PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for *vihuma*

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

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

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

I. The medicine and what it is used for

vihuma is authorized for treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). It contains simoctocog alfa as the active substance and it is given by intravenous injection.

Further information about the evaluation of *vihuma*'s benefits can be found in *vihuma*'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

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

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

Important risks of *vihuma*, together with measures to minimise such risks and the proposed studies for learning more about *vihuma'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 SPC 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 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 *vihuma* is not yet available, it is listed under 'missing information' below.

II.A. List of important risks and missing information

Important risks of *vihuma* 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 *vihuma*. 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	- Inhibitor development (antibodies against rhFVIII) - Hypersensitivity reactions, including anaphylactic reactions - Cardiovascular events
Important Potential Risks	- Thromboembolic events - Medication error including safety in home therapy setting
Missing Information	- Safety in pregnant or breastfeeding women - Safety in previously untreated patients - Children < 2 years - Immune tolerance induction (ITI)

II.B. Summary of important risks

Important identified risk: Inhibitor development (antibodies against rhFVIII)	
Evidence for linking the risk to the medicine	The formation of inhibitors against factor VIII is the most important complication in haemophilia treatment. Inhibitors are antibodies against factor VIII produced by the body's immune system, and which can cause the medicine to stop working, resulting in a loss of bleeding control and potentially fatal massive bleeding episodes.
Risk factors and risk groups	Inhibitors occur in up to 30% of patients with severe haemophilia A, most frequently in young children after less than 20 days of exposure (treatment). The main genetic risk factors are a family history of inhibitors and certain types of mutations on the factor VIII gene.

Important identified risk: Inhibitor development (antibodies against rhFVIII)	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 4.8 Package leaflet sections 2, 3 and 4
Additional pharmacovigilance activities	Participation in European Haemophilia Safety Surveillance (EUHASS)

Important identified risk: Hypersensitivity reactions, including anaphylactic reactions	
Evidence for linking the risk to the medicine	As with any protein product given into a vein, allergic-type hypersensitivity reactions may occur. In some cases, allergic reactions may be life-threatening, therefore this risk is considered as important identified risk. Usually patients recover fully after treatment.
Risk factors and risk groups	Risk groups are patients with a history of previous reactions to FVIII products or known hypersensitivity to any of the constituents of the drug.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.8 Package leaflet sections 2 and 4
Additional pharmacovigilance activities	Participation in EUHASS

Important identified risk: Cardiovascular events	
Evidence for linking the risk to the medicine	Patients with existing cardiovascular risk factors - like raised blood pressure, raised blood sugar, smoking, and overweight and obesity - may have a higher risk of events involving the heart or blood vessels when being treated with factor VIII products like *vihuma*.
Risk factors and risk groups	The most important behavioural risk factors of heart disease and stroke are unhealthy diet, physical inactivity, tobacco use and harmful use of alcohol. These risk factors may show up in individuals as raised blood pressure, raised blood glucose, raised blood lipids, and overweight and obesity. The incidence of hypertension, smoking and diabetes may be higher in haemophilia patients than in the general male

Important identified risk: Cardiovascular events	
	population. In addition, a positive association between antiretroviral therapy and cardiovascular events has been observed among the general population.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 Package leaflet section 2

Important potential risk: Thromboembolic events	
Evidence for linking the risk to the medicine	In patients who receive *vihuma* via central venous access devices (CVAD), local blood clots may form at the catheter site which may increase the risk of subsequent bacterial infection at the catheter site. Clot formation may also result in a malfunction of the CVAD. Very rarely local blood clots may travel into the lungs and cause a life-threatening or fatal reaction.
Risk factors and risk groups	Risk factors for thromboembolic events: Obesity; age (elderly); hypertension; diabetes mellitus; hyperlipidaemia; history of vascular disease; history of thrombotic episodes; acquired or inherited thrombophilic disorders; prolonged periods of immobilisation; hypovolaemia; renal insufficiency; liver disease (cirrhosis, impaired liver function, etc.); atrial fibrillation; severe muscle haemorrhage, crush injury, or orthopaedic surgery in haemophilia patients; increased blood viscosity Risk factors for central venous catheters (CVC)-related thrombosis: • Inherited coagulation disorders • Factor V Leiden • Prothrombin G20210A mutation • Cancer or active cancer treatment • Prior thromboembolism • Acquired (temporary) hypercoagulable state • High platelet count at CVC insertion • Age (elderly and very young children) • Type of CVC (higher risk with CVCs made of polyethylene) • Number of CVC lumina

Important potential risk: Thromboembolic events	
	• Vascular trauma • Duration of stay of CVC
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 Package leaflet section 2
Additional pharmacovigilance activities	Participation in EUHASS

Important potential risk: Medication error including safety in home therapy settings	
Evidence for linking the risk to the medicine	Especially at the beginning of home therapy, errors in the administration or dosing of *vihuma* may occur and thorough training is needed. The package leaflet of *vihuma* clearly describes how the medicine should be given. Patients requiring treatment with *vihuma* may be trained to self-inject the clotting factor product or receive it by a trained family member.
Risk factors and risk groups	Not applicable
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 6.3, 6.4 and 6.6 Package leaflet sections 3 and 5

Missing information: Safety in pregnant or breastfeeding women	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 Package leaflet section 2

Missing information: Safety in previously untreated patients	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 Package leaflet section 4

Missing information: Children < 2 years	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 4.8 Package leaflet sections 3 and 4

Missing information: Immune tolerance induction (ITI)	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4

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 authorization or specific obligation of *vihuma*.

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

There are no studies required for *vihuma*.