Summary of the Risk Management Plan (RMP) for STELARA® (ustekinumab)

Marketing Authorisation Holder (MAH): Janssen-Cilag AG

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of STELARA® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of STELARA® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Janssen-Cilag AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of STELARA®.

Summary of Risk Management Plan for STELARA (ustekinumab)

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

STELARA's Summary of Product Characteristics (SmPC) and Package Leaflet (PL) give essential information to healthcare professionals and patients on how STELARA should be used.

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

I. The Medicine and What it is Used For

STELARA is authorized for plaque psoriasis, psoriatic arthritis (PsA), pediatric plaque psoriasis, Crohn's disease (CD), and ulcerative colitis (UC) (see SmPC for the full indications). It contains ustekinumab as the active substance, and it is given by the intravenous (IV) or subcutaneous (SC) route of administration.

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

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

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of STELARA, together with measures to minimize such risks and the proposed studies for learning more about STELARA'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 PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized 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 (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report 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 STELARA is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of STELARA 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 STELARA. 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 (eg, on the long-term use of the medicine).

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

II.B. Summary of Important Risks

Important Potential Risk: Serious infections (including mycobacterial and salmonella infections)	
Evidence for linking the risk to the medicine	Published nonclinical and medical literature suggest that inhibition of interleukin (IL)-12/23 may predispose patients to serious infections. 'Serious infections (including mycobacterial and salmonella infections)' is considered an important potential risk with STELARA based upon the theoretical risk identified from nonclinical data and in humans who are genetically deficient for the cytokines that are inhibited by STELARA (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 STELARA is currently unknown. Across clinical trials in all indications for which STELARA 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 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-tumor necrosis factor (TNF)s, other immunosuppressants, or other biologics. *Tuberculosis (TB)* The most common risk factors for the development of TB include conditions impairing the development of effective cell-mediated immunity to the infection (ie, 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 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 (ie, 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 intracellulare* complex (MAC) disease included male sex (odds ratios [OR]=2.1; 95% confidence interval [CI] 1.0 to 4.5) and age >50 years (OR=26.5; 95% CI 10.9 to 67.3). Similarly, in a United

Important Potential Risk: Serious infections (including mycobacterial and salmonella infections)	
	States (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 disease [IBD]; or impaired immunity from acquired immune deficiency syndrome, sickle cell disease, malaria, anti-rejection drugs taken after organ transplants, and corticosteroids).
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.3 (Contraindications), 4.4 (Special Warnings and Precautions for Use), 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction), 4.6 (Fertility, Pregnancy and Lactation), and 4.8 (Undesirable Effects) PL sections 2 and 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: STELARA UC/CD postauthorization safety study (PASS) using Swedish Registers STELARA UC PASS using the French Nationwide Claims Database (SNDS) See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Malignancy	
Evidence for linking the risk to the medicine	There is a theoretical risk of malignancy associated with administration of STELARA 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. Because 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 STELARA therapy, the risk of malignancies other than NMSC was not increased compared with the general US population. There was no evidence of an increased risk of malignancy through approximately 5 years of follow-up in CD patients and approximately 4 years of follow-up in UC patients treated with STELARA. Long-term effects of STELARA 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 is 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 psoralen and ultraviolet A and immunosuppressants, including cyclosporin and possibly methotrexate (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 IBD patients include but are not limited to smoking, ongoing inflammation, and carcinogenic effects of immunosuppressive drugs.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 (Special Warnings and Precautions for Use) and 4.8 (Undesirable Effects) PL section 2 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: STELARA UC/CD PASS using Swedish Registers STELARA UC PASS using SNDS See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Cardiovascular events	
Evidence for linking the risk to the medicine	The risk of developing cardiovascular (CV) events in subjects on anti-IL-12/23p40 therapy such as STELARA is currently unknown. A numeric imbalance in rates of investigator-reported major adverse cardiovascular events (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 Marketing Authorization Holder show that the overall rates of myocardial infarction and stroke with up to 5 years of treatment with STELARA 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. Through approximately 5 years of follow-up in CD clinical trials and approximately 4 years of follow-up in UC clinical trials, the incidence of serious MACE was low in ustekinumab-treated subjects and placebo-treated subjects, with no consistent evidence that ustekinumab increases cardiovascular risk. 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	Risk factors for the development of CV disease are well known and include hypertension, hypercholesterolemia, diabetes, smoking, age, male sex, obesity, and family history. The PsA, psoriasis, and CD populations share certain risk factors, such as increased CV risk, increased body weight, and increased body mass index.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: STELARA UC/CD PASS using Swedish Registers (MACE only) STELARA UC PASS using SNDS (MACE only) See section II.C of this summary for an overview of the postauthorization development plan.

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. Depression has been identified as an ADR for STELARA (SmPC section 4.8 [Undesirable Effects] and PL section 4) based on a safety signal identified in the placebo-controlled period from the Phase 2 and Phase 3 psoriasis clinical trials. The incidence of serious depression including suicidality across indications remains low. The available safety data from clinical studies and postmarketing experience 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 STELARA.
Risk factors and risk groups	Risk factors for depression include older age and associated neurological conditions; uncontrolled, poorly treated psoriasis; recent childbirth; stressful life events; a personal or family history of depression; and selected medical comorbid conditions including psoriatic conditions and IBD. Suicide rates are twice as high in families of suicide victims.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.8 (Undesirable Effects) PL section 4 Additional risk minimization measures: None

Important Potential Risk: Venous thromboembolism	
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 immobilization, hospitalization, surgical interventions, oral contraceptive use, etc). Venous thromboembolism (VTE) was originally identified as an important potential risk based on data collected through 44 weeks of treatment in the ustekinumab CD clinical trials. Through approximately 5 years of follow-up in CD clinical trials and approximately 4 years of follow-up in UC clinical trials, while there is a slight imbalance across treatment groups in the reporting of all vascular thrombotic events, the overall incidences per 100 subject-years (~0.1 [~1%]) observed among STELARA-treated subjects in both the CD and UC populations are within the range reported in the IBD literature. Overall, safety results from the CD clinical trials through Week 272, UC clinical trials through Week 220, and clinical trials conducted for other indications, as well as cumulative postmarketing data, do not indicate an increased rate with ustekinumab treatment.
Risk factors and risk groups	Patients suffering from IBD, namely CD and UC, are more prone to thromboembolic complications compared with the general population. A study of IBD patients conducted in the United Kingdom reported that there was increased risk of VTE during disease flares and chronic activity. In a Danish population study that included children and adults, the highest risk of VTE was in the 0 to 20 years age group with a hazard ratio 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. The risk has also been reported to be greater for males (incidence rate of 1.34/1000 person-years [PY]) than for females (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 to 10.5) and 2.97 (95% CI 0.99 to 8.92), respectively.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: RRA-20745 STELARA UC/CD PASS using Swedish Registers STELARA UC PASS using SNDS See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Exposure during pregnancy	
Evidence for linking the risk to the medicine	The effects of ustekinumab during pregnancy are not known. Toxicokinetic analyses have confirmed that ustekinumab can cross the placenta; however, nonclinical studies have shown no effect. Cumulative safety data do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition, or postnatal development (SmPC section 4.6 [Fertility, Pregnancy and Lactation]), but cases of exposure during pregnancy are limited. 'Exposure during pregnancy' is considered an important potential risk because of the limitations of nonclinical investigations on this topic and the limited data in humans related to exposure during pregnancy.
Risk factors and risk groups	Patients who do not follow guidance on use of contraception or use contraception incorrectly are at risk for pregnancy. Most of the systemic antipsoriatic therapies are associated with significant toxic effects to the fetus and are recommended to be avoided during pregnancy. A recent update on the safety of IBD medications in pregnancy summarized that the available data provide reassuring information for providers caring for women with IBD and of childbearing age, although long-term effects of IBD medications on offspring need to be examined.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.6 (Fertility, Pregnancy and Lactation) Package Leaflet section 2 Additional risk minimization measures: None

Missing Information: Long-term safety in pediatric psoriasis patients 6 years and older	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CNTO1275PSO4056 (Pediatric Psoriasis Registry) See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CNTO1275PSO4056 (Pediatric Psoriasis Registry) See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Long-term safety in adult patients with moderately to severely active Crohn's disease	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: RRA-20745 STELARA UC/CD PASS using Swedish Registers See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Long-term safety in adult patients with moderately to severely active ulcerative colitis	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: STELARA UC/CD PASS using Swedish Registers STELARA UC PASS using SNDS See section II.C of this summary for an overview of the post-authorization development plan.

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies that are conditions of the marketing authorization or specific obligations of STELARA.

II.C.2. Other Studies in Postauthorization Development Plan

Study	Purpose of Study
CNTO1275PSO4056 (Pediatric Psoriasis Registry)	Objective: to confirm the long-term safety profile of STELARA use in pediatric patients 6 years and older and to explore any potential effect on growth and development in pediatric patients 6 years and older in-line with the consideration in the STELARA PIP. To address the safety concerns of: • Long-term safety in pediatric psoriasis patients 6 years and older • Long-term impact on growth and development in pediatric psoriasis patients 6 years and older.
RRA-20745	Objective: to monitor the long-term safety profile of STELARA use in adult patients with moderately to severely active CD To address the safety concerns of: • Long-term safety in adult patients with moderately to severely active Crohn's disease • Venous thromboembolism.
PCSIMM002807 (STELARA UC/CD PASS using Swedish Registers)	Objective: to evaluate the long-term safety of STELARA in adult patients with moderately to severely active UC or CD. To address the safety concerns of: • Venous thromboembolism • Malignancy • Cardiovascular events (MACE only) • Serious infections (including mycobacterial and salmonella infections) • Long-term safety in adult patients with moderately to severely active ulcerative colitis • Long-term safety in adult patients with moderately to severely active Crohn's disease
PCSIMM002659 (STELARA UC PASS using SNDS)	Objective: to evaluate the long-term safety of STELARA in adult patients with moderately to severely active UC. To address the safety concerns of: • Venous thromboembolism • Malignancy • Cardiovascular events (MACE only) • Serious infections (including mycobacterial and salmonella infections) • Long-term safety in adult patients with moderately to severely active ulcerative colitis