Swiss Summary of the Risk Management Plan (RMP) for Vonicog alfa (VEYVONDI)

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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 VEYVONDI 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 VEYVONDI 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 VEYVONDI.

Summary of risk management plan for VEYVONDI (Vonicog alfa)

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

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

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

I. The medicine and what it is used for

VEYVONDI is authorised for von Willebrand disease (vWD) (see SmPC for the full indication). It contains vonicog alfa as the active substance and it is given by intravenous infusion.

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

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

Important risks of VEYVONDI, together with measures to minimise such risks and the proposed studies for learning more about VEYVONDI'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 package leaflet 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, including periodic safety update report (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 VEYVONDI is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of VEYVONDI 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 VEYVONDI. 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 • Thromboembolic events (particularly in patients with low ADAMTS13 levels as well as other risk factors, and concomitant overuse of FVIII)
Important potential risks	• Inhibitor formation
Missing information	• Insufficient clinical data on use in pregnancy and lactation • Insufficient clinical data on use in geriatric patients

II.B Summary of important risks

Important Identified Risk: Hypersensitivity reactions	
Evidence for linking the risk to the medicine	Clinical trials, potential mechanism of action of risk.
Risk factors and risk groups	Patients with previous history of hypersensitivity to vonicog alfa or any other constituents of the product. VWD patients who have developed antibodies against VWF are at increased risk to develop anaphylactic reactions after re-exposure to VWF.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.8. PL section 2 and 4 Additional risk minimisation measures: No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • European Haemophilia Safety Surveillance System (EUHASS registry) See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: Thromboembolic events (particularly in patients with low ADAMTS13 levels as well as other risk factors, and concomitant overuse of FVIII)	
Evidence for linking the risk to the medicine	Clinical trials, potential mechanism of action of risk.
Risk factors and risk groups	Thromboembolic events can occur, particularly in patients with known clinical or laboratory risk factors including low ADAMTS13 levels. Administration of vonicog alfa with a FVIII product containing VWF would pose an additional risk of thrombotic events. Patients with sustained excessive FVIII:C plasma levels may be at increased risk of thrombotic events.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.8 and 4.9. PL section 2 and 3 Additional risk minimisation measures: No additional risk minimisation measures

Important Identified Risk: Thromboembolic events (particularly in patients with low ADAMTS13 levels as well as other risk factors, and concomitant overuse of FVIII)	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • EUHASS registry 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	Potential mechanism of action of risk.
Risk factors and risk groups	VWD patients who have developed antibodies against VWF are at risk to develop anaphylactic reactions after re-exposure to VWF. Inhibitor development in patients with VWD is a rare complication of treatment and mainly occurs in patients with severe inherited type 3 VWD. The risk for VWD patients to develop antibodies in response to exogenously administered VWF is highly variable in individual patients and can only partially be explained by genetic factors. Mutations in the VWF gene which have been reported to be associated with VWD are very heterogeneous. The development of neutralizing antibodies against VWF is frequently reported in patients with partial or complete VWF gene deletions but also in patients carrying nonsense or frameshift mutations. Since not all cases of type 3 VWD caused by large gene deletions are associated with the development of anti- VWF antibodies, it is highly probable that additional genetic or environmental factors contribute to the risk of developing antibodies against VWF. A positive family history of anti-VWF antibodies is considered as a major risk factor. Patients previously treated with pdVWF concentrates may be at risk to express binding antibodies against VWF prior to first exposure to vonicog alfa.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. PL section 2 and 4 Additional risk minimisation measures: No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • EUHASS registry See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Insufficient clinical data on use in pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Additional risk minimisation measures:

	No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: EUHASS registry

Missing Information: Insufficient clinical data on use in geriatric patients	
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: EUHASS registry

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 VEYVONDI.

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

Study name: EUHASS registry

Purpose of the study: The EUHASS registry serve to collect further safety information in patients with vWD.