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Swiss Summary of the Risk Management Plan (RMP) for Nplate® (Romiplostim)

RMP Summary: Version 1, February 2023
EU RMP: Version 21.1, 9 August 2022

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 Nplate® 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" 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 Nplate® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

AMGEN Switzerland AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Nplate®.

Overview of disease epidemiology

Nplate® is used to treat adult patients with primary immune thrombocytopenia (ITP) and children aged 1 year and over with chronic ITP who may or may not have had their spleen removed and who have previously been treated with corticosteroids or immunoglobulins, where these treatments don't work (see SmPC for the full indication).

It contains romiplostim as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Nplate®'s benefits can be found in Nplate®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage. Link to product's EPAR summary landing page on the EMA webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/Nplate

Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Nplate®, together with measures to minimize such risks and the proposed studies for learning more about Nplate®'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 public (eg. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.
In the case of Nplate®, these measures are supplemented with additional risk minimization measures mentioned under relevant important 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 Nplate® is not yet available, it is listed under "missing information" below.

List of Important Risks and Missing Information

Important risks of Nplate® 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 Nplate®.
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	Romiplostim medication errors (dosing/administration)
Important potential risks	Neutralizing antibodies that cross-react with eTPO
Missing information	None

eTPO endogenous thrombopoietin

Summary of Important Risks

Important identified risk: Medication errors	
Evidence for linking the risk to the medicine	Although a low number of reports of medication error were received from clinical studies, postmarketing data has provided real-world examples of the kinds of medication error that are possible.
Risk factors and risk groups	Subjects with ITP receiving (and/or self-administering [adult subjects]) treatment with romiplostim.
Risk minimization measures	Routine risk minimization measures • To be found in relevant sections of the product information • Pack size: None • Legal status: Restricted medical prescription Additional risk minimization measures: • Dosing calculator • Home administration training pack (not in Switzerland)

Important identified risk: Immune response (antibodies that cross-react with the protein that controls how many platelets are made) (neutralizing antibodies that cross-react with endogenous thrombopoietin [eTPO])	
Evidence for linking the risk to the medicine	There is limited evidence for this risk, with a report from a pediatric ITP clinical study where a weak positive neutralizing antibody to TPO developed, in the absence of an antibody response to romiplostim. This suggested a pre-existing endogenous antibody response to TPO.
Risk factors and risk groups	Not available
Risk minimization measures	Routine risk minimization measures • To be found in relevant sections of product information • Pack size: None • Legal status: Restricted medical prescription Additional risk minimization measures: • None
Additional pharmacovigilance activities	Antibody testing at the request of treating physician

Postauthorization Development Plan

Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Nplate®.

Other Studies in Postauthorization Development Plan

There are no studies required for Nplate®.

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Version	Approval Date Procedure	Change
5.0	At time of authorization 14 November 2008 No associated procedure number as this was submitted during the review of the marketing authorization application (MAA)	Safety Concerns: Important Identified Risks • Reoccurrence of thrombocytopenia after cessation of romiplostim • Increased bone marrow reticulin • Thrombocytosis • Important Potential Risks • Thrombotic/thromboembolic complications • Neutralizing antibodies that cross-react with eTPO • Progression of existing hematological malignancies or MDS • Bone marrow fibrosis • Potential consequences of off-label use in indications where risk-benefit ratio has not been adequately studied • Romiplostim medication errors (dosing/administration) • Leukocytosis and anemia in the preclinical setting Important missing Information • Pregnant women • Lactating women • Pediatric patients • Patients of different racial and/or ethnic origins • Patients with renal, hepatic, cardiac, and pulmonary impairment • Patients with bone marrow stem cell disorder and/or any active malignancy • Patients concurrently receiving rituximab or alkylating agents
6.0	13 February 2009 EMN829429/2009	The following new important potential risks were added: • Renal impairment • Bleeding in patients with variable platelet count • Bleeding in patients who do not respond to treatment with romiplostim
7.0	10 March 2010 EMA/488402/2010	No major changes
7.1	27 September 2010 EMEA/H/C/942/II/010/G	No major changes
8.0	28 September 2010 EMA/73535/2011	The following risks were recategorized from important potential risks to important identified risks and the description of each was modified: • Risk of bleeding during the period of low platelet counts in patients with variable platelet counts (previously read: bleeding in patients with variable platelet count) • Risk of bleeding in ITP patients who have consistently low platelet counts (previously read: bleeding in patients who do not respond to treatment with romiplostim)
9.0	24 March 2011 Not available	No major changes

Version	Approval Date Procedure	Change
10.0	05 May 2011 Not available	The following risk was recategorized from an important potential risk to an important identified risk and the description was modified: • Progression of existing MDS in patients with refractory anemia with excess blasts – 1 (RAEB-1) (previously read: progression of existing hematological malignancies or MDS)
10.1	20 June 2011 Not available	The following description was modified: • Progression of existing MDS (previously read: Progression of existing MDS in patients with RAEB-1)
10.2	14 September 2011 PSU015 PSU016 RMP021	The following risk was recategorized from an important potential risk to an important identified risk: • Thrombotic/thromboembolic complications
11.0	22 February 2012 EMEA/H/C/942/II/0022	Updated to include a proposed action plan to address the risk of medication errors for patients who self-administer romiplostim
11.1	08 August 2012 EMEA/H/C/942/II/0022	The following risk was recategorized from an important potential risk to an important identified risk: • Romiplostim medication errors (dosing/administration)
11.2	17 October 2012 EMEA/H/C/942/II/0022	No major changes
12.0	17 September 2012 EMA/H/C/942/PSU/016 and EMA/H/C/942/RMP/022	The following was added as an important identified risk: • Hypersensitivity reactions The following was removed as an important potential risk: • Potential consequences of off-label use in indications where risk-benefit ratio has not been adequately studied
13	02 April 2013 EMEA/H/C/942/R/037	Contents of RMP versions 12.0 and 11.2 were consolidated into a single version according to the new template format
14	01 July 2014 EMA/H/C/942/R/037	Patient Education Brochure was removed as an additional risk minimization activity Section SV.4 was updated and the off-label table was replaced with this new text Sections V and VI updated to include key elements, and not the exact wording of the SmPC Minor changes have been made throughout the document to align with the revised EU RMP template
15	22 October 2014 EMEA/H/C/000942/II/0045	Re-introduction of the dose calculator guide as an additional risk minimization activity for the important identified risk of romiplostim medication errors (dosing/administration)
16	14 November 2014 Not available	Addition of data from completed Study 20080009 Updated to reflect discontinued status of Study 20080046 (Nplate Pregnancy Exposure Registry [NPER]) Minor changes have been made throughout the document to align with the revised EU RMP template
17	16 June 2016 EMEA/H/C/000942/II/0057	Updated to reflect completed status of Study 20120269 Updated to reflect completed status for the following additional studies: • Study 20080279 • Study 20060198 Updated to reflect discontinued status of Study 20080091 Medication error information updated to include recommendations for vial overfill table Added Study 20140195 as a Category 3 study Added Study 20140451 as a Category 4 study

Version	Approval Date Procedure	Change
18	23 November 2016 EMEA/H/C/000942/II/0060/G	Added pediatric population aged ≥ 1 year old, for the indication of chronic ITP patients who are refractory to other treatments (eg, corticosteroids, immunoglobulins) Removed pediatric patients aged ≥ 1 year old as missing information Added final study results from Study 20080091
18.1	30 June 2017 EMEA/H/C/000942/II/0060/G	Part I Product(s) overview, updated to align with latest proposed SmPC Module SIII.2 updated to include the latest clinical trial exposure as of 20 March 2017 Module SIV.1 updated to include the latest clinical trial exposure, duration of exposure, and frequency rate of rare ADRs Module SVII Important identified and potential risks, updated to include latest data from pediatric ITP safety set Updates made to reflect study completion and clinical study reports were provided for: • Study 20090340 • Study 20090488 (PLATEAU) • Study 20140451 (UKITP registry) Annex 11, included updated mock-up of dosing calculator (version 2.1)
18.2	29 September 2017 EMEA/H/C/000942/II/0060/G	Part I Product(s) overview, updated to align with the latest proposed SmPC Module SV.1 Action Taken by Regulatory Authorities and/or MAH for Safety Reasons: added MDS update to USPI (dated 05 June 2017) to the table of cumulative list of actions taken for safety reasons Module SVI.4 Potential for Medication Errors: added text on colors of the vial caps for 3 product presentations and text to clarify that self-administration is not allowed for pediatric patients Module SVII.3 Details of Important Identified and Potential Risks From Clinical Development and Postauthorization Experience: To the medication errors table, added text on colors of the vial caps for 3 product presentations and text to clarify that self-administration is not allowed for pediatric patients Part V Risk Minimization Measures: Updated routine and additional risk minimization measures for the important identified risk of medication errors. Added sections of the SmPC and package leaflet which provide information on colors of the vial caps for 3 product presentations and text to clearly state that self-administration is not allowed for pediatric patients Annex 11, Updated text on HAT pack to clearly state that self-administration is not allowed for pediatric patients Annex 11, Included an updated mock-up of HAT pack (version 1.1) which clearly states that self-administration is not allowed for pediatric patients and that the HAT pack is intended for use with adult patients and not with pediatric patients

Version	Approval Date Procedure	Change
18.3	06 November 2017 EMEA/H/C/000942/II/0060/G	Removed Use in pediatric patients (≥ 1 year of age) as missing information Removed Study 20101221 from the pharmacovigilance plan Removed Study 20140195 from the pharmacovigilance plan and development plan
19.0	15 December 2017 EMEA/H/C/000942/II/0060/G	Upversioned dosing calculator to version 3.0 and HAT pack to version 2.0 in Annex 11 Added composite 125/250/500 mcg image of product cartons and vials to the dosing calculator in Annex 11
20.0	Date of RMP: 14 May 2020 Procedure: EMEA/H/C/000942/II/0077	Updated the RMP in accordance with the EU RMP template (Rev 2) **Safety Concerns** Missing Information Removed: • Use in patients with different racial and/or ethnic origins **Pharmacovigilance Plan** Removed expert advisory bone marrow panel meetings
20.1	Date of RMP: 29 September 2020 Approval Date: 10 December 2020 Procedure: EMEA/H/C/000942/II/0077	**Other changes:** • Indication amended.

21.0	Date of RMP:
	16 November 2021
	Procedure:
	EMEA/H/C/000942/II/0083
		Safety concerns:
		• Important identified risks removed:
		  • Reoccurrence of thrombocytopenia after cessation of romiplostim
		  • Increased bone marrow reticulin
		  • Thrombocytosis
		  • Risk of bleeding in ITP patients who have consistently low platelet counts
		  • Risk of bleeding during the period of low platelet counts in patients with variable platelet counts
		  • Hypersensitivity reactions
		• Important potential risks removed:
		  • Bone marrow fibrosis
		  • Concurrent leukocytosis and anemia
		  • Renal impairment
		• Missing information removed:
		  • Use in pregnant or breastfeeding women
		  • Use in patients with bone marrow stem cell disorder and/or any active malignancy
		  • Use in patients with renal, hepatic, cardiac, or pulmonary impairment
		  • Use in patients concurrently receiving rituximab or alkylating agents
		
		Pharmacovigilance Plan:
		Removed completed category 3 Study 20070797

Version	Approval Date Procedure	Change
21.1	Date of RMP: 09 August 2022 Approval Date: To be determined Procedure: EMEA/H/C/000942/II/0083	**Safety concerns:** • Important identified risks removed: • Progression of existing myelodysplastic syndrome • Thrombotic/thromboembolic complications **Part II: Module SII - Nonclinical Part of the Safety Specification:** • **Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage** Text for progression of existing myelodysplastic syndrome (MDS) listed as an important identified risk for romiplostim is now replaced with reference to the relevant sections of the SmPC

This summary was last updated in February 2023.