EU Risk Management Plan

For

Uzpruvo 45 mg solution for injection in pre-filled syringe

Uzpruvo 90 mg solution for injection in pre-filled syringe

Uzpruvo 130 mg solution for infusion

(ustekinumab)

RMP version to be assessed as part of this application:

RMP Version number: 1.4

Data lock point for this RMP: 26-SEP-2024

Date of final sign-off: 29-NOV-2024

Rationale for submitting an updated RMP: RMP updated according to the Day 195 Joint Assessment Report.

Summary of significant changes in this RMP: "Non-melanoma skin cancer" has been replaced with "skin cancer" in Module SVII.3.1. "Presentation of Important Identified Risks and Important Potential Risks". "Non-melanoma skin cancer" has been replaced with "skin cancer" in Part V.1. "Routine Risk Minimization Measures" and in Part V.3 "Summary of risk minimisation measures". The Part VI "Summary of activities in the risk management plan by medicinal product" has been updated in line with the issues raised in other parts of the RMP.

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

Version number: 1.0

Approved with procedure: EMEA/H/C/006101

Date of approval (opinion date): 09/November/2023

Qualified Person Responsible for Pharmacovigilance (QPPV) name: Dr. Andreas Iwanowitsch

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.

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Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) (International non-proprietary name or common name)	Ustekinumab.
Pharmacotherapeutic group(s) ((Anatomical Therapeutic Chemical classification [ATC] Code))	Immunosuppressants, Interleukin (IL) inhibitors, ATC code: L04AC05.
Marketing Authorisation Holder (MAH)	STADA Arzneimittel AG
Medicinal products to which this Risk Management Plan (RMP) refers	3.
Invented name(s) in the European Economic Area (EEA)	Uzpruvo 45 mg solution for injection in pre-filled syringe Uzpruvo 90 mg solution for injection in pre-filled syringe Uzpruvo 130 mg solution for infusion
Marketing authorisation procedure	Centralised procedure.
Brief description of the product	Chemical class: Immunosuppressants, IL inhibitors.
	Summary of mode of action: Ustekinumab is a recombinant, fully human Ig G, subclass 1, κ light chain (IgG1κ) monoclonal antibody that specifically binds to the shared p40 protein subunit of the human cytokines IL-12 and IL-23. Ustekinumab inhibits human IL-12 and IL-23 activities by preventing p40 from binding to the shared IL-12Rβ1 protein subunit of human IL-12 and IL-23 receptors on the surface of immune cells. The primary mechanism of action is binding of the antigen binding fragment (Fab) domain of ustekinumab to the p40 protein subunit of both IL-12 and IL-23, thus preventing the cytokines from binding to IL-12 and IL-23 receptor complexes on the surface of natural killer (NK) cells or T cells thereby initiating downstream immune-response signalling pathways.

	Important information about its composition: Ustekinumab is a recombinant fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines IL-12 and IL-23.
Hyperlink to the Product Information	Please refer to Module 1.3.1.
Indication(s) in the EEA	Current: **Uzpruvo 45 mg solution for injection in pre-filled syringe and 90 mg solution for injection in pre-filled syringe:** Plaque psoriasis Uzpruvo 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 (MTX) or psoralen and ultraviolet (PUVA). Paediatric plaque psoriasis Uzpruvo is indicated for the treatment of 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. Psoriatic arthritis (PsA) Uzpruvo, alone or in combination with MTX, is indicated for the treatment of active PsA in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Crohn's disease Uzpruvo is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor (TNF) α antagonist or have medical contraindications to such therapies.
	Proposed (if applicable): **Uzpruvo 130 mg solution for infusion** Crohn's disease Uzpruvo is indicated for the treatment of adult patients with moderately to severely active Crohn's disease 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.

Dosage in the EEA	Current: **<u>Uzpruvo 45 mg solution for injection in pre-filled syringe and 90 mg solution for injection in pre-filled syringe:</u>** Uzpruvo is intended for use under the guidance and supervision of physicians experienced in the diagnosis and treatment of conditions for which ustekinumab is indicated. <u>Posology</u> *<u>Plaque psoriasis</u>* The recommended posology of ustekinumab is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment. *<u>PsA</u>* The recommended posology of ustekinumab is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment. Paediatric population: the safety and efficacy of ustekinumab in children with psoriasis less than 6 years of age or in children with PsA less than 18 years of age have not yet been established. *<u>Paediatric plaque psoriasis (6 years and older)</u>* The recommended dose of ustekinumab is based on body weight. Ustekinumab should be administered at weeks 0 and 4, then every 12 weeks thereafter. To calculate the volume of injection (mL) for patients <60 kg, use the following formula: body weight (kg) × 0.0083 (mL/kg). The calculated volume should be rounded to the nearest 0.01 mL and administered using a 1 mL graduated syringe. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment. *<u>Crohn's Disease</u>* The first subcutaneous administration of 90 mg ustekinumab 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.

	Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit 16 weeks after the IV induction dose or 16 weeks after switching to the 8-weekly maintenance dose. Immunomodulators and/or corticosteroids may be continued during treatment with ustekinumab. In patients who have responded to treatment with ustekinumab, corticosteroids may be reduced or discontinued in accordance with standard of care. In Crohn's disease, if therapy is interrupted, resumption of treatment with subcutaneous dosing every 8 weeks is safe and effective. *Paediatric population*: the safety and efficacy of ustekinumab for the treatment of Crohn's disease in children less than 18 years have not yet been established. No data are available.
	Proposed (if applicable): **Uzpruvo 130 mg solution for infusion** Uzpruvo concentrate for solution for infusion is intended for use under the guidance and supervision of physicians experienced in the diagnosis and treatment of Crohn's disease. Uzpruvo concentrate for solution for infusion should only be used for the intravenous induction dose. Posology *Crohn's Disease* Uzpruvo treatment is to be initiated with a single intravenous dose based on body weight. The infusion solution is to be composed of the number of vials of Uzpruvo 130 mg as specified in the following table:

Body weight of patient at the time of dosing	Recommended dose[a]	Number of 130 mg Uzpruvo vials
≤ 55 kg	260 mg	2
> 55 kg to ≤ 85 kg	390 mg	3
> 85 kg	520 mg	4

	The first subcutaneous dose should be given at week 8 following the intravenous dose. For the posology of the subsequent subcutaneous dosing regimen, see the SmPC of the Uzpruvo solution for injection (vial) and solution for injection in pre-filled syringe.
Pharmaceutical form(s) and strengths	Current (if applicable): Uzpruvo 45 mg solution for injection in pre-filled syringe Each pre-filled syringe contains 45 mg ustekinumab in 0.5 mL.

	Uzpruvo 90 mg solution for injection in pre-filled syringe Each pre-filled syringe contains 90 mg ustekinumab in 1 mL.
	Proposed (if applicable): Uzpruvo 130 mg concentrate for solution for infusion Each vial contains 130 mg ustekinumab in 26 mL (5 mg/mL).
Is/will the product be subject to additional monitoring in the European Union (EU)?	Yes.

Part II: Safety specification

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

Not applicable. Omitted module for biosimilar products.

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

Uzpruvo (ustekinumab) has been developed as a proposed biosimilar to Stelara (the originator). The reference product Stelara sourced from the EU, United States of America (US), Japan (JP) or China (CN) are referred in this document as "EU-Stelara", "US-Stelara", "JP-Stelara" or "CN-Stelara", respectively.

The non-clinical development program for Uzpruvo has been designed in accordance with the current regulatory requirements for the non-clinical development of biosimilar monoclonal antibodies:

- EMA/CHMP/BMWP/403543/2010: Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues
- FDA Guidance for Industry: Scientific Considerations in demonstrating Biosimilarity to a reference product, April 2015

Physicochemical and functional pharmacological data generally indicated similarity among multiple batches of Uzpruvo and the originator product. No animal in vivo studies evaluating efficacy, toxicity, pharmacology or drug interactions of Uzpruvo were neither deemed necessary nor requested by the agencies European Medicines Agency (EMA) and United States Food Drug Administration (FDA) in the scientific advice meetings to support the clinical studies.

The Chinese National Medical Products Administration (NMPA) requested two non-clinical studies with Uzpruvo for approval of Uzpruvo as a biosimilar in China, therefore the applicant has conducted two *in vivo* studies in Cynomolgus monkeys:

One (1) single dose pharmacokinetic (PK) study to evaluate the PK profile of ustekinumab after a single s.c. injection of XXX or CN-Stelara to Cynomolgus monkeys. The animals were randomly assigned to receive a low dose (0.9 mg/kg) or high dose (9 mg/kg) of Uzpruvo or CN-Stelara. In addition, development of antidrug antibodies was monitored in this study.

One (1) repeat dose toxicity study to evaluate the toxicity and toxicokinetic (TK) profile of Uzpruvo administered by s.c. injection to Cynomolgus monkeys. The objectives of this study were to evaluate the toxicity and toxicokinetic (TK) profile of Uzpruvo administered by subcutaneous (s.c.) injection once weekly for 4 weeks, and to assess the reversibility during a 4-week recovery period. Meanwhile, TK, immunogenicity, and immunotoxicity profiles were compared between Uzpruvo and a comparator ustekinumab injection (CN-Stelara). The animals received either excipient control (diluted formulation buffer), Uzpruvo at doses of 5, 15 or 45 mg/kg or CN-Stelara at a dose of 45 mg/kg. TK, immunogenicity and immunotoxicity profiles were compared between Uzpruvo and Stelara.

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

Toxicity

There was no apparent toxicity or irritation at the injection sites in Cynomolgus monkeys following s.c. injection of Uzpruvo or Stelara once weekly for 4 weeks. No mortality or morbidity was noted in any animals throughout the study. There were no treatment-related effects on vital functions, the cardiovascular system, the central nervous systems, and there were no respiratory or macroscopic or microscopic findings.

The no observed adverse effect level (NOAEL) of Uzpruvo was considered to be 45 mg/kg under the conditions of this study.

Safety Pharmacology

No studies to evaluate safety pharmacology of Uzpruvo have been conducted in accordance with the European Economic Area (EMA) and Food and Drug Administration (FDA) guidance for development of biosimilar.

Part II: Module SIII - Clinical trial exposure

Two (2) company-sponsored clinical trials have been conducted with ustekinumab since the Development International Birth Date (DIBD). One (1) of them was a completed phase I clinical trial, the other one was a completed phase III pivotal clinical trial.

Table SIII.1: Cumulative subject exposure from clinical trials

Treatment	Number of subjects
Uzpruvo	292
Comparator: EU-Stelara	486
Comparator: US-Stelara	97
Total subjects	**875**

Table SIII.2: Cumulative subject exposure to Uzpruvo from clinical trials by Gender

Gender	Number of subjects
Male	148
Female	144
Total subjects	**292**

Table SIII.3: Cumulative subject exposure to Uzpruvo from clinical trials by race

Race	Number of subjects
Asian	13
Black or African American	1
Caucasian/White	265
American Indian or Alaska Native	2
Native Hawaiian or other Pacific Islander	1
Australian Aborigine/Torres Strait Islander	1
Multiple	5
Other	4
Total subjects	**292**

Table SIII.4: Cumulative subject exposure to Uzpruvo from clinical trials by ethnicity

Ethnicity	Number of subjects
Japanese	7
Non-Japanese	91
Hispanic or Latino	1
Non-Hispanic or Latino	193
Total subjects	**292**

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

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

Known hypersensitivity to ustekinumab or its excipients

Reason for exclusion: patients with known hypersensitivity to ustekinumab or excipients should not use.

Is it considered to be included as missing information?: no

Rationale: use in this population is contraindicated in section 4.3 "Contraindications" of the summary of product characteristics (SmPC).

Current active infections or recent history

Reason for exclusion: criterion to avoid a potential safety bias.

Is it considered to be included as missing information?: no

Rationale: comprehensive wording concerning infections (is currently in section 4.4 "Special warnings and precautions for use" of the SmPC.

Previous history of active or latent tuberculosis (TB)

Reason for exclusion: to avoid any possible impact by ustekinumab, in relationship with its immunosuppressant effect, on the treatment of a current or recent infection

Is it considered to be included as missing information?: yes

Immunosuppressive therapy

Reason for exclusion: criterion to avoid a potential safety bias.

Is it considered to be included as missing information?: yes

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.2: 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 program
Breastfeeding women	

Type of special population	Exposure
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Japanese: 20 Hispanic or Latino: 4
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other	Not included in the clinical development program

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable since the product is not commercialised.

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

Potential for misuse for illegal purposes

Ustekinumab is not structurally or pharmacologically related to any drug known to cause abuse or dependence, and it is not expected to have a potential for misuse as a recreational drug.

Part II: Module SVII - Identified and potential risks

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

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

Not all adverse reactions are necessarily considered a risk for the medicinal product in a given therapeutic context and not all risks qualify as important to be included in the list of safety concerns for the purpose of risk management planning.

The information available for ustekinumab has been analysed and those risks not considered important for inclusion in the list of safety concerns in the RMP (along with the reason of not inclusion) are detailed below:

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Gastrointestinal disorders: diarrhoea, nausea, vomiting.
- General disorders and administration site conditions: fatigue, injection site erythema, injection site pain, injection site reactions (including haemorrhage, haematoma, induration, swelling and pruritus), asthenia.
- Immune system disorders: rash, urticaria.
- Musculoskeletal and connective tissue disorders: back pain, myalgia, arthralgia.
- Nervous system disorders: dizziness, headache.
- Respiratory, thoracic and mediastinal disorders: oropharyngeal pain, nasal congestion.
- Skin and subcutaneous tissue disorders: pruritus, acne.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- Nervous system disorders: facial palsy.
- Respiratory, thoracic and mediastinal disorders: allergic alveolitis, eosinophilic pneumonia, organising pneumonia.
- Skin and subcutaneous tissue disorders: pustular psoriasis, skin exfoliation, exfoliative dermatitis, bullous pemphigoid.

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

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

Published non-clinical and medical literature suggest that inhibition of IL-12/23 may predispose patients to serious infections. "Serious infection (including mycobacterial and salmonella infections)" is considered an important potential risk with Uzpruvo based upon the theoretical risk identified from non-clinical data and in humans who are genetically deficient for the cytokines that are inhibited by Uzpruvo (IL-12/23p40 or IL-12Rβ1). However, the risk of developing serious infections (including mycobacterial and salmonella infections) in subjects on anti-IL-12/23p40 therapy such as Uzpruvo is currently unknown.

Across clinical trials in all indications for which the originator product 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.

Risk-benefit impact:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Important potential risk 2: Malignancy

There is a theoretical risk of malignancy associated with administration of ustekinumab based on scientific literature pertaining to inhibition of IL-12/23. In the pooled controlled portion of clinical trials across indications, the rate of malignancy other than non-melanoma skin cancer (NMSC) was low and was balanced between the ustekinumab and comparator groups.

Since malignancies tend to take a long time to develop, long-term follow up is most relevant. In psoriasis patients treated for up to 5 years of continuous therapy with the originator product, the risk of malignancies other than NMSC was not increased compared with the general US population

Long-term effects of the originator product on existing malignancies or in patients with a history of malignancy are not known. In light of the theoretic risk and the longer latency period for the development of malignancy, the topic warrants continued surveillance and malignancy considered an important potential risk.

Risk-benefit impact:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Important potential risk 3: Cardiovascular (CV) events

The risk of developing CV events in subjects on anti-IL-12/23p40 therapy such as Uzpruvo is currently unknown.

A numeric imbalance in rates of investigator reported major adverse cardiovascular event (MACE) was observed between ustekinumab- and placebo-treated subjects in the controlled portions of Phase 2 and Phase 3 trials in psoriasis, resulting predominantly from an imbalance in event rates from a smaller Phase 2 trial. Additional analyses performed internally by the MAH of the originator product show that the overall rates of myocardial infarction and stroke with up to 5 years of treatment with the originator product in psoriasis patients are comparable with expected rates in either the general population or in the psoriasis population, and comparable to rates in trials of other biologics. Across indications, analysis of MACE in controlled portions of the pooled clinical trial data does not currently suggest a significant increased risk of MACE in subjects treated with ustekinumab.

In summary, the totality of the currently available data does not suggest that ustekinumab increases the risk of MACE; however, in light of the imbalance of CV events in the short-term placebo-controlled portions of the psoriasis clinical trials and the known increased risk of these events in the psoriasis and PsA populations, CV events are considered an important potential risk for ustekinumab.

Risk-benefit impact:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Important potential risk 4: Serious depression including suicidality

Psoriasis patients can have an increased risk for depression and, in rare cases, suicide.

The available safety data from clinical studies and post-marketing experience of the originator product have not identified a safety signal of suicidal ideation or suicidal attempt (including completed suicide). However, based on the severity of these events, serious depression including suicidality is considered an important potential risk for ustekinumab.

Risk-benefit impact:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Important potential risk 5: Venous thromboembolism (VTE)

Patients with IBD can have an increased risk for blood clots in veins due to their underlying condition and other risk factors (dehydration, use of catheters, prolonged immobilisation, hospitalisation, surgical interventions, oral contraceptive use, etc.).

VTE was originally identified as an important potential risk based on data collected through 44 weeks of treatment in the ustekinumab Crohn's disease clinical trials with the originator product. The rate of VTE as measured by the number of cases observed per time of treatment (i.e., per 100 years of treatment of subjects) was approximately twice as high in the ustekinumab group compared with the placebo group, but both rates are within the broad range of incidence rates reported in the literature for IBD. Overall, safety results from the Crohn's disease clinical trials through Week 96, UC trials through Week 44, and from clinical trials conducted for other indications, as well as cumulative post-marketing data, do not indicate an increased rate with ustekinumab treatment.

Risk-benefit impact:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

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

Insufficient data on long-term safety are available for this population group.

Risk-benefit impact:

Since there is scarce experience with the use of ustekinumab in long-term use in paediatric psoriasis patients 6 years and older, this use needs to be further studied.

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

Insufficient data on long-term safety are available for this population group.

Risk-benefit impact:

Since there is scarce experience with the use of ustekinumab in long-term impact on growth and development in paediatric psoriasis patients 6 years and older, this use needs to be further studied.

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

Insufficient data on long-term safety are available for this population group.

Risk-benefit impact:

Since there is scarce experience with the use of ustekinumab in long-term use in adult patients with moderately to severely active Crohn's disease, this use needs to be further studied.

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 identified risk	
Serious systemic hypersensitivity reactions	All additional pharmacovigilance activities for this risk have been completed. The risk is well characterized and risk management is adequately addressed through routine pharmacovigilance and routine risk minimization.
Important potential risk	
Exposure during pregnancy	A cumulative review of postmarketing data revealed no increased risk of birth defects or adverse pregnancy and infant outcomes. All additional pharmacovigilance activities for this safety concern have been completed. The MAH believes additional PV activities will not further characterize this risk. Risk management is adequately addressed through routine pharmacovigilance and routine risk minimization.

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:

Ustekinumab may alter T-cell mediated immunity through modulation of TNF-α.

Evidence source(s) and strength of evidence:

Published non-clinical and medical literature suggest that inhibition of IL-12/23 may predispose patients to serious infections. "Serious infection (including mycobacterial and salmonella infections)" is considered an important potential risk with Uzpruvo based upon the theoretical risk identified from non-clinical data and in humans who are genetically deficient for the cytokines that are inhibited by Uzpruvo (IL-12/23p40 or IL-12Rβ1). However, the risk of developing serious infections (including mycobacterial and salmonella infections) in subjects on anti-IL-12/23p40 therapy such as Uzpruvo is currently unknown.

Across clinical trials in all indications for which the originator product 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.

Characterisation of the risk:

Risk severity ranges from mild infectious processes to sepsis and death.

Risk factors and risk groups:

Serious infections

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.

TB

The most common risk factors for the development of TB 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.

A risk factor for the development of TB is exposure to TB, and patients who were born or lived in countries considered by the World Health Organization (WHO) to have a high TB burden (incidence: >300 TB cases/100,000 population/year) 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 TB. The possibility of latent TB must be considered, especially in patients who have immigrated from or travelled to countries with a high prevalence of TB or had close contact with a person with active TB. In patients who are severely ill or immunocompromised, tuberculin tests may yield false negative results.

Non-TB mycobacterial (NTM) infections

A retrospective/prospective review performed in Australia, found that significant risks for non-HIV-associated pulmonary Mycobacterium avium/Mycobacterium intracellular complex (MAC) disease included male sex (odds ratio (OR)=2.1; 95% CI: 1.0-4.5) and age >50 years (OR=26.5; 95% CI: 10.9-67.3). 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). 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.

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 [IBD]; or impaired immunity from acquired immune deficiency syndrome, sickle cell disease, malaria, anti-rejection drugs taken after organ transplants, and corticosteroids).

Preventability:

Section 4.3 of the SmPC states that ustekinumab is contraindicated in case of clinically important, active infection. In addition, according to section 4.4 of the SmPC, 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.

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

No public health impact is expected.

Important potential risk 2: Malignancy

Potential mechanisms:

Ustekinumab may alter T-cell mediated immunity, which may influence the appearance of malignancy, but the mechanism is yet unknown.

Evidence source(s) and strength of evidence:

There is a theoretical risk of malignancy associated with administration of ustekinumab based on scientific literature pertaining to inhibition of IL-12/23. In the pooled controlled portion of clinical trials across indications, the rate of malignancy other than non-melanoma skin cancer (NMSC) was low and was balanced between the ustekinumab and comparator groups.

Since malignancies tend to take a long time to develop, long-term follow up is most relevant. In psoriasis patients treated for up to 5 years of continuous therapy with the originator product, the risk of malignancies other than NMSC was not increased compared with the general US population

Long-term effects of the originator product on existing malignancies or in patients with a history of malignancy are not known. In light of the theoretic risk and the longer latency period for the development of malignancy, the topic warrants continued surveillance and malignancy considered an important potential risk.

Characterisation of the risk:

The risk for lymphoma, leukaemia, and Hepatosplenic T-cell Lymphoma (HSTCL) includes death. The risk for NMSC includes disfigurement, and possibly death in rare cases of metastatic squamous cell skin cancer. The risk for melanoma includes disfigurement, death, and metastatic disease. The risk for MCC includes metastatic disease and death.

Risk factors and risk groups:

Among psoriasis patients, 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 MTX, has been associated with squamous cell carcinoma in psoriasis patients. 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.

Risk factors for the development of malignancy can differ by cancer site. However, in general, factors that can increase risk of malignancies in Crohn’s disease patients include but are not limited to smoking, ongoing inflammation, and carcinogenic effects of immunosuppressive drugs.

Preventability:

Section 4.4 of the SmPC states that all patients, in particular those greater than 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:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

No public health impact is expected.

Important potential risk 3: Cardiovascular (CV) events

Potential mechanisms:

Unknown.

Evidence source(s) and strength of evidence:

The risk of developing CV events in subjects on anti-IL-12/23p40 therapy such as Uzpruvo is currently unknown.

A numeric imbalance in rates of investigator reported major adverse cardiovascular event (MACE) was observed between ustekinumab- and placebo-treated subjects in the controlled portions of Phase 2 and Phase 3 trials in psoriasis, resulting predominantly from an imbalance in event rates from a smaller Phase 2 trial. Additional analyses performed internally by the MAH of the originator product show that the overall rates of myocardial infarction and stroke with up to 5 years of treatment with the originator product in psoriasis patients are comparable with expected rates in either the general population or in the psoriasis population, and comparable to rates in trials of other biologics. Across indications, analysis of MACE in controlled portions of the pooled clinical trial data does not currently suggest a significant increased risk of MACE in subjects treated with ustekinumab.

In summary, the totality of the currently available data does not suggest that ustekinumab increases the risk of MACE; however, in light of the imbalance of CV events in the short-term placebo-controlled portions of the psoriasis clinical trials and the known increased risk of these events in the psoriasis and PsA populations, CV events are considered an important potential risk for ustekinumab.

Characterisation of the risk:

The risk includes a wide range of cardiovascular events such as myocardial infarction and stroke that can lead to severe disabilities and death.

Risk factors and risk groups:

The risk factors in the development of CV disease are well known and include hypertension, hypercholesterolemia, diabetes, smoking, age, male gender, obesity, and family history. The PsA and the psoriasis populations share certain risk factors such as increased CV risk, increased body weight, and increased body mass index, which have also been observed in Crohn’s disease patients.

Preventability:

Unknown.

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

No public health impact is expected.

Important potential risk 4: Serious depression including suicidality

Potential mechanisms:

Unknown.

Evidence source(s) and strength of evidence:

Psoriasis patients can have an increased risk for depression and, in rare cases, suicide.

The available safety data from clinical studies and post-marketing experience of the originator product have not identified a safety signal of suicidal ideation or suicidal attempt (including completed suicide). However, based on the severity of these events, serious depression including suicidality is considered an important potential risk for ustekinumab.

Characterisation of the risk:

Major depression has detrimental consequences on the lives of affected individuals with approximately 80% of them experiencing difficulties with work, home or social activities as a result of their condition, increasing the risk of suicidal ideation and death[Pilon, 2022].

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 IBD. Suicide rates are twice as high in families of suicide victims.

Preventability:

Unknown.

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

No public health impact is expected.

Important potential risk 5: Venous thromboembolism (VTE)

Potential mechanisms:

Unknown.

Evidence source(s) and strength of evidence:

Patients with IBD can have an increased risk for blood clots in veins due to their underlying condition and other risk factors (dehydration, use of catheters, prolonged immobilisation, hospitalisation, surgical interventions, oral contraceptive use, etc.).

VTE was originally identified as an important potential risk based on data collected through 44 weeks of treatment in the ustekinumab Crohn's disease clinical trials with the originator product. The rate of VTE as measured by the number of cases observed per time of treatment (i.e. per 100 years of treatment of subjects) was approximately twice as high in the ustekinumab group compared with the placebo group, but both rates are within the broad range of incidence rates reported in the literature for IBD. Overall, safety results from the Crohn's disease clinical trials through Week 96, UC trials through Week 44, and

from clinical trials conducted for other indications, as well as cumulative post-marketing data, do not indicate an increased rate with ustekinumab treatment.

Characterisation of the risk:

VTE is a multifactorial disease associated with vascular endothelial damage, stasis of blood flow, and hypercoagulation that can ultimately lead to death.

Risk factors and risk groups:

Patients suffering from IBD, namely Crohn's disease and UC, are more prone to thromboembolic complications compared with the general population.

A study of IBD patients conducted in the UK reported that there was increased risk of VTE during disease flares and chronic activity. In a Danish population study that included children and adults, and the highest risk of VTE was in the 0 to 20 years age group with an hazard ratio (HR) of 6.6 (95% CI: 3.3 to 13.2), compared with 1.6 (95% CI: 1.5 to 1.8) for the ≥60 years age group. Risk has also been reported to be greater for males, with an incidence rate of 1.34/1000 patient-years (PY), than for females with an incidence rate of 0.73/1000 PY. Smoking and the need for steroid treatment have also been shown to be risk factors for VTE with ORs of 3.46 (95% CI 1.14-10.5) and 2.97 (95% CI: 0.99-8.92), respectively.

Preventability:

Unknown.

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

No public health impact 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:

Insufficient data on long-term safety are available for this population group.

Anticipated risk/consequence of the missing information:

Since there is scarce experience with the use of ustekinumab in long-term use in paediatric psoriasis patients 6 years and older, this use needs to be further studied.

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

Evidence source:

Insufficient data on long-term safety are available for this population group.

Anticipated risk/consequence of the missing information:

Since there is scarce experience with the use of ustekinumab in long-term impact on growth and development in paediatric psoriasis patients 6 years and older, this use needs to be further studied.

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

Evidence source:

Insufficient data on long-term safety are available for this population group.

Anticipated risk/consequence of the missing information:

Since there is scarce experience with the use of ustekinumab in long-term use in adult patients with moderately to severely active Crohn's disease, this use needs to be further studied.

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 (CV) events Serious depression including suicidality Venous thromboembolism (VTE)
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

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities include routine follow-up of all adverse drug reaction reports lacking information on the batch number and/or brand name. Therefore, all appropriate measures are taken for biological medicinal products to clearly identify the names of the products and batch numbers.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific Adverse Reaction Follow-up Questionnaires

Topic of interest questionnaires (TOIQ) and targeted follow-up questionnaires (TFUQ) will be used for the following safety concerns:

- Serious infections (including mycobacterial and salmonella infections): Topic of interest (TOI) TFUQ to collect information on serious infections and opportunistic infections and TOI TFQU to collect information on tuberculosis
- Malignancy: TOI TFUQ to collect information on cardiovascular events on malignancies (including lymphoma, second and secondary malignancies)
- Cardiovascular events: TOI TFUQ to collect information on cardiovascular events
- Venous thromboembolism: TOIQ to collect information on venous thromboembolism

The forms are provided in Annex 4 of the RMP.

Other Forms of Routine Pharmacovigilance Activities

Not applicable.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities will be conducted.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable as no post-authorisation efficacy studies are planned.

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. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.3 of the SmPC states that ustekinumab is contraindicated in case of clinically important, active infection. In addition, according to section 4.4 of the SmPC, caution should be exercised when considering the use of ustekinumab in patients with a chronic infection or a history of recurrent infection. Prior to initiating treatment with ustekinumab, patients should be evaluated for TB infection. Ustekinumab must not be given to patients with active TB. Treatment of latent TB infection should be initiated prior to administering ustekinumab. Anti-TB therapy should also be considered prior to initiation of ustekinumab in patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving ustekinumab should be monitored closely for signs and symptoms of active TB during and after treatment. 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. Section 4.4 of the SmPC also states that because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly. Section 4.6 of the SmPC states that 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. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.

Safety concern	Routine risk minimisation activities
Malignancy	Routine risk communication: SmPC sections 4.4 and 4.8. In order to inform patients of this risk, corresponding text is also present in the PIL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4 of the SmPC states that all patients, in particular those greater than 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. In order to inform patients of this risk, corresponding text is also present in the PIL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.
Cardiovascular (CV) 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: Legal status: Restricted medical prescription.
Serious depression including suicidality	Routine risk communication: SmPC section 4.8. In order to inform patients of this risk, corresponding text is also present in the PIL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.
Venous thromboembolism (VTE)	Routine risk communication: None.

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.
Long-term safety in paediatric psoriasis patients 6 years and older	Routine risk communication: SmPC section 4.2. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.
Long-term impact on growth and development in paediatric psoriasis patients 6 years and older	Routine risk communication: SmPC section 4.2. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: 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: Legal status: Restricted medical prescription.

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

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
Serious infections (including mycobacterial and salmonella infections)	Routine risk minimisation measures: SmPC sections 4.3, 4.4, 4.5, 4.6 and 4.8. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4. Section 4.3 of the SmPC states that ustekinumab is contraindicated in case of clinically important, active infection. In addition, according to section 4.4 of the SmPC, caution should be exercised when considering the use of ustekinumab in patients with a chronic infection or a history of recurrent infection. Prior to initiating treatment with ustekinumab, patients should be evaluated for TB infection. Ustekinumab must not be given to patients with active TB. Treatment of latent TB infection should be initiated prior to administering ustekinumab. Anti-TB therapy should also be considered prior to initiation of ustekinumab in patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving ustekinumab should be monitored closely for signs and symptoms of active TB during and after treatment. 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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: TOI TFUQs for serious infections and tuberculosis. Additional pharmacovigilance activities: None.

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
	monitored and ustekinumab should not be administered until the infection resolves. Section 4.4 of the SmPC also states that because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly. Section 4.6 of the SmPC states that 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. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	
Malignancy	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. In order to inform patients of this risk, corresponding text is also present in the PIL section 2. Section 4.4 of the SmPC states that all patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: TOI TFUQ. Additional pharmacovigilance activities: None.

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
	treatment, should be monitored for the appearance of skin cancer. In order to inform patients of this risk, corresponding text is also present in the PIL section 2. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	
Cardiovascular (CV) events	Routine risk minimisation measures: Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: TOI TFUQ. Additional pharmacovigilance activities: None.
Serious depression including suicidality	Routine risk minimisation measures: SmPC section 4.8. In order to inform patients of this risk, corresponding text is also present in the PIL section 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Venous thromboembolism (VTE)	Routine risk minimisation measures: Legal status: Restricted medical prescription. Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: TOIQ. Additional pharmacovigilance activities:

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
	None.	None.
Long-term safety in paediatric psoriasis patients 6 years and older	Routine risk minimisation measures: SmPC section 4.2. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Long-term impact on growth and development in paediatric psoriasis patients 6 years and older	Routine risk minimisation measures: SmPC section 4.2. Legal status: Restricted medical prescription. Additional risk minimisation measures: 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 measures: Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Part VI: Summary of the risk management plan

Summary of risk management plan for Uzpruvo (ustekinumab)

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

Uzpruvo's summaries of product characteristics (SmPCs) and their package leaflet give essential information to health care professionals and patients on how Uzpruvo should be used.

This summary of the RMP for Uzpruvo 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 Uzpruvo's RMP.

I. The medicine and what it is used for

Uzpruvo 45 mg solution for injection in pre-filled syringe, 90 mg solution for injection in pre-filled syringe and 130 mg solution for infusion indicated for the treatment of plaque psoriasis, paediatric plaque psoriasis and psoriatic arthritis Crohn's disease (see SmPC for the full indications). They contain ustekinumab as the active substance and it is given by the intravenous or subcutaneous route of administration.

Further information about the evaluation of Uzpruvo's benefits can be found in Uzpruvo's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: (link to the EPAR summary landing page).

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

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals ;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the 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 Uzpruvo is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Uzpruvo are risks that need special risk management activities to further investigate or minimize 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 Uzpruvo. 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 (CV) events Serious depression including suicidality Venous thromboembolism (VTE)
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

II.B Summary of important risks

Important potential risk: Serious infections (including mycobacterial and salmonella infections)	
Evidence for linking the risk to the medicine	Published non-clinical and medical literature suggest that inhibition of IL-12/23 may predispose patients to serious infections. "Serious infection (including mycobacterial and salmonella infections)" is considered an important potential risk with Uzpruvo based upon the theoretical risk identified from non-clinical data and in humans who are genetically deficient for the cytokines that are inhibited by Uzpruvo (IL-12/23p40 or IL-12Rβ1). However, the risk of developing serious infections (including mycobacterial and salmonella infections) in subjects on anti-IL-12/23p40 therapy such as Uzpruvo is currently unknown. Across clinical trials in all indications for which the originator product 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.

Important potential risk: Serious infections (including mycobacterial and salmonella infections)	
Risk factors and risk groups	Serious infections 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. TB The most common risk factors for the development of TB 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. A risk factor for the development of TB is exposure to TB, and patients who were born or lived in countries considered by the World Health Organization (WHO) to have a high TB burden (incidence: >300 TB cases/100,000 population/year) 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 TB. The possibility of latent TB must be considered, especially in patients who have immigrated from or travelled to countries with a high prevalence of TB or had close contact with a person with active TB. In patients who are severely ill or immunocompromised, tuberculin tests may yield false negative results. Non-TB mycobacterial (NTM) infections A retrospective/prospective review performed in Australia, found that significant risks for non-HIV-associated pulmonary Mycobacterium avium/Mycobacterium intracellular complex (MAC) disease included male sex (odds ratio (OR)=2.1; 95% CI: 1.0-4.5) and age >50 years (OR=26.5; 95% CI: 10.9-67.3). 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). 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. Salmonella Factors that could increase risk of salmonella infection include activities that result in close contact with salmonella (eg, international travel, owning a pet bird or reptile) and health issues that weaken resistance to infection (eg, stomach or bowel disorders leading to use of antacids; recent antibiotic use; inflammatory bowel

Important potential risk: Serious infections (including mycobacterial and salmonella infections)	
	disease [IBD]; or impaired immunity from acquired immune deficiency syndrome, sickle cell disease, malaria, anti-rejection drugs taken after organ transplants, and corticosteroids).
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4, 4.5, 4.6 and 4.8. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4. Section 4.3 of the SmPC states that ustekinumab is contraindicated in case of clinically important, active infection. In addition, according to section 4.4 of the SmPC, caution should be exercised when considering the use of ustekinumab in patients with a chronic infection or a history of recurrent infection. Prior to initiating treatment with ustekinumab, patients should be evaluated for TB infection. Ustekinumab must not be given to patients with active TB. Treatment of latent TB infection should be initiated prior to administering ustekinumab. Anti-TB therapy should also be considered prior to initiation of ustekinumab in patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving ustekinumab should be monitored closely for signs and symptoms of active TB during and after treatment. 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. Section 4.4 of the SmPC also states that because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly. Section 4.6 of the SmPC states that 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. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.

Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	There is a theoretical risk of malignancy associated with administration of ustekinumab based on scientific literature pertaining to inhibition of IL-12/23. In the pooled controlled portion of clinical trials across indications, the rate of malignancy other than non-melanoma skin cancer (NMSC) was low and was balanced between the ustekinumab and comparator groups. Since malignancies tend to take a long time to develop, long-term follow up is most relevant. In psoriasis patients treated for up to 5 years of continuous therapy with the originator product, the risk of malignancies other than NMSC was not increased compared with the general US population Long-term effects of the originator product on existing malignancies or in patients with a history of malignancy are not known. In light of the theoretic risk and the longer latency period for the development of malignancy, the topic warrants continued surveillance and malignancy considered an important potential risk.
Risk factors and risk groups	Among psoriasis patients, 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 MTX, has been associated with squamous cell carcinoma in psoriasis patients. 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. Risk factors for the development of malignancy can differ by cancer site. However, in general, factors that can increase risk of malignancies in Crohn's disease patients include but are not limited to smoking, ongoing inflammation, and carcinogenic effects of immunosuppressive drugs.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC sections 4.4 and 4.8. In order to inform patients of this risk, corresponding text is also present in the PIL section 2. Section 4.4 of the SmPC states that all patients, in particular those greater than 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. In order to inform patients of this risk, corresponding text is also present in the PIL section 2. Legal status: Restricted medical prescription.

Important potential risk: Malignancy	
	Additional risk minimisation measures: None.

Important potential risk: Cardiovascular (CV) events	
Evidence for linking the risk to the medicine	The risk of developing CV events in subjects on anti-IL-12/23p40 therapy such as Uzpruvo is currently unknown. A numeric imbalance in rates of investigator reported major adverse cardiovascular event (MACE) was observed between ustekinumab- and placebo-treated subjects in the controlled portions of Phase 2 and Phase 3 trials in psoriasis, resulting predominantly from an imbalance in event rates from a smaller Phase 2 trial. Additional analyses performed internally by the MAH of the originator product show that the overall rates of myocardial infarction and stroke with up to 5 years of treatment with the originator product in psoriasis patients are comparable with expected rates in either the general population or in the psoriasis population, and comparable to rates in trials of other biologics. Across indications, analysis of MACE in controlled portions of the pooled clinical trial data does not currently suggest a significant increased risk of MACE in subjects treated with ustekinumab. In summary, the totality of the currently available data does not suggest that ustekinumab increases the risk of MACE; however, in light of the imbalance of CV events in the short-term placebo-controlled portions of the psoriasis clinical trials and the known increased risk of these events in the psoriasis and PsA populations, CV events are considered an important potential risk for ustekinumab.
Risk factors and risk groups	The risk factors in the development of CV disease are well known and include hypertension, hypercholesterolemia, diabetes, smoking, age, male gender, obesity, and family history. The PsA and the psoriasis populations share certain risk factors such as increased CV risk, increased body weight, and increased body mass index, which have also been observed in Crohn's disease patients.
Risk minimisation measures	Routine risk minimisation measures: Legal status: Restricted medical prescription. Additional risk minimisation measures: None.

Important potential risk: Serious depression including suicidality	
Evidence for linking the risk to the medicine	Psoriasis patients can have an increased risk for depression and, in rare cases, suicide. The available safety data from clinical studies and post-marketing experience of the originator product have not identified a safety signal of suicidal ideation or suicidal attempt (including completed suicide). However, based on the severity of these events, serious depression including suicidality is considered an important potential risk for ustekinumab.
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 IBD. Suicide rates are twice as high in families of suicide victims.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. In order to inform patients of this risk, corresponding text is also present in the PIL section 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.

Important potential risk: Venous thromboembolism (VTE)	
Evidence for linking the risk to the medicine	Patients with IBD can have an increased risk for blood clots in veins due to their underlying condition and other risk factors (dehydration, use of catheters, prolonged immobilisation, hospitalisation, surgical interventions, oral contraceptive use, etc.). VTE was originally identified as an important potential risk based on data collected through 44 weeks of treatment in the ustekinumab Crohn's disease clinical trials with the originator product. The rate of VTE as measured by the number of cases observed per time of treatment (i.e. per 100 years of treatment of subjects) was approximately twice as high in the ustekinumab group compared with the placebo group, but both rates are within the broad range of incidence rates reported in the literature for IBD. Overall, safety results from the Crohn's disease clinical trials through Week 96, UC trials through Week 44, and from clinical trials conducted for other

Important potential risk: Venous thromboembolism (VTE)	
	indications, as well as cumulative post-marketing data, do not indicate an increased rate with ustekinumab treatment.
Risk factors and risk groups	Patients suffering from IBD, namely Crohn's disease and UC, are more prone to thromboembolic complications compared with the general population. A study of IBD patients conducted in the UK reported that there was increased risk of VTE during disease flares and chronic activity. In a Danish population study that included children and adults, and the highest risk of VTE was in the 0 to 20 years age group with an hazard ratio (HR) of 6.6 (95% CI: 3.3 to 13.2), compared with 1.6 (95% CI: 1.5 to 1.8) for the ≥60 years age group. Risk has also been reported to be greater for males, with an incidence rate of 1.34/1000 patient-years (PY), than for females with an incidence rate of 0.73/1000 PY. Smoking and the need for steroid treatment have also been shown to be risk factors for VTE with ORs of 3.46 (95% CI 1.14-10.5) and 2.97 (95% CI: 0.99-8.92), respectively.
Risk minimisation measures	Routine risk minimisation measures: Legal status: Restricted medical prescription. Additional risk minimisation measures: None.

Missing information: Long-term safety in paediatric psoriasis patients 6 years and older	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.

Missing information: Long-term impact on growth and development in paediatric psoriasis patients 6 years and older	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2. Legal status: Restricted medical prescription.

Missing information: Long-term impact on growth and development in paediatric psoriasis patients 6 years and older	
	Additional risk minimisation measures: None.

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

II.C Post-authorisation development plan

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

There are no studies that are conditions of the marketing authorisation or specific obligations of Uzpruvo.

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

There are no studies required for Uzpruvo.

Part VII: Annexes

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Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not Applicable.

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not Applicable.

Annex 4 - Specific adverse drug reaction follow-up forms

Table of Contents

- Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Serious Infections and Opportunistic Infections
- Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Tuberculosis (TB)
- Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Malignancies (including Lymphoma, Second and Secondary Malignancies)
- Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Cardiovascular Events
- Topic of lnterest Questionnaire (TOIQ) for Venous Thromboembolism (VTE)

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

Topic of Interest Targeted Follow-Up Questionnaire (TOI TFUQ) for Serious Infections and Opportunistic Infections

Manufacturer Control Number: Drug generic (TRADENAME):
Date of Report: [dd-MMM-yyyy]

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, immunosuppressive 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):

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Topic of Interest Targeted Follow-Up Questionnaire (TOI TFUQ) for Tuberculosis (TB)

Manufacturer Control Number: Drug generic (TRADENAME):
Date of Report: [dd-MMM-yyyy]

1. Relevant medical/occupational history (*Check all that apply and provide details below*)

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

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: [dd-MMM-yyyy]
2nd PPD results (if applicable): mm of induration
Date of second PPD: [dd-MMM-yyyy]
☐ 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

Other laboratory results

Laboratory Test		Test Result	Date: [dd-MMM-yyyy]
AFB Smear	Sputum		
	Other (specify)		
Culture	Sputum		
	Other (specify)		
PCR MTb			
Quantiferon TB Gold			

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Topic of Interest Targeted Follow-Up Questionnaire (TOI TFUQ) for Malignancies (including Lymphoma, Second and Secondary Malignancies)

Manufacturer Control Number: Drug generic (TRADENAME):
Date of Report: [dd-MMM-yyyy]

1. Relevant Medical/Family History (*Provide prior diagnoses and details for checked items below*)

☐ Previous malignancy (Provide specific diagnosis):
☐ Occupational/Exposure history:
☐ Excessive sun exposure (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 oesophagus, Bowen's disease. 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, doxorubicine, cyclosporine, biologics)

Medication	Indication	Dose/Route of Administration	Start Date/Stop Date (dd-MMM-yyyy)

☐ 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)

MCN:

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:
☐ [l 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 (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) (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) (*List*):

(Ref. http//ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf)
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, faecal occult blood, Prostatic Specific Antigen, digital rectal exam, HPV vaccine etc.)

Screening Test/Preventive Measure	Date (dd-MMM-yyyy)	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

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Topic of Interest Targeted Follow-Up Questionnaire (TOI TFUQ) for Cardiovascular Events

Manufacturer Control Number: Drug generic (TRADENAME):
Date of Report: [dd-MMM-yyyy]

1. Drug Details:

Number of doses (e.g., injections, infusions) given prior to cardiovascular event:
Recent **dose change? Details:**
When did the patient **last** receive the product **before the current dose?**
Date: [dd-MMM-yyyy], Time:
Date and time of dose (e.g., injections, infusions) **after which this** cardiovascular event occurred:
[dd-MMM-yyyy], Time
Date and time of onset of cardiovascular event **reported now**: [dd-MMM-yyyy], Time

2. 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/Hypertriglyceridemia
☐ Myocardial infarction
☐ Diabetes mellitus
☐ Family history of long QT syndrome
☐ Other (Specify):

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MCN:

3. Adverse Event: Patient's symptoms/Signs (*Check all that apply and provide details below*)

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

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Topic of Interest Questionnaire (TOIQ) for Venous Thromboembolism (VTE)

Manufacturer Control Number: Date of Report: [dd-MM M-yyyy]
Product Generic (TRADE) Name:

1. Adverse Event Description

Patient's clinical signs and symptoms

☐ Leg/Calf Oedema	☐ Pain in Leg/Calf	☐ Haemoptysis
☐ Dyspnoea	☐ Chest Pain/Discomfort	☐ Syncope
☐ Tachypnoea	☐ Tachycardia	☐ Cough
☐ Headache	☐ Blurred vision	☐ Abdominal pain
☐ Nausea	☐ Vomiting	☐ Other symptoms:

Was patient on VTE prophylaxis? ☐ No ☐ Yes details:

2. Medical History and Concurrent Conditions

Provide details:

Is the patient overweight or 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?	
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 (i.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:

Genetic 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:

☐ Reduced mobility (paralysis, paresis, travel etc.)	☐ Recent surgery
☐ Indwelling central venous catheters	☐ Recent trauma
☐ Recent discontinuation of anticoagulants (e.g., heparin, warfarin, DOACs)	
☐ Hormone replacement therapy (HRT)	☐ Hormonal contraceptives

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MCN:

☐ Polycystic ovary syndrome (PCOS)
☐ Postpartum (up to 3 months after childbirth)
☐ Phlebitis
☐ Inflammatory bowel disease
☐ Diabetes mellitus
☐ Hypertension
☐ Pregnancy
☐ Lupus
☐ 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 to 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-Dimer		
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), Plasma		
Thrombophilia interpretation		
Anticardiolipin antibodies (IgG and IgM) or beta-2 glycoproteins antibodies		
Antiphospholipid antibodies(IgG and IgM)		
Lupus anticoagulant		
Heparin antibodies		
ANA and ANCA		

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MCN:

Diagnostic Test	Results at baseline or prior to use of product (Include date and value/details)	Test results after use of product (Include date and value/details)
IL6 levels		
ADAMTS13 Activity Assay		
Ceruloplasmin		
Direct Coombs test		
Complement C3, C4		
MethylenetetraHydrofolate 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		
Echo cardiography		
Duplex Ultrasonography		
MRI scan		
CT scan		
Contrast Venography		
Pulmonary Angiography		
Ventilation-Perfusion Scanning		

Provide details of any additional diagnostic results:

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Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not Applicable.

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

Not Applicable.

Annex 7 - Other supporting data (including referenced material)

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Zheng M, Jullien D, Eyerich K. The Prevalence and Disease Characteristics of Generalized Pustular Psoriasis. Am J Clin Dermatol. 2022;23(Suppl 1):5-12.

Annex 8 – Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change
0.4 (1.0)	At the time of authorisation: Approval date: 09/November/2023 Procedure number: EMEA/H/C/006101	RMP version 0.4 was approved and, therefore, considered as version 1.0. Initial RMP.
1.1	Approval date: Not approved yet. Procedure number: EMEA/H/C/006101	Line extension to include the following presentations: 45 mg solution for injection and 130 mg solution for infusion. No changes in safety concerns, PV plan, Post-authorisation efficacy plan or risk minimisation measures.
1.2	Approval date: Not approved yet. Procedure number: EMEA/H/C/006101	All references to Uzpruvo 45 mg solution for injection have been removed. The important identified risk 'Serious systemic hypersensitivity reactions' has been removed from the summary of safety concerns and throughout the requested updated RMP, including the Topic of Interest Questionnaire (TOIQ) for Hypersensitivity and Anaphylactic Reaction. The Part VI "Summary of activities in the risk management plan by medicinal product" has been updated in line with the issues raised in other parts of the RMP.
1.3	Approval date: Not approved yet. Procedure number: EMEA/H/C/006101	The important potential risk 'Exposure during pregnancy' has been removed from the summary of safety concerns and throughout the requested updated RMP. The Part VI "Summary of activities in the risk management plan by medicinal product" has been updated in line with the issues raised in other parts of the RMP.
1.4	Approval date: Not approved yet. Procedure number: EMEA/H/C/006101	"Non-melanoma skin cancer" has been replaced with "skin cancer" in Module SVII.3.1. "Presentation of Important Identified Risks and Important Potential Risks". "Non-melanoma skin cancer" has been replaced with "skin cancer" in Part V.1. "Routine Risk Minimization Measures" and in Part V.3 "Summary of risk minimisation measures". The Part VI "Summary of activities in the risk management plan by medicinal product" has been updated in line with the issues raised in other parts of the RMP.