Swiss Summary of the Risk Management Plan (RMP) for Nonacog gamma (RIXUBIS)

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Marketing Authorization Holder: Takeda Pharma AG

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 risk as well as to prevent or minimise them.

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

Summary of risk management plan for RIXUBIS (nonacog gamma)

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

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

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

I. The medicine and what it is used for

RIXUBIS is authorised for treatment and prophylaxis of bleeding in patients with haemophilia B. It contains RIXUBIS as the active substance and it is given by injection.

Further information about the evaluation of RIXUBIS's benefits can be found in RIXUBIS's EPAR, including in its plain-language summary, available on the European medicines agency (EMA) website, under the medicine's webpage: https:/www.ema.europa.eu/en/documents/overview/rixubis-epar-summary-public_en.pdf

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

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

Measures to minimise 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 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, 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 RIXUBIS is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of RIXUBIS are risks that need special risk management activities to further investigate or minimise 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 RIXUBIS. 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	• Hypersensitivity reactions (including reactions/antibodies to CHO protein)
Important potential risks	• Inhibitor formation • Thromboembolic events (e.g., DIC and fibrinolysis) • Nephrotic Syndrome following attempted ITI in haemophilia B patients with FIX inhibitors and a history of allergic reactions
Missing information	• No clinical data on use of RIXUBIS for ITI • No data on the use of RIXUBIS for continuous infusion • Insufficient data regarding the degree to which factor IX levels can be affected by the aPTT reagent in aPTT potency assay • Use in pregnancy and lactation

II.B Summary of important risks and missing information

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important Identified Risk – Hypersensitivity reactions (including reactions/antibodies to CHO protein)	
Evidence for linking the risk to the medicine	Hypersensitivity reactions (including reactions/antibodies to CHO protein) has been reported in scientific literature and post-marketing surveillance.
Risk factors and risk groups	Patients with previous history of hypersensitivity to RIXUBIS or any other constituents of the product. The risk for hypersensitivity reactions is highest during the early phases of initial exposure to factor IX concentrates in PUPs, in particular in patients with high-risk gene mutation. Potential increased risk of hypersensitivity reactions in patients with inhibitors.
Risk minimization measures	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4, and 4.8 PL section 2 and 4 **Additional risk minimisation measures:** No risk minimisation measures.
Additional pharmacovigilance activities	EUHASS and PedNet registries See Section II.C of this summary for an overview of the post-authorisation development plan

Important Potential Risk – Inhibitor formation	
Evidence for linking the risk to the medicine	Inhibitor formation has been reported in scientific literature.
Risk factors and risk groups	PUPs and MTPs with high-risk gene mutations (such as large deletions, nonsense/stop mutations, gross deletions/insertions or complete gene deletion). Other risk factors include family history of inhibitors, association with atopia, effects of recent immunisations, race and age at first exposure.
Risk minimization measures	**Routine risk minimisation measures:** SmPC sections 4.4, and 4.8. PL section 2 **Additional risk minimisation measures:** No risk minimisation measures.
Additional pharmacovigilance activities	EUHASS and PedNet registries See Section II.C of this summary for an overview of the post-authorisation development plan

Important Potential Risk – Thromboembolic events (e.g., DIC and fibrinolysis)	
Evidence for linking the risk to the medicine	Thromboembolic events (e.g., DIC and fibrinolysis) has been reported in scientific literature, clinical study and other factor IX products.
Risk factors and risk groups	Patients with previous history of hypersensitivity to RIXUBIS or any other constituents of the product. The risk for hypersensitivity reactions is highest during the early phases of initial exposure to factor IX concentrates in PUPs, in particular in patients with high-risk gene mutation. Potential increased risk of hypersensitivity reactions in patients with inhibitors.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4, and 4.8. PL sections 2 and 4 **Additional risk minimisation measures:** No risk minimisation measures.
Additional pharmacovigilance activities	EUHASS and PedNet registries See Section II.C of this summary for an overview of the post-authorisation development plan

Important Potential Risk – Nephrotic Syndrome following attempted ITI in haemophilia B patients with FIX inhibitors and a history of allergic reactions	
Evidence for linking the risk to the medicine	Nephrotic syndrome following attempted ITI in haemophilia B patients with FIX inhibitors and a history of allergic reactions has been reported in scientific literature.
Risk factors and risk groups	Patients using RIXUBIS regularly and patients with a history of factor IX inhibitors in association with an allergic phenotype.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4, and 4.8 PL section 2 and 4 **Additional risk minimisation measures:** No risk minimisation measures.

Additional pharmacovigilance activities	EUHASS and PedNet registries See Section II.C of this summary for an overview of the post-authorisation development plan

Missing Information – No clinical data on use of RIXUBIS for ITI	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4, and 4.8. **Additional risk minimisation measures:** No risk minimisation measures.
Additional pharmacovigilance activities	EUHASS and PedNet registries See Section II.C of this summary for an overview of the post-authorisation development plan

Missing Information – No data on the use of RIXUBIS for continuous infusion	
Risk minimization measures	**Routine risk minimisation measures:** SmPC section 4.2 **Additional risk minimisation measures:** No risk minimisation measures.
Additional pharmacovigilance activities	EUHASS and PedNet registries See Section II.C of this summary for an overview of the post-authorisation development plan

Missing Information – Insufficient data regarding the degree to which factor IX levels can be affected by the aPTT reagent in an aPTT potency assay	
Risk minimization measures	**Routine risk minimisation measures:** SmPC section 4.2 **Additional risk minimisation measures:** No risk minimisation measures.
Additional pharmacovigilance activities	EUHASS and PedNet registries See Section II.C of this summary for an overview of the post-authorisation development plan

Missing Information – Use in Pregnancy and Lactation	
Risk minimization measures	**Routine risk minimisation measures:** SmPC section 4.6 **Additional risk minimisation measures:** No risk minimisation measures.

Additional pharmacovigilance activities	EUHASS and PedNet registries See Section II.C of this summary for an overview of the post-authorisation development plan

II.C. Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of RIXUBIS.

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

Study name	Purpose of the study
Participation in registries (e.g., EUHASS and PedNet registries) and review of the data provided by the registries to further characterize the safety concerns for long term safety follow-up.	The EUHASS and PedNet registries serve to collect further safety information in patients with hemophilia B.