Risk Management Plan Summary

TREMFYA® (guselkumab)

100 mg/ml
pre-filled syringe and pre-filled pen

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Based on EU RMP version 9.1 and Swiss addendum version 5.0

Marketing authorization holder: Janssen-Cilag AG, Gubelstr. 34, 6300 Zug

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 minimize them.

The RMP summary of TREMFYA® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the product information «Arzneimittelinformation / Information sur le medicament» 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 TREMFYA® in Switzerland is the «Arzneimittelinformation / Information sur le medicament» (see www.swissmedicinfo.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 TREMFYA®.

Summary of Risk Management Plan for TREMFYA® (guselkumab)

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

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

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

I. The Medicine and What it is Used For

TREMFYA is authorized for use in adults for the treatment of moderate to severe plaque psoriasis and active psoriatic arthritis (PsA) (see SmPC for the full indication). It contains guselkumab as the active substance and it is given by subcutaneous injection.

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

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

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

Important risks of TREMFYA, together with measures to minimize such risks and the proposed clinical trials for learning more about TREMFYA'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 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 (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization 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 TREMFYA is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of TREMFYA 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 TREMFYA. 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 infection Malignancy Serum sickness Major adverse cardiovascular events (MACE) Suicidal ideation and behavior
Missing information	Exposure during pregnancy Use in patients ≥65 years of age Long-term safety of guselkumab

II.B. Summary of Important Risks

Important potential risk: Serious infection	
Evidence for linking the risk to the medicine	Nonclinical data in mice suggest that blockade of interleukin (IL)-23 may predispose patients to infection. Although serious infections were reported in patients treated with guselkumab in clinical trials and in the postmarketing setting, available cumulative information does not suggest an increased risk of serious infection in patients treated with guselkumab.

Important potential risk: Serious infection	
Risk factors and risk groups	Risk factors for the development of serious infection include clinically significant metabolic and endocrine disorders such as diabetes, obesity, thyroid disorders, cardiovascular (CV) disorders, and renal and hepatic disorders; advanced age; and the concomitant use of corticosteroids, other biologics (including tumor necrosis factor [TNF]α inhibitors), and other immunosuppressants. *TB* The most common risk factors for the development of tuberculosis (TB) include conditions that weaken the immune system (ie, advanced age, human immunodeficiency virus [HIV] infection), alcohol abuse, malignancy, corticosteroids or other immunosuppressive drugs such as methotrexate (MTX), connective tissue disease, renal failure, diabetes, and pregnancy. Exposure to TB is also a risk factor for the development of 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 who 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 who had close contact with a person with active TB. In patients who are severely ill or immunocompromised, tuberculin tests may yield false negative results.
Risk minimization measures	Routine risk minimization measures: • *SmPC Section 4.3 (Contraindications)* • *SmPC Section 4.4 (Special Warnings and Precautions for Use) and Package Leaflet Section 2* Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *C0168Z03 (PSOLAR)* • *CNTO1959PSO4001 (PsoBest)* 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	No increased risk for malignancy was observed following the conduct of a 5-week intravenous (subchronic) and a 24-week SC (chronic) study with a 3-month recovery of guselkumab in cynomolgus monkeys conducted by the Marketing Authorization Holder (MAH). Although there are no validated models for carcinogenicity evaluations in cynomolgus monkeys, neoplasia has been observed in this species following repeated administration of other immunosuppressive drugs indicated in the treatment of psoriasis. Most data in the published literature pertaining to models of IL-23 ablation suggest that blockade of IL-23 may actually reduce the risk of carcinogenesis. A limited number of studies in the literature present conflicting data supporting an increased risk of malignancy in mice deficient for IL-23 and p19 exposed to ultraviolet-B (UVB) radiation. Although malignancies have been reported in patients treated with guselkumab in clinical trials and in the postmarketing setting, available cumulative information does not suggest an increased risk of malignancy in patients treated with guselkumab.
Risk factors and risk groups	Among psoriasis patients, an increased risk of solid cancers appears to be related to alcohol use and cigarette smoking. In addition, exposure to psoralen + ultraviolet-A (PUVA) radiation 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 alcohol and tobacco use and obesity), family history of cancer, and certain environmental exposures.
Risk minimization measures	Routine risk minimization measures: None. Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *C0168Z03 (PSOLAR)* • *CNTO1959PSO4001 (PsoBest)* See Section II.C of this summary for an overview of the postauthorization development plan.

Important potential risk: Serum sickness	
Evidence for linking the risk to the medicine	Although an infrequent occurrence, serum sickness has been reported in the published literature in association with the use of other monoclonal antibody (mAb) therapies.
Risk factors and risk groups	Not known.
Risk minimization measures	Routine risk minimization measures: • *SmPC Section 4.3 (Contraindications)* • *SmPC Section 4.4 (Special Warnings and Precautions for Use) and PL Section 2* Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *C0168Z03 (PSOLAR)* • *CNTO1959PSO4001 (PsoBest)* See Section II.C of this summary for an overview of the postauthorization development plan.

Important potential risk: Major adverse cardiovascular events (MACE)	
Evidence for linking the risk to the medicine	Evidence for an increased background risk of CV disease (ie, heart attack, stroke, and death related to heart attack and stroke) in patients with psoriasis (including PsA) is cited in the published literature. Although MACE were reported in patients treated with guselkumab in clinical trials and in the postmarketing setting, available cumulative information does not suggest an increased risk of MACE in patients treated with guselkumab.

Risk factors and risk groups	The risk factors for the development of CV disease are well known and include hypertension, hypercholesterolemia, diabetes, smoking, advanced age, male sex, obesity, and family history. Patients with psoriasis have been shown to be at increased risk for CV events (ie, MACE, defined as CV death, nonfatal MI, or nonfatal stroke) compared with the general population. Literature suggests psoriasis may be an independent risk factor due to the high inflammatory burden of psoriatic disease. Additionally, at least some CV risk factors occur more frequently in the psoriasis population compared with the general population. Specifically, these CV risk factors include pre-existing MACE conditions; uncontrolled or poorly controlled concomitant diseases such as diabetes, hypertension, hyperlipidemia, and obesity; and patient characteristics such as smoking. Of these, the association between psoriasis and dyslipidemia is less clear, with some studies showing that patients with psoriasis have significant dyslipidemia while others do not show a correlation. Notably, patients with severe psoriasis are more likely to demonstrate CV risk factors such as obesity, diabetes, and hypertension compared with those with no or mild psoriasis.
Risk minimization measures	Routine risk minimization measures: None. Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *C0168Z03 (PSOLAR)* • *CNTO1959PSO4001 (PsoBest)* See Section II.C of this summary for an overview of the postauthorization development plan.

Important potential risk: Suicidal ideation and behavior	
Evidence for linking the risk to the medicine	The available literature evidence suggests a higher incidence and prevalence of psychiatric disorders, including depression, among patients with psoriasis compared to those without psoriasis. Clinical trial and postmarketing data available with guselkumab do not suggest an increased risk of suicidal ideation and behavior events with guselkumab treatment beyond what is already expected in psoriasis patients.

Risk factors and risk groups	Psoriasis is a multisystem disease and is associated with clinically significant emotional distress, changes in body image, difficulties in close relationships, and impaired daily activities (Picardi et al, 2013). Subsequently, patients with uncontrolled moderate to severe psoriasis are at increased risk of depression and suicidal ideation and behavior. Other risk factors for suicidal ideation and behavior include a family history of suicide (Fancher, 2007), previous suicide attempts, history of mental disorders, history of alcohol and substance abuse (Cohen et al, 2016), older age and its associated neurological conditions, recent childbirth, stressful life events, a personal or family history of depression, and selected medical comorbid conditions.
Risk minimization measures	Routine risk minimization measures: None. Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.

Missing information: Exposure during pregnancy	
Risk minimization measures	Routine risk minimization measures: • *SmPC Section 4.6 (Fertility, Pregnancy, and Lactation) and Package Leaflet Section 2* Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *C0168Z03 (PSOLAR)* • *CNTO1959PSO4001 (PsoBest)* • *PCSIMM001324 (TREMFYA [guselkumab] pregnancy healthcare database study)* See Section II.C of this summary for an overview of the postauthorization development plan.

Missing information: Use in patients ≥65 years of age	
Risk minimization measures	Routine risk minimization measures: • *SmPC Section 4.2 (Posology and Method of Administration).* Additional risk minimization measures: None.

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *C0168Z03 (PSOLAR)* • *CNTO1959PSO4001 (PsoBest)* See Section II.C of this summary for an overview of the postauthorization development plan.

Missing information: Long-term safety of guselkumab	
Risk minimization measures	Routine risk minimization measures: None. Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *C0168Z03 (PSOLAR)* • *CNTO1959PSO4001 (PsoBest)* See Section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization Development Plan

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

There are no clinical trials that are conditions of the marketing authorization or specific obligation of TREMFYA.

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

Trial	Purpose of the Trial
C0168Z03 (PSOLAR)	To study the long-term safety of guselkumab To address the safety concerns of: • Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Exposure during pregnancy • Use in patients ≥65 years of age • Long-term safety of guselkumab
CNTO1959PSO4001 (PsoBest)	To study the long-term safety of guselkumab To address the safety concerns of: • Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Exposure during pregnancy • Use in patients ≥65 years of age • Long-term safety of guselkumab
PCSIMM001324 (TREMFYA [guselkumab] pregnancy healthcare database study)	To monitor pregnancy outcomes in women exposed to guselkumab during pregnancy and linked infant outcomes up to 1 year of age. To address the safety concerns of: Exposure during pregnancy