Swiss Summary of the Risk Management Plan (RMP) for Susoctocog alfa (Antihaemophilic Factor VIII (recombinant), Porcine sequence) (OBIZUR®)

Version 5.0, 22-May-2022
Based on EU RMP version 6.0, 22-June-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 risk as well as to prevent or minimize them.

The RMP summary of OBIZUR 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 OBIZUR 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 OBIZUR.

Summary of risk management plan for OBIZUR (Susoctocog alfa)

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

OBIZUR's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how OBIZUR should be used.

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

I. The medicine and what it is used for

OBIZUR is authorized for treatment of bleeding episodes in patients with acquired haemophilia caused by antibodies to Factor VIII (see SmPC for the full indication). It contains: Susoctocog alfa (Antihemophilic Factor (Recombinant), Porcine Sequence) as the active substance and it is given through intravenous route of administration.

Further information about the evaluation of OBIZUR can be found at:

https://www.ema.europa.eu/en/documents/product-information/obizur-epar-product-information_en.pdf which is the link to link to product's EPAR summary landing page on the EMA webpage

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

Important risks of OBIZUR, together with measures to minimize such risks and the proposed studies for learning more about OBIZUR'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.

In the case of OBIZUR, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below:

- Health care professional brochure including a detailed calculation of vials for a patient weighing for example 70 kg.
- An online video to further elaborate on the required calculation and administration of the drug.

In addition to these measures, information about adverse reactions 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 OBIZUR is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of OBIZUR 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 OBIZUR. 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	Neutralizing inhibitory antibodies to OBIZUR
	Anamnestic reactions
	Lack of Efficacy due to o Neutralizing antibodies against the product o Anamnestic reactions o Use of lower than the recommended initial dosing for the product
Important potential risks	Hypersensitivity and allergic reactions to the active substance, any of the excipients or to baby hamster kidney (BHK) protein
	Thromboembolic events
	Dose dispensing errors
Missing information	No data on pregnant and lactating women or fertility
	Insufficient data on use in subjects < 18 years of age

II.B Summary of important risks

Important Identified Risk: Neutralizing inhibitory antibodies to OBIZUR	
Evidence for linking the risk to the medicine	Final clinical study report: OBI-1-301/OBI-1-301a. Risk Assessment of the Potential Immunogenicity of OBI-1 in AHA Patients that was included in Annex 12 of EU Risk Management Plan (RMP) (Version 2, dated 07 November 2016). Inhibitory antibodies against porcine Factor VIII (measured using a modification of the Nijmegen variation of the Bethesda assay) were detected before and after exposure to OBIZUR. Inhibitor titers of up to 29 Bethesda units were recorded at baseline yet subjects responded positively to OBIZUR. It is recommended that treatment should be based on clinical judgment and not based on detection of inhibitory antibodies by the Bethesda assay.
Risk factors and risk groups	Risk groups include populations that have a high-titre anti- porcine FVIII inhibitor and potential corresponding lack of efficacy. Risk factors include pre-dose high anti-porcine inhibitor >100 BU/mL, low

	baseline FVIII activity, inhibitors involving the C1 domain [44]. Populations that have high titre anti- porcine FVIII inhibitor and potential corresponding lack of efficacy.
Risk minimization measures	**Routine risk minimization measures:** Section 4.4 Special warnings and precautions for use, of the SmPC Section 4.8 Undesirable effects, of the SmPC Section 5.1 Pharmacodynamic properties, of the SmPC Section 5.2 Pharmacokinetic properties, of the SmPC Legal status: Prescription only **Additional risk minimization measures:** No risk minimization measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** See II.C. Post-authorisation development plan of this summary for an overview of the post-authorization development plan.

Important Identified Risk: Anamnestic reactions	
Evidence for linking the risk to the medicine	Sources: Final clinical study report (fCSR): OBI-1-301/OBI-1-301a. EMA Type II variation for OBIZUR label Procedure No. EMEA/H/C/002792/II/0030. This is based on safety and efficacy data from 29 subjects with AHA treated with OBI-1 in the phase 2/3 open-label clinical study OBI-1-301/OBI-1-301a (CSR OBI-1-301). Seven of the subjects developed anamnestic reactions with increase in antirpFVIII and or anti-hFVIII antibody levels >10 BU. Based on the re-analysis of the OBI-1-301 clinical trial from the safety data, there is evidence of an association of anamnestic reaction with rpFVIII therapy with a known frequency very common.
Risk factors and risk groups	Risk groups include populations that have a high-titre anti- porcine FVIII inhibitor and potential of developing anamnestic reaction leading to lack of efficacy. Risk factors include pre-dose high antiporcine inhibitor. Populations that have high titre anti- porcine FVIII inhibitor and potential corresponding lack of efficacy.
Risk minimization measures	**Routine risk minimization measures:** Section 4.4 Special warnings and precautions for use, of the SmPC Section 4.8 Undesirable effects, of the SmPC Section 5.1 Pharmacodynamic properties, of the SmPC Section 5.2 Pharmacokinetic properties, of the SmPC Legal status: Prescription only **Additional risk minimization measures:** No risk minimization measures.

Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** See II.C. Post-authorisation development plan of this summary for an overview of the post-authorization development plan.

Important Identified Risk: Lack of Efficacy due to Neutralizing antibodies against the product, Anamnestic reactions, Use of lower than the recommended initial dosing for the product	
Evidence for linking the risk to the medicine	Scientific Literature: Final clinical study report (fCSR): OBI-1-301/OBI-1-301a. EMA Type II variation for OBIZUR label Procedure No. EMEA/H/C/002792/II/0030. Renewal of the marketing authorization assessment report. Procedure no.: EMEA/H/C/002792/R/0033 Lack of drug effect PTs is 54 % (25 out of 46 events) of all PTs in the SOC “General and administration site disorders” There were 30 SARs, 18 referring to PTs related to drug effect decreased/drug ineffective/ Condition aggravated and thus accounting for 60 % of the serious adverse event PTs reported in this SOC General and administration site disorders”. Majority of patients receive lower than the currently recommended dose of 200 IU. Lack of drug effect is associated with 68% of these reports. In addition, development of inhibitory antibodies as well as anamnestic reaction has been associated with lack of drug effect. These reports constitute a prominent safety concern for OBIZUR.
Risk factors and risk groups	Response to treatment may depend on patient-specific dosing requirements due to differences of PK parameters. The baseline anti-rpFVIII titer may help to identify those patients for whom rpFVIII is unlikely to be efficacious [57].
Risk minimization measures	**Routine risk minimization measures:** Section 4.4 Special warnings and precautions for use, of the SmPC Section 4.8 Undesirable effects, of the SmPC Section 5.1 Pharmacodynamic properties, of the SmPC Section 5.2 Pharmacokinetic properties, of the SmPC Legal status: Prescription only **Additional risk minimization measures:** No risk minimization measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** See II.C. Post-authorisation development plan of this summary for an overview of the post-authorization development plan

Important potential risk: Hypersensitivity and allergic reactions to the active substance, any of the excipients or to baby hamster kidney (BHK) protein	
Evidence for linking the risk to the medicine	Scientific literature: Following production of rFVIII in a BHK protein expression system, several studies have detected an immunologic response (i.e. BHK antibody production) in haemophilia A patients administered the treatment [58], [59], [60]. However, the incidence of a hypersensitive response in AHA patients from rFVIII treatment, excipients or BHK proteins, remains unknown at this time.
Risk factors and risk groups	Patients with previous history of hypersensitivity and allergic reactions to the active substance, any of the excipients or to baby hamster kidney (BHK) protein may be at increased risk. Development of antibodies or activation of complement that could trigger hypersensitivity.
Risk minimization measures	**Routine risk minimization measures:** Section 4.3 Contraindications of the SmPC. Section 4.4 Special warnings and precautions for use, of the SmPC. Section 4.8 Undesirable effects, of the SmPC. Legal status: Prescription only **Additional risk minimization measures:** No risk minimization measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** See II.C. Post-authorisation development plan of this summary for an overview of the post-authorization development plan

Important potential risk: Thromboembolic events	
Evidence for linking the risk to the medicine	Scientific literature
Risk factors and risk groups	Patients with AHA are often at higher background risk for thromboembolic events due to a high prevalence of risk factors including advanced age, recent surgical procedures and comorbid conditions including liver disease, malignancy and autoimmune disorders.
Risk minimization measures	**Routine risk minimization measures:** Section 4.4, Special warnings and precautions for use, of the SmPC. Legal status: Prescription only **Additional risk minimization measures:** No risk minimization measures.
Additional	**Additional pharmacovigilance activities:**

pharmacovigilance activities	See II.C. Post-authorisation development plan of this summary for an overview of the post-authorization development plan

Important potential risk: Dose dispensing errors	
Evidence for linking the risk to the medicine	Scientific literature.
Risk factors and risk groups	Patients receiving OBIZUR.
Risk minimization measures	**Routine risk minimization measures:** Section 4.2, Posology and method of administration of the SmPC. Legal status: Prescription only **Additional risk minimization measures:** Health care professional brochure including a detailed calculation of vials for a patient weighing for example 70 kg. An online video to further elaborate on the required calculation and administration of the drug.

Missing Information: No data on pregnant and lactating women or fertility	
Risk minimization measures	**Routine risk minimization measures:** Section 4.6, Fertility, pregnancy and lactation, of the SmPC Legal status: Prescription only **Additional risk minimization measures:** No risk minimization measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** No additional pharmacovigilance activities.

Missing Information: Insufficient data on use in subjects < 18 years of age	
Risk minimization measures	**Routine risk minimization measures:** Section 4.2, Posology and method of administration, under the Section Paediatric population of the SmPC. Section 5.1, Pharmacodynamic properties, of the SmPC. Legal status: Prescription only **Additional risk minimization measures:** No risk minimization measures.

II.C. Post-authorisation development plan

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

There are no studies for Obizur which are required as a condition of the marketing authorization.

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

There are no studies required for Obizur in post-authorisation developmental plan