Enspryng® (Satralizumab)
Injektionslösung zur subkutanen Anwendung, 120 mg/1 ml
Zul.-Nr. 67617

Public Risk Management Plan (RMP) Summary

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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 "Enspryng" 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 "Enspryng" in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. "Roche Pharma (Schweiz) AG" is fully responsible for the accuracy and correctness of the content of the published summary RMP of Enspryng.

PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR ENSPRYNG® (SATRALIZUMAB*)*

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

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

This summary of the RMP for *Enspryng* 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 *Enspryng's* RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Enspryng is authorized as monotherapy or in combination with immunosuppressive therapy for the treatment of neuromyelitis optica spectrum disorders (also known as Devic's disease) in adult and adolescent patients from 12 years of age who have antibodies to the aquaporin-4 (AQP4) receptor in their blood (see SmPC for the full indication). It contains satralizumab as the active substance, and it is given subcutaneously.

Further information about the evaluation of *Enspryng's* benefits can be found in *Enspryng's* EPAR, including in its plain-language summary, available on the EMA Web site, under the medicine's Web page:

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

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of *Enspryng*, together with measures to minimize such risks and the proposed studies for learning more about *Enspryng'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 as to ensure that the medicine is used correctly.

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- 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.

In the case of Enspryng, these measures are supplemented with *additional risk-minimization* measures mentioned under relevant risks below.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, 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 Enspryng is not yet available, it is listed under "missing information" below.

II.A List of Important Risks and Missing Information

Important risks of *Enspryng* 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 *Enspryng*. 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 about 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	• Serious infections
Important potential risks	• Serious hypersensitivity • Hepatotoxicity • Major cardiovascular events • Gastrointestinal perforations • Malignancy
Missing information	• Use in pregnant and breastfeeding women

II.B Summary of Important Risks

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Important identified risk: Serious infections	
Evidence for linking the risk to the medicine	Serious infections is a class effect of IL-6 inhibitors. Although the overall rate of serious infections was comparable across treatment groups in both Phase III studies (BN40898 and BN40900), considering the small clinical database resulting from the rarity of the disease, serious infection is considered an important identified risk for satralizumab.
Risk factors and risk groups	Generally, immunocompromised patients or patients using satralizumab in combination withimmunosuppressive therapy may be at higher risk of serious infections. However, no increased risk of serious infections or opportunistic infections was observed in the satralizumab group compared with the placebo group in Study BN40898 with satralizumab in combination with immunosuppressive therapy. In addition, neutropenia may potentially increase the risk of serious infection, although no association between Grade 3 and Grade 4 neutropenia and serious infection were observed in the satralizumab studies.
Important identified risk: Serious infections	

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Risk-minimization measures	**Routine risk-minimization measures:** **Routine risk communication:** SmPC Section 4.2 – Posology and method of administration, dose modification advice for neutropenia SmPC Section 4.4 - Special warnings and precautions for use: Infections, neutrophil count PL Section 2 – What you need to know before you use Enspryng: warnings and precautions - infections **Routine risk-minimization activities recommending specific clinical measures to address the risk:** · SmPC Sections 4.2 and 4.4 provide monitoring and dose modification/treatment management recommendations for neutropenia PL Section 2 provides Instructions on recognition of signs and symptoms of infections, laboratory tests and treatment interruption/delay **Other risk minimization measures beyond the Product Information:** · Medicine's legal status: The medicinal product is subject to restricted medical prescription **Additional risk-minimization measures:** · Patient alert card
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** · Study WN42349 See Section II.C of this summary for an overview of the post-authorization development plan.

IL-6=interleukin-6; PL=package leaflet; SmPC=summary of product characteristics

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Important potential risk: Serious hypersensitivity	
Evidence for linking the risk to the medicine	No anaphylaxis or serious hypersensitivity reactions have been observed in the clinical development program with satralizumab, however, as therapeutic protein products may lead to hypersensitivity and anaphylaxis, serious hypersensitivity is considered an important potential risk for satralizumab.
Risk factors and risk groups	Patients with known hypersensitivity to satralizumab's active substance or to any of its excipients.
Risk-minimization measures	**Routine risk-minimization measures:** **Routine risk communication:** SmPC Section 4.2 - Posology and method of administration, administration by the patient and/or caregiver SmPC Section 4.3 – Contraindications PL Section 2 - What you need to know before you use Enspryng: Do not use Enspryng, warnings and precautions PL Section 4 – Possible side effects **Routine risk-minimization activities recommending specific clinical measures to address the risk:** · SmPC Section 4.2 provide management guidelines (initial administration of satralizumab under HCP's supervision and instructions in case of symptoms of serious allergic reactions) · SmPC Section 4.3 includes a contraindication to satralizumab for hypersensitivity to the active substance or any of the excipients · PL Section 4 provides instructions on recognition of signs and symptoms of hypersensitivity reactions and on the need to access emergency care in case of such reactions, as well as treatment interruption/discontinuation
Important potential risk: Serious hypersensitivity	

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	Other risk minimization measures beyond the Product Information: • Medicine's legal status: The medicinal product is subject to restricted medical prescription. **Additional risk-minimization measures:** None

PL=package leaflet; SmPC=summary of product characteristics

Important potential risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Hepatotoxicity is an important potential or identified risk of other anti-IL-6R antibodies. Liver enzyme elevations were observed in satralizumab-treated patients in both Phase III studies with satralizumab. However, there is no evidence showing an increased risk of hepatotoxicity in patients treated with satralizumab compared with patients on placebo in the clinical development program with satralizumab.
Risk factors and risk groups	In general, known risk factors for hepatotoxicity include age, gender, drug-interactions, high alcohol intake, malnutrition, HCV, HBV, HIV infections, and genetic predisposition. Patients with hepatic steatosis, alcohol liver disease, and other acquired or inherited liver diseases may be at a higher risk for developing hepatotoxicity. Patients pre- or concomitantly treated with other medications associated with hepatotoxicity may be at higher risk for hepatotoxicity.

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Important potential risk: Hepatotoxicity	
Risk-minimization measures	**Routine risk-minimization measures:** **Routine risk communication:** SmPC Section 4.2 - Posology and method of administration, dose modification advice for liver enzyme abnormalities, special populations: hepatic impairment · SmPC Section 4.4 - Special warnings and precautions for use: Liver enzymes · SmPC Section 4.8 – Undesirable effects PL Section 2 - What you need to know before you use Enspryng: Do not use Enspryng, warnings and precautions – liver enzymes
	· PL Section 4 – Possible side effects **Routine risk-minimization activities recommending specific clinical measures to address the risk:** SmPC Sections 4.2 and 4.4 provide monitoring and dose modification/treatment management recommendations for liver enzyme abnormalities PL Section 2 provides Instructions on recognition of relevant signs and symptoms and laboratory tests, on the need to seek immediate medical attention **Other risk minimization measures beyond the Product Information:** Medicine's legal status: The medicinal product is subject to restricted medical prescription **Additional risk-minimization measures:** · None

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Important potential risk: Hepatotoxicity	
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** · Study WN42349 See Section II.C of this summary for an overview of the post-authorization development plan.

HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency; IL-6R=interleukin-6 receptor; PL=package leaflet; SmPC=summary of product characteristics

Important potential risk: Major cardiovascular events	
Evidence for linking the risk to the medicine	A greater proportion of patients experienced elevations in total cholesterol or triglycerides in the satralizumab group compared with the placebo group in both Phase III studies BN40898 and BN40900. Although no increased risk of cardiovascular events was observed with satralizumab treatment, considering the limited exposure to satralizumab during the clinical studies and the exclusion of patients with serious uncontrolled cardiovascular disease in the Phase III studies, major cardiovascular event is considered a potential risk for satralizumab in susceptible patient population.
Risk factors and risk groups	Known risk factors accounting for more than 90% of major cardiovascular events are previous myocardial infarction, smoking, history of hypertension, diabetes, sedentary life style, abdominal obesity, psychosocial factors, alcohol consumption, and lack of daily consumption of fruits and vegetables. In addition, prior or concomitant treatments, including treatment for NMOSD (e.g., corticosteroids or mycophenolate), may be associated with hypertension, a risk factor for major cardiovascular events. Patients with evidence of serious uncontrolled cardiovascular disease were excluded from participation in the Phase III studies BN40898 and BN40900.

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Important potential risk: Major cardiovascular events	
Risk-minimization measures	**Routine risk-minimization measures:** **Routine risk communication:** · SmPC Section 4.8 - Undesirable effects · PL Section 4 – Possible side effects **Routine risk-minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Medicine's legal status: The medicinal product is subject to restricted medical prescription **Additional risk-minimization measures:** · None

NMOSD=neuromyelitis optica spectrum disorder; SmPC=summary of product characteristics

Important potential risk: gastrointestinal perforations	
Evidence for linking the risk to the medicine	There were no cases of GI perforation in patients treated with satralizumab in the completed Phase I study in the RA population and the Phase III studies BN40898 and BN40900 (CCOD: 07 June 2019)
Risk factors and risk groups	GI perforations have been reported in patients with rheumatoid arthritis rarely, either in association with the disease itself or in association with the use of non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, or other RA therapies including IL-6 inhibitors, as well as a consequence of advanced age or a history of diverticulitis (Jagpal and Curtis 2018)
Risk minimization measures	**Routine risk communication:**

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Important potential risk: gastrointestinal perforations	
	Section Warning & Precautions in the Swiss Summary of Product Characteristics *Diverticular/intestinal perforation* During treatment with IL-6 receptor inhibitors in rheumatoid arthritis (RA) patients, the occurrence of diverticular and intestinal perforation has been observed. In the pivotal studies with Enspryng, patients with a history of known diverticulitis were excluded. An increased risk of diverticular/intestinal perforation, as occurs with other inhibitors of the IL-6 receptor, cannot be ruled out under treatment with Enspryng. Enspryng should be used with caution in patients with a history of intestinal ulceration or diverticulitis. If acute abdominal pain occurs, patients should be examined immediately so that a gastrointestinal perforation can be detected early on. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Enspryng should be used with caution in patients with a history of intestinal ulceration or diverticulitis. • If acute abdominal pain occurs, patients should be examined immediately so that a gastrointestinal perforation can be detected early on. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Satralizumab is a prescription-only medicine **Additional risk minimization measures:** • Patient Alert Card
Additional pharmacovigilance activities	The risk will be monitored via routine pharmacovigilance activities.The Open label extension period of the pivotal studies BN40898 and BN40900 are ongoing, and safety data (including gastrointestinal perforations) will be continuously collected in the OLE period

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Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	In the double-blind period of both Phase III studies, malignancies were reported by 2 (2.7%) patients in the placebo group (breast cancer and hepatic cancer) and 1 (1.0%) patient in the satralizumab group (squamous cell carcinoma, location: cheek). In the open label extension by June 2019 (CCOD of Safety Update), 1 additional patient reported a malignancy (basal cell carcinoma) No carcinogenicity studies have been performed to establish the carcinogenic potential of satralizumab. In a 6-month chronic toxicity study in cynomolgus monkeys, no proliferate lesions have been observed.

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Important potential risk: Malignancy	
Risk factors and risk groups	IL-6 is a pleiotropic cytokine with immunomodulatory properties involved in both pro- and anti-inflammatory processes through: • The classical anti-inflammatory pathway in leukocytes and liver cells via the membrane-associated IL-6 receptor, promoting regeneration of tissue • The pro-inflammatory trans-pathway via the soluble form of IL-6 receptor, involved in a range of diseases, including cancer. Both classical-and trans-signalling pathways activate JAK tyrokinases followed by phosphorylation of STAT3, which is involved in various physiological processes, including immune function, cell growth, differentiation, haematopoiesis and inflammation (Niwa et al. 2005; Kampan et al. 2018). IL-6 is produced and secreted by various types of cells, including tumour cells, and is involved in the proliferation and differentiation of malignant cells. Increased levels of IL-6 in serum and tumour tissue have been measured in numerous cancers, including colorectal (Waldner 2012), breast (Dethlefson et al. 2013), cervical (Wei et al. 2003), lung (Chang et al. 2013), prostate (Culig et al. 2012), ovarian (Maccio and Madeddu. 2013), renal cell (Alundtag et al. 2005), and pancreatic cancers (Miura et al. 2015), as well as multiple myeloma (Singh et al. 2015) and melanoma. IL-6 is one of the important growth factors in melanoma genesis and development and has been shown to increase melanoma cell migration and invasion (Hoejberg et al. 2012, Linnskog et al. 2014, Mohapatra et al. 2019).

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Important potential risk: Malignancy	
	High levels of circulating IL-6 and the consequent hyperactivation of JAK/STAT3 signalling present in a large number of patients with hematopoietic malignancies and solid tumours have been associated with poor prognosis and shorter survival (Kumari et al. 2016, Johnson et al. 2018, Verhoeven et al. 2019). Blocking IL-6 signalling or decreasing IL-6 levels has shown to be effective in the treatment of inflammatory conditions and is being investigated as a potential therapeutic strategy for cancers characterized by IL-6 overexpression, including breast, ovarian, and pancreatic cancer, as well as B cell chronic lymphocytic leukaemia (Kumari et al. 2016, Johnson et al. 2018). Further supporting the therapeutic properties of IL-6 inhibition in malignancies is the use of an anti-IL-6 antibody (siltuximab) for the treatment of Castleman's disease, a lymphoproliferative disorder.
Risk minimization measures	**Routine risk communication:** *Section Warning & Precautions in the Swiss Summary of Product Characteristics* *Malignancies* Immunomodulating drugs can increase the risk of malignancies. The impact of treatment with Enspryng on the development of malignancies is not known. **Routine risk minimization activities recommending specific clinical measures to address the risk:** none **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Satralizumab is a prescription-only medicine **Additional risk minimization measures:** none

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Important potential risk: Malignancy	
Additional pharmacovigilance activities	The risk will be monitored via routine pharmacovigilance activities. The Open label extension period of the pivotal studies BN40898 and BN40900 are ongoing, and safety data (including malignancy adverse events) will be continuously collected in the OLE period.

Missing information: Use in pregnant and breastfeeding women	
Risk-minimization measures	**Routine risk-minimization measures:** **Routine risk communication:** SmPC Section 4.6 Fertility, pregnancy and lactation: Pregnancy, breastfeeding SmPC Section 5.3 Preclinical safety data: Reproductive toxicity PL Section 2 - What you need to know before you use Enspryng: pregnancy and breastfeeding
Missing information: Use in pregnant and breastfeeding women	

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	Routine risk-minimization activities recommending specific clinical measures to address the risk: None **Other risk minimization measures beyond the Product Information:** Medicine's legal status: The medicinal product is subject to restricted medical prescription **Additional risk-minimization measures:** · None
Additional pharmacovigilance activities	Study WN42856

PL=package leaflet; SmPC=summary of product characteristics

II.C Post-Authorization Development Plan

II.C.1 Studies That Are Conditions of the Marketing Authorization

Not applicable

II.C.2 Other Studies in Post-Authorization Development Plan

Study short name: A multicentre, single arm, open-label study to evaluate the long-term safety and efficacy of satralizumab in patients with neuromyelitis optica spectrum disorder.

Purpose of the study: To provide patients from the ongoing satralizumab studies in NMOSD, Study BN40898 and Study BN40900, with long-term satralizumab treatment. The study aims to collect longitudinal safety and efficacy data and to further evaluate the risks of serious infections and hepatotoxicity in NMOSD patients treated with satralizumab.

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