriasis severity[15].

A cohort study using the United Kingdom General Practice Research Database showed that patients with severe psoriasis have a 6-year reduction in life expectancy, with cardiovascular death accounting for the greatest proportion of excess mortality[16].

Risk factors and risk groups:

The risk factors in the development of cardiovascular disease are well known and include hypertension, hypercholesterolemia, diabetes, smoking, age, male sex, obesity, and family history[2,15].

Psoriatic arthritis and the psoriasis populations share certain risk factors such as increased cardiovascular risk, increased body weight, and increased body mass index, which have also been observed in patients with Crohn's disease[2,15].

Preventability:

Considering the unknown mechanism for this risk, the occurrence of cardiovascular events in patients receiving ustekinumab cannot be fully prevented. However, identifying the risk factors, e.g. hypertension, could allow early detection and timely intervention, thereby decreasing the potential for worsening severity and complications.

Impact on the risk-benefit balance of the product:

Cardiovascular events could have a marked impact on the patient's quality of life, and in more severe cases, have a fatal outcome. Considering the characteristics of the target population of ustekinumab and risk minimisation measures in place, the impact of this risk on the benefit-risk balance of ustekinumab is acceptable.

Public health impact:

No impact on public health is expected.

Important potential risk 4: Serious depression including suicidality

Potential mechanisms:

Patients with moderate to severe psoriasis are at an increased risk for depressive symptoms due to the underlying condition and other risk factors[7,8]. Overlapping biological mechanisms seem to contribute to the close connection of psoriasis and depression, as elevated levels of proinflammatory cytokines are present in both conditions[17].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of ustekinumab as reflected in the Product Information and the summary of safety concerns for the reference product STELARA[1,2].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency of depression is 'uncommon' (i.e. ≥1 in 1,000 to <1 in 100), based on the overall experience with ustekinumab from fourteen Phase II and Phase III clinical studies, encompassing data from 6,709 patients with psoriasis and/or psoriatic arthritis, Crohn's disease, and ulcerative colitis, and the post-marketing experience.

No events of serious depression including suicidality occurred in the Phase I comparative study SB17-1001 and the Phase III comparative study SB17-3001.

The psychological impact of psoriasis is substantial, as patients are at risk for a number of psychiatric comorbidities, including depression, anxiety, and substance abuse. Additionally, depression and psychological stress have been shown to potentially trigger or exacerbate psoriasis[8]. Coexisting inflammatory conditions (e.g. cardiometabolic disease, inflammatory bowel disease) and their sequelae may increase the disease burden[7].

Several studies confirmed improvements in both skin and psychological symptoms under biologic therapy; however, the reduction in depressive symptoms may not have been a direct effect of the improvement in skin symptoms[17].

Risk factors and risk groups:

Risk factors for depression include older age and associated neurological conditions; uncontrolled, poorly treated psoriasis; recent childbirth; stressful life events; a personal or family history of depression; and selected medical comorbid conditions including psoriatic conditions and inflammatory bowel disease[2].

Risk factors associated with suicide in individuals with depression include male gender, family history of psychiatric disorder, previous attempted suicide, severe depression, hopelessness, and comorbid disorders (e.g. anxiety and misuse of alcohol and drugs)[18]. Suicide rates are twice as high in families of suicide victims[2].

Preventability:

Considering the patient population and characteristics of the underlying condition, the occurrence of depression including suicidality in patients with psoriasis receiving ustekinumab cannot be fully prevented. Early detection of psychological vulnerability and managing the depression in these patients may significantly improve their quality of life.

Impact on the risk-benefit balance of the product:

Depression is an uncommon adverse effect of the ustekinumab therapy, but it could have a marked impact on the patient's quality of life, and in more severe cases, lead to suicide. Considering the infrequent occurrence in clinical practice and risk minimisation measures in place, the impact of this risk on the benefit-risk balance of ustekinumab is acceptable.

Public health impact:

No impact on public health is expected.

Important potential risk 5: Venous thromboembolism

Potential mechanisms:

The mechanism by which ustekinumab may cause venous thromboembolism has not yet been elucidated.

Patients with inflammatory bowel disease are at risk of thromboembolism due to the underlying condition and other risk factors (e.g. dehydration, use of catheters, prolonged immobilisation, hospitalisation, surgical interventions, and oral contraceptive use). The hypercoagulable nature of the disease seems to stem from a complex interplay of systems that include the coagulation cascade, natural coagulation inhibitors, fibrinolytic system, endothelium, immune system, and platelets[19].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of ustekinumab as reflected in the Product Information and the summary of safety concerns for the reference product STELARA[1,2].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency of venous thromboembolism in patients receiving ustekinumab has not yet been established.

No events of venous thromboembolism occurred in the Phase I comparative study SB17-1001 and the Phase III comparative study SB17-3001. One event of thrombophlebitis occurred in one subject in the EKSUNBI treatment group in study SB17-3001. The event was of moderate severity, and it was assessed as not related to EKSUNBI.

Venous thromboembolism events encompass a broad scope of events ranging from a simple deep vein thrombosis to severe life-threatening pulmonary embolism. After an initial venous thromboembolism event, long-term complications can include post-thrombotic syndrome, chronic thromboembolic pulmonary hypertension, and recurrence of disease[19].

Generally, three months of anticoagulation are necessary to complete the treatment of an acute episode of venous thromboembolism. The goal of such treatment is to suppress the acute episode of thrombosis, whereas the aim of subsequent anticoagulation is to prevent new episodes of venous thromboembolism events that are unrelated to the index event[20].

Venous thromboembolism events are likely to have a significant impact on the patients' physical and psychological health. There might be loss of independence and inability to perform daily activities, and even need for medical and social support. Discontinuation of ustekinumab in relation to venous thromboembolism occurrence might prevent patients from continuing treatment.

Risk factors and risk groups:

Patients suffering from inflammatory disease, including Crohn's disease and ulcerative colitis, are more prone to thromboembolic complications compared with the general population[2].

Clinical factors that increase the likelihood of a venous thromboembolic event among patients with inflammatory bowel disease include active and more extensive disease, surgery (particularly colorectal), hospitalisation, pregnancy, and the use of corticosteroids or tofacitinib. Additionally, although younger age may be associated with a higher relative risk of venous thromboembolic events among patients with inflammatory bowel disease, older patients have a much higher incidence of venous thromboembolism, and therefore present more often with such events[19].

Preventability:

Considering the nature of the patient population and their underlying disease, the occurrence of venous thromboembolism in patients receiving ustekinumab cannot be fully prevented.

Guidelines recommend venous thromboembolism prophylaxis for patients with inflammatory bowel disease admitted with a disease-flare who do not have hemodynamically significant

bleeding. On the other hand, the benefits of continued, post-discharge prophylaxis are not yet known and need to be weighed against risk of bleeding and polypharmacy[19].

Impact on the risk-benefit balance of the product:

Venous thromboembolism events may have a marked impact on the patient's quality of life. Considering the anticipated benefits of the therapy and the risk minimisation measures in place, the impact of this risk on the benefit-risk balance of ustekinumab is acceptable.

Public health impact:

No impact on public health is expected.

SVII.3.2 Presentation of the missing information

Missing information 1: Long-term safety in paediatric psoriasis patients 6 years and older

Evidence source:

This missing information is based on the safety profile of ustekinumab as reflected in the Product Information and the summary of safety concerns for the reference product STELARA[1,2].

Population in need of further characterisation:

The safety profile of ustekinumab is not expected to differ in paediatric psoriasis patients 6 years and older, but the long-term impact of ustekinumab use in this population requires further investigation.

Missing information 2: Long-term impact on growth and development in paediatric psoriasis patients 6 years and older

Evidence source:

This missing information is based on the safety profile of ustekinumab as reflected in the Product Information and the summary of safety concerns for the reference product STELARA[1,2].

Population in need of further characterisation:

The safety profile of ustekinumab is not expected to differ in paediatric psoriasis patients 6 years and older, but the long-term impact of ustekinumab use in this population requires further investigation.

Missing information 3: Long-term safety in adult patients with moderately to severely active Crohn's disease

Evidence source:

This missing information is based on the safety profile of ustekinumab as reflected in the Product Information and the summary of safety concerns for the reference product STELARA[1,2].

Population in need of further characterisation:

The safety profile of ustekinumab is not expected to differ with long-term administration in adult patients with moderately to severely active Crohn's disease, but the long-term use of ustekinumab in this population requires further investigation.

Missing information 4: Long-term safety in adult patients with moderately to severely active ulcerative colitis

Evidence source:

This missing information is based on the safety profile of ustekinumab as reflected in the Product Information and the summary of safety concerns for the reference product STELARA[1,2].

Population in need of further characterisation:

The safety profile of ustekinumab is not expected to differ with long-term administration in adult patients with moderately to severely active ulcerative colitis, but the long-term use of ustekinumab in this population requires further investigation.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Serious infections (including mycobacterial and *Salmonella* infections) Malignancy Cardiovascular events Serious depression including suicidality Venous thromboembolism
Missing information	Long-term safety in paediatric psoriasis patients 6 years and older Long-term impact on growth and development in paediatric psoriasis patients 6 years and older Long-term safety in adult patients with moderately to severely active Crohn's disease Long-term safety in adult patients with moderately to severely active ulcerative colitis

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

III.1 Routine pharmacovigilance activities

The pharmacovigilance plan does not include any routine pharmacovigilance activities beyond signal management and reporting of adverse reactions.

Efforts will be made to obtain follow-up information on brand name, and batch/lot number when the suspect drug(s) is not clear.

Table III.1. Targeted follow-up questionnaire

Safety Concern	Purpose/Description
Serious infections (including mycobacterial and salmonella infections)	Targeted follow-up questionnaire to collect information on Serious infection and opportunistic infections and Targeted follow-up questionnaire to collect information on tuberculosis
Malignancy	Targeted follow-up questionnaire to collect information on malignancy (including lymphoma, second and secondary malignancies)
Cardiovascular events	Targeted follow-up questionnaire to collect information on cardiovascular events
Venous thromboembolism	Targeted follow-up questionnaire to collect information on Venous thromboembolism'

The respective follow-up questionnaire forms are provided in Annex 4.

III.2 Additional pharmacovigilance activities

There are no ongoing or planned additional pharmacovigilance activities.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

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

Safety concern	Routine risk minimisation activities
Serious infections (including mycobacterial and *Salmonella* infections)	Routine risk communication SmPC sections 4.3, 4.4, 4.5, 4.6 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and EKSUNBI should not be administered until the infection resolves per the SmPC section 4.4. Guidance regarding evaluation of patients for TB infection, treatment of latent TB, and administration of anti-TB therapy in patients with a history of latent active TB prior to initiation of EKSUNBI is provided on the SmPC section 4.4. Patients should be monitored for signs and symptoms of active TB during and after EKSUNBI treatment per the SmPC section 4.4. Recommendation on administration of live vaccines to patients receiving ustekinumab and to infants exposed to ustekinumab in utero is provided on the SmPC section 4.5 and 4.6, and PL section 2. Guidance for patients who have recently had or are going to have a vaccination is provided on PL section 2. Guidance for patients who have had a recent infection, have any abnormal skin openings(fistulae), are over 65 years of age, or have recently been exposed to someone who might have TB is provided on PL section 2. Patients are instructed to report any symptoms suggestive of infection without delay per the PL section 4.

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

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription
Malignancy	Routine risk communication SmPC sections 4.4 and 4.8 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.4 • Guidance for monitoring patients for the appearance of skin cancer Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription
Cardiovascular events	Routine risk communication None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription
Serious depression including suicidality	Routine risk communication SmPC section 4.8 PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription

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

Safety concern	Routine risk minimisation activities
Venous thromboembolism	Routine risk communication None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription
Long-term safety in paediatric psoriasis patients 6 years and older	Routine risk communication None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription
Long-term impact on growth and development in paediatric psoriasis patients 6 years and older	Routine risk communication None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription
Long-term safety in adult patients with moderately to severely active Crohn's disease	Routine risk communication None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription

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

Safety concern	Routine risk minimisation activities
Long-term safety in adult patients with moderately to severely active ulcerative colitis	Routine risk communication None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription

PL = package leaflet; PUVA = psoralen and ultraviolet A; SmPC = summary of product characteristics.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious infections (including mycobacterial and *Salmonella* infections)	Routine risk minimisation SmPC sections 4.3, 4.4, 4.5, 4.6 and 4.8 PL sections 2 and 4 Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Targeted Follow-up Questionnaires (TFUQs) for serious infections and TB Additional pharmacovigilance activities None
Malignancy	Routine risk minimisation SmPC sections 4.4 and 4.8 PL section 2 Subject to restricted medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection TFUQ

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation None	Additional pharmacovigilance activities None
Cardiovascular events	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection TFUQ Additional pharmacovigilance activities None
Serious depression including suicidality	Routine risk minimisation SmPC section 4.8 PL section 4 Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None
Venous thromboembolism	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection TFUQ Additional pharmacovigilance activities None
Long-term safety in paediatric psoriasis patients 6 years and older	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		None
Long-term impact on growth and development in paediatric psoriasis patients 6 years and older	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None
Long-term safety in adult patients with moderately to severely active Crohn's disease	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None
Long-term safety in adult patients with moderately to severely active ulcerative colitis	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None

PL = package leaflet; SmPC = summary of product characteristics.

Part VI: Summary of the risk management plan

SUMMARY OF RISK MANAGEMENT PLAN FOR EKSUNBI(USTEKINUMAB)

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

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

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

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

I. The medicine and what it is used for

EKSUNBI is authorised in adults for plaque psoriasis, paediatric plaque psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis (see SmPC for the full indications). It contains ustekinumab as the active substance, and it is given by the intravenous or subcutaneous route of administration.

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

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

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

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

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

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

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

In addition to these measures, information about adverse reactions 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 EKSUNBI is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

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

List of important risks and missing information	
Important identified risks	None
Important potential risks	Serious infections (including mycobacterial and *Salmonella* infections) Malignancy Cardiovascular events Serious depression including suicidality Venous thromboembolism
Missing information	Long-term safety in paediatric psoriasis patients 6 years and older Long-term impact on growth and development in paediatric psoriasis patients 6 years and older Long-term safety in adult patients with moderately to severely active Crohn's disease Long-term safety in adult patients with moderately to severely active ulcerative colitis

II.B Summary of important risks

Important potential risk: Serious infections (including mycobacterial and *Salmonella* infections)	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of ustekinumab as reflected in the Product Information and the summary of safety concerns for the reference product STELARA.
Risk factors and risk groups	Risk factors for the development of serious infections include diabetes and other comorbidities, as well as the

	concomitant use of steroids, anti-TNFs, other immunosuppressants, or other biologics (EMA, 2024).
Risk minimisation measures	Routine risk minimisation SmPC sections 4.3, 4.4, 4.5, 4.6 and 4.8 PL sections 2 and 4 Subject to restricted medical prescription Additional risk minimisation None

European Medicines Agency (2024). "Stelara: EPAR - Risk-management-plan summary." Retrieved Apr 02, 2024, from https://www.ema.europa.eu/en/documents/rmp-summary/stelara-epar-risk-management-plan-summary_en.pdf.

Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of ustekinumab as reflected in the Product Information and the summary of safety concerns for the reference product STELARA.
Risk factors and risk groups	Among patients with psoriasis, increased risk of solid cancers appears to be related to alcohol drinking and cigarette smoking. In addition, exposure to PUVA and immunosuppressants, including cyclosporin and possibly methotrexate, has been associated with squamous cell carcinoma in patients with psoriasis. General risk factors for malignancy include increasing age, lifestyle factors (such as use of alcohol and tobacco and obesity), family history of cancer, and certain environmental exposures (EMA, 2024). Risk factors for the development of malignancy can differ by cancer site. However, in general, factors that can increase risk of malignancies in patients with inflammatory bowel disease include smoking, ongoing inflammation, and carcinogenic effects of immunosuppressive drugs (EMA, 2024).
Risk minimisation measures	Routine risk minimisation SmPC sections 4.4 and 4.8 PL section 2 Subject to restricted medical prescription Additional risk minimisation None

European Medicines Agency (2024). "Stelara: EPAR - Risk-management-plan summary." Retrieved Apr 02, 2024, from https://www.ema.europa.eu/en/documents/rmp-summary/stelara-epar-risk-management-plan-summary_en.pdf.

Important potential risk: Cardiovascular events	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of ustekinumab as reflected in the Product Information and the summary of safety concerns for the reference product STELARA.
Risk factors and risk groups	The risk factors in the development of cardiovascular disease are well known and include hypertension, hypercholesterolemia, diabetes, smoking, age, male sex, obesity, and family history (EMA, 2024; Ryan, 2015). Psoriatic arthritis and the psoriasis populations share certain risk factors such as increased cardiovascular risk, increased body weight, and increased body mass index, which have also been observed in patients with Crohn's disease (EMA, 2024; Ryan, 2015).
Risk minimisation measures	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None

European Medicines Agency (2024). "Stelara: EPAR - Risk-management-plan summary." Retrieved Apr 02, 2024, from https://www.ema.europa.eu/en/documents/rmp-summary/stelara-epar-risk-management-plan-summary_en.pdf.
Ryan, C. and B. Kirby (2015). "Psoriasis is a systemic disease with multiple cardiovascular and metabolic comorbidities." Dermatologic Clinics 33(1): 41-55.

Important potential risk: Serious depression including suicidality	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of ustekinumab as reflected in the Product Information and the summary of safety concerns for the reference product STELARA.
Risk factors and risk groups	Risk factors for depression include older age and associated neurological conditions; uncontrolled, poorly treated psoriasis; recent childbirth; stressful life events; a personal or family history of depression; and selected medical comorbid conditions including psoriatic conditions and inflammatory bowel disease (EMA, 2024). Risk factors associated with suicide in individuals with depression include male gender, family history of psychiatric disorder, previous attempted suicide, severe depression, hopelessness, and comorbid disorders (e.g. anxiety and misuse of alcohol and drugs) (Hawton, 2013). Suicide rates are twice as high in families of suicide victims (EMA, 2024).

Important potential risk: Serious depression including suicidality	
Risk minimisation measures	Routine risk minimisation SmPC section 4.8 PL section 4 Subject to restricted medical prescription Additional risk minimisation None

European Medicines Agency (2024). "Stelara: EPAR - Risk-management-plan summary." Retrieved Apr 02, 2024, from https://www.ema.europa.eu/en/documents/rmp-summary/stelara-epar-risk-management-plan-summary_en.pdf.
Hawton, K., et al. (2013). "Risk factors for suicide in individuals with depression: a systematic review." Journal of Affective Disorders 147(1-3): 17-28.

Important potential risk: Venous thromboembolism	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of ustekinumab as reflected in the Product Information and the summary of safety concerns for the reference product STELARA.
Risk factors and risk groups	Patients suffering from inflammatory disease, including Crohn's disease and ulcerative colitis, are more prone to thromboembolic complications compared with the general population (EMA, 2024). Clinical factors that increase the likelihood of a venous thromboembolic event among patients with inflammatory bowel disease include active and more extensive disease, surgery (particularly colorectal), hospitalisation, pregnancy, and the use of corticosteroids or tofacitinib. Additionally, although younger age may be associated with a higher relative risk of venous thromboembolic events among patients with inflammatory bowel disease, older patients have a much higher incidence of venous thromboembolism, and therefore present more often with such events (Cheng, 2020).

Important potential risk: Venous thromboembolism	
Risk minimisation measures	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None

Cheng, K. and A. S. Faye (2020). "Venous thromboembolism in inflammatory bowel disease." World Journal of Gastroenterology 26(12): 1231.
European Medicines Agency (2024). "Stelara: EPAR - Risk-management-plan summary." Retrieved Apr 02, 2024, from https://www.ema.europa.eu/en/documents/rmp-summary/stelara-epar-risk-management-plan-summary_en.pdf.

Missing information: Long-term safety in paediatric psoriasis patients 6 years and older	
Risk minimisation measures	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None

Missing information: Long-term impact on growth and development in paediatric psoriasis patients 6 years and older	
Risk minimisation measures	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None

Missing information: Long-term safety in adult patients with moderately to severely active Crohn's disease	
Risk minimisation measures	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None

Missing information: Long-term safety in adult patients with moderately to severely active ulcerative colitis	
Risk minimisation measures	Routine risk minimisation Subject to restricted medical prescription

	Additional risk minimisation None

II.C Post-authorisation development plan

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

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

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

There are no studies required for EKSUNBI.

Part VII: Annexes

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Annex 4 – Specific adverse drug reaction follow-up forms

Targeted Follow-up Questionnaire (TFUQ) for Serious Infections and Opportunistic Infections

Targeted Follow-up Questionnaire (TFUQ) for Tuberculosis (TB)

Targeted Follow-up Questionnaire (TFUQ) for Malignancies (including Lymphoma, Second and Secondary Malignancies)

Targeted Follow-up Questionnaire (TFUQ) for Cardiovascular Events

Targeted Follow-up Questionnaire (TFUQ) for Venous Thromboembolism (VTE)

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

Questionnaire: Serious Infections and Opportunistic Infections

To the Health Care Provider: Complete this form as a supplement to the Health Care Professional Adverse Event Follow-Up Form provided.

Manufacturer Control Number		**Date of Report**	
TRADE NAME of the product			

1. Medical History and Concurrent Conditions

☐ Prior history of exposure to TB
Details

☐ Prior history of exposure to Hepatitis B/C
Details

Details of vaccination history

☐ The patient was considered immunocompromised *(underlying diagnoses, 1mmunosuppress1ve therapy etc)*
Details:

Other relevant medical history or any known risk factors for acquiring specific infection in question:

2. Adverse Event Details

☐ The infection was present prior to starting the product
☐ There were unusual features of the patient's presentation or clinical course
Details:

Type of infection (e.g., pneumonia, endocarditis, etc.) and location if relevant (e.g., subcutaneous abscess of the forearm or TB of the CNS):

Questionnaire: Tuberculosis (TB)

To the Health Care Provider: Complete this form as a supplement to the Health Care Professional Adverse Event Follow-Up Form provided.

Manufacturer Control Number		**Date of Report**	
TRADE NAME of the product			

1. Relevant medical/occupational history

Check all that apply and provide details below.

☐ Weight loss≥10% of ideal body weight
☐ Diabetes
☐ Gastrectomy or jejunoileal bypass
☐ Organ/tissue transplant
☐ Prior BCG vaccination
☐ Recent travel to endemic area
☐ Resident/employee at high risk setting (e.g. , correctional institute, homeless shelter, nursing home, refugee camp, etc.)
☐ Head/Neck carcinoma
☐ Leukemia/Lymphoma
☐ Household contact/Exposure to TB
☐ Prior/prolonged steroid use
☐ IV drug abuse
☐ Prior/prolonged immunosuppressant use'
☐ Silicosis
☐ Positive HIV test

Details:

2. Diagnostics

☐ Purified Protein Derivative (PPD) testing was performed. Indicate test used
  ☐ Intradermal skin test
  ☐ Multipuncture skin test

Number of units administered: _____

PPD Result: _____ mm of induration (0, if no induration)
Date of PPD: _____

2nd PPD results (if applicable): _____ mm of indurat1on
Date of second PPD: _____

☐ False negative test (e.g. , time of injection to time of evaluation too long/short, evaluator of induration, etc.)? Explain reasons:

☐ The subject had active TB
☐ Prophylactic therapy was given

Time elapsed from onset of TB symptoms to institution of treatment:

Type of tuberculosis
☐ Pulmonary
☐ Extrapulmonary; Location
☐ Disseminated; Location
☐ Multi-drug Resistant TB

Questionnaire: Tuberculosis (TB)

3. Other laboratory results

Laboratory Test		Test Result	Date
AFB Smear	Sputum		
	Other(specify)		
Culture	Sputum		
	Other(specify)		
PCR MTb			
Quantiferon TB Gold			

Questionnaire: Malignancies (including Lymphoma, Second and Secondary Malignancies)

To the Health Care Provider: Complete this form as a supplement to the Health Care Professional Adverse Event Follow-Up Form provided.

Manufacturer Control Number		**Date of Report**	
TRADE NAME of the product			

1. Relevant Medical/Family History

Provide prior diagnoses and details for checked items below

☐ Previous malignancy
If checked, provide specific diagnosis:

☐ Occupational/Exposure history:
☐ Excessive sun exposure
If checked, describe:

☐ History of PUVA (Psoralen + Ultraviolet-A rays)
☐ History of radiation
Dose of radiation:
Area treated:
Age (or date of therapy) of the patient when they were treated with radiation:
Indication for radiation:
Any radiation induced changes?:
☐ Pre-malignant lesions, e.g. , Barret's esophagus, Bowen's disease.
If checked, provide details:

Viral infections ☐ EBV ☐ HIV ☐ HPV ☐ HBV or HCV
☐ Other relevant risk factors for malignancy (Excluding medications)
☐ Family history of malignancy (Provide specific diagnoses for each)
☐ In first degree relatives
☐ In more distant relatives
☐ Previous history of tumor necrosis factor (TNF) blocker therapy (With medication names, dates of exposure and the total number of doses or an approximation)
Age at first exposure to any TNF blocker
☐ Previous administration of other immunosuppressive medications, antineoplastic medications, or other drugs, which have a risk for malignancy stated in their label. (e.g., other biologics, methotrexate, azathioprine, cyclosporine, 6-mercaptopurine, prednisone, or other)
Include drug indication, dose levels, and treatment duration (e.g., methotrexate, clophosphamide, vincristine, doxorubicin, cyclosporine, biologics)

Medication	Indication	Dose/Route of Administration	Start Date	Stop Date

☐ Cytogenetic abnormalities detected at any point in time? (Include those relevant for any malignancy including myeloma -this could be germline genetic diseases predisposing for malignancy e.g., Down's syndrome, neurofibromatosis etc , or cytogenetic abnormalities relevant to myeloma)

Questionnaire: Malignancies (including Lymphoma, Second and Secondary Malignancies)

2. Diagnostics

Histopathologic diagnosis (Include the histopathology report):

Include malignancy stage, location of primary tumor, metastases, lymph node involvement and staging system used:

Additional diagnostic information, including finding that support specified staging, specialty consultations (Attach reports, if available):

Final diagnosis:

☐ Lymphoma
☐ Non-Hodgkin's lymphoma
Histologic subtype: Immunophenotype: Cytogenetics:
☐ Hodgkin's lymphoma
Histologic subtype:

Was the lymphoma tissue tested for Epstein-Barr virus (EBV) (e.g., by in situ hybridization and/or immunohistology analysis)? ☐ No ☐ Yes *(If yes, attach report)*
If Yes, Test Result: ☐ EBV positive ☐ EBV negative

☐ Second malignancy (A cancer that is unrelated to the treatment of a prior malignancy and is not a metastasis from the initial malignancy) If yes, list.

☐ Secondary malignancy (A cancer caused by treatment for a previous malignancy e.g., Treatment with radiation or chemotherapy. It is NOT considered a metastasis of the initial malignancy) If yes, list.

(Ref. Malignancy screening/Preventive measures (Include those that are relevant to the specific malignancy that is being reported, e.g., recent mammography, breast exam, Pap smear, sigmoidoscopy or colonoscopy, fecal occult blood, Prostatic Specific Antigen, digital rectal exam, HPV vaccine, etc)

Screening Test/Preventive Measure	Date	Results (Including units and reference ranges where applicable)

3. Treatment

What was the response to the first treatment for malignancy?
☐ Complete response
☐ Partial response
☐ Stable disease
☐ Progressive disease

Questionnaire: Cardiovascular Events

To the Health Care Provider: Complete this form as a supplement to the Health Care Professional Adverse Event Follow-Up Form provided.

Manufacturer Control Number		**Date of Report**	
TRADE NAME of the product			

1.Drug Details

Number of doses (e.g., injections, infusions) given prior to cardiovascular event:

Recent dose change? ☐Yes ☐No
If yes, provide details:

When did the patient **last** receive the product **before** the current dose?
Date: Time:

Date and time of dose (e.g., injections, infusions) after which this cardiovascular event occurred
Date: Time:

Date and time of onset of cardiovascular event reported now
Date: Time:

2. Relevant Medical History Details

Relevant Medical History
Provide prior diagnoses relevant laboratory data [including echo and ischemic evaluation], dates, etc. below

☐Hypertension
☐Hyperlipidemia/Hypercholesterolemia/Hypertriglyceridemia
☐Obesity
☐Coronary artery disease
☐Myocardial infarction
☐Valvular heart disease
☐History of percutaneous coronary intervention
☐Coronary artery bypass graft
☐Congenital heart disease
☐Arrhythmias
☐Cardiomyopathy
☐Pericarditis
☐Congestive heart failure
☐Peripheral artery disease
☐Diabetes mellitus
☐Renal impairment
☐Liver disease
☐Headaches
☐Head trauma
☐Transient ischemic attack
☐Ischemic cerebrovascular accident
☐Hemorrhagic cerebrovascular accident
☐other (Specify)

Relevant family history

☐Coronary disease
☐Stroke
☐Hyperlipidemia/Hypercholesterolemia/Hypertriglyceridem1a
☐Myocardial infarction

Questionnaire: Cardiovascular Events

- ☐ Diabetes mellitus
- ☐ Family history of long QT syndrome
- ☐ Other (Specify):

3. Adverse Event: Patient's Symptoms/Signs

Check all that apply and provide details below

- ☐ Dizziness
- ☐ Palpitations
- ☐ Edema
- ☐ Syncope
- ☐ Visual disturbance
- ☐ Sensory changes
- ☐ Jaw pain
- ☐ Facial weakness
- ☐ other relevant details:
- ☐ Exercise intolerance
- ☐ Dyspnea
- ☐ Cough
- ☐ Sudden death
- ☐ Sweating
- ☐ Left arm pain
- ☐ Extremity paralysis
- ☐ Chest discomfort
- ☐ Hemoptysis
- ☐ General malaise
- ☐ Aphasia
- ☐ Nausea/vomiting
- ☐ Ataxia
- ☐ Altered gait
- ☐ Transient weakness (i.e., slurred speech)

Questionnaire: Venous Thromboembolism

To the Health Care Provider: Complete this form as a supplement to the Health Care Professional Adverse Event Follow-Up Form provided.

Manufacturer Control Number		**Date of Report**	
TRADE NAME of the product			

1. Adverse Event Description

Patient's clinical signs and symptoms

☐ Leg/Calf Edema	☐ Pain in Leg/Calf	☐ Hemoptysis
☐ Dyspnea	☐ Chest Pain/Discomfort	☐ Syncope
☐ Tachypnoea	☐ Tachycardia	☐ Cough
☐ Headache	☐ Blurred vision	☐ Abdominal pain
☐ Nausea	☐ Vomiting	☐ Other symptoms

Was patient on VTE prophylaxis? ☐ Yes ☐ No
If yes, provide details:

2. Medical History and Concurrent Conditions

Provide details.

Is the patient overweight obese?	☐ No ☐ Yes	
If available, please provide height/weight and BMI Does the patient have a sedentary lifestyle?	☐ No ☐ Yes, Details:	
Has the subject been travelling and or sitting for long periods of time (> 4 hours) prior to the event?	☐ No ☐ Yes, Details:	
Is there a current history of smoking?	☐ No ☐ Yes, Details:	
Is there a prior history of smoking?	☐ No ☐ Yes, Details:	
Is there a history of cancer?	☐ No ☐ Yes, Details:	
Any past medical history of autoimmune disease (1.e., collagen-vascular disease, inflammatory bowel disease) or myeloproliferative disease?	☐ No ☐ Yes, Details:	
Does the subject have a history of a previous clotting disorder or a diagnosis of a hypercoagulable state?	☐ No ☐ Yes, Details:	
Is there a prior history of varicose veins, trauma to the involved leg or pelvis, DVT/PE/VTE?	☐ No ☐ Yes, Details:	
Is there a history of blood transfusion?	☐ No ☐ Yes, Details:	
Was the patient (female) pregnant at the time of event?	☐ No ☐ Yes, Details:	
Is there a history of cardiovascular disorder?	☐ No ☐ Yes, Details:	
Is there a history of organ transplantation?	☐ No ☐ Yes, Details:	

Generic risk factors

☐ Dysfibrinogenemia	☐ Antiphospholipid syndrome	☐ Factor V Leiden mutation
☐ Protein C or S deficiency	☐ Elevated factor VIII levels	☐ Anti-thrombin deficiency
☐ Hyperhomocysteinemia	☐ Prothrombin gene mutation	☐ Blood-clotting disorder
☐ Thrombophilia		

Acquired risk factors

Questionnaire: Venous Thromboembolism

- ☐ Reduced mobility (paralysis, paresis, travel etc.)
- ☐ Indwelling central venous catheters
- ☐ Recent discontinuation of anticoagulants (e.g., heparin, warfarin, DOACs)
- ☐ Hormone replacement therapy (HRT)
- ☐ Polycystic ovary syndrome (PCOS)
- ☐ Postpartum (up to 3 months after childbirth)
- ☐ Phlebitis
- ☐ Inflammatory bowel disease
- ☐ Diabetes mellitus
- ☐ Hypertension
- ☐ Recent surgery
- ☐ Recent trauma
- ☐ Hormonal contraceptives
- ☐ Pregnancy
- ☐ Myeloproliferative disorders
- ☐ Hyperlipidemia
- ☐ Dehydration
- ☐ Other significant medical co-morbidities or risk factors for DVT, specify:

If yes to any of the above, provide details.

Provide Well's score, if calculated.

3. Relevant results of diagnostic tests including laboratory tests, imaging, biopsies, etc.

Note the levels/conclusion, date performed, normal ranges as well as any other details. Alternatively, attach full reports of the diagnostic tests.

Diagnostic Test	Results at baseline or prior use of product (Include date and value/details)	Test results after use of product (Include date and value/details}
CBC with smear (microscopic evaluation)		
ESR		
Platelet count		
Antibodies to platelet factor 4 (PF4)		
Fibrinogen levels		
Clauss fibrinogen assay		
D-Dime		
Clotting Profile (PT, aPTT- prior to an anticoagulation treatment)		
Thrombin time (Bovine) Plasma		
Prothrombin		
Antithrombin activity		
Factor V Leiden		
Protein C activity		
Protein S activity		
C-reactive protein		
Homocystein levels		
Dilute Russells Viper Venom Time (DRVVT), Plasma		
Activated Protein C Resistance V (APCRV),		

Questionnaire: Venous Thromboembolism

Plasma		
Thrombophilia interpretation		
Anticardiolipin antibodies (lgG and lgM) or beta-2 glycoproteins antibodies		
Antiphospholipid antibodies (lgG and lgM)		
Lupus anticoagulant		
Heparin antibodies		
ANAand ANCA		
IL6levels		
ADAMTS13 Activity Assay		
Ceruloplasmin		
Direct Coombs test		
Complement C3, C4		
MethyleneletraHydrofolate reductase gene mutation		
Prothrombin gene mutation (G20210A)		
Occult blood in stool		
COVID-19 test		
Troponins		
Brain Natriuretic Peptide		
Arterial Blood Gases		
Chest X-Ray		
Electrocardiography		
Echocardiography		
Duplex Ultrasonography		
MRI scan		
CT scan		
Contrast Venography		
Pulmonary Angiography		
Ventilation-Perfusion Scanning		

Provide details of any additional diagnostic results:

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

Not applicable.