Haemate P®/Humate-P® / Haemwill (name of product in Finland)

(Human plasma coagulation factor VIII, human von Willebrand factor)

Public Summary of Risk Management Plan

(Extract from the EU Risk Management Plan Version 1.1; 11-Mar-2022)

Part VI: Summary of the risk management plan

Summary of Risk Management Plan for Haemate P (human plasma coagulation factor VIII (FVIII), human von Willebrand factor)

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

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

I. The medicine and what it is used for

Haemate P is authorized for prophylaxis and treatment of haemorrhage or surgical bleeding, when desmopressin or 1-deamino-8-D arginine vasopressin (DDAVP), treatment alone is ineffective or contra-indicated in patient with VWD. Haemate P is authorized for prophylaxis and treatment of bleeding in patients with hemophilia A. Haemate P may be used in the management of acquired factor VIII deficiency and for treatment of patients with antibodies against factor VIII (see SmPC for the full indication). It contains human plasma coagulation factor VIII (FVIII), human von Willebrand factor (VWF) as the active substance and it is given by injection.

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

Important risks of Haemate P, together with measures to minimize such risks and the proposed studies for learning more about Haemate P'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 addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Safety Update Report (PSUR) assessment so that

immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Haemate P 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 Haemate P. 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	• Development of FVIII/VWF inhibitors • Thromboembolic events
Important potential risks	• Transmission of infectious agents
Missing information	• Not applicable

FVIII = Human Coagulation Factor VIII, VWF = von Willebrand Factor

II.B Summary of important risks

Important identified risk: Development of FVIII/VWF inhibitors	
Evidence for linking the risk to the medicine	Data obtained from literature and the company safety database. An important identified risk associated with FVIII/VWF replacement therapy is the development of inhibitors (ie, neutralizing antibodies) against FVIII or VWF, rendering treatment with antihemophilic factors less effective or ineffective. This risk is recognized as being significantly higher in PUPs. Inhibitors to FVIII occur in approximately 30% of PUPs with hemophilia A (Hashemi el al, 2015). A recent publication (Peyvandi et al, 2016) reported inhibitor development in 26,8% of PUPs treated with pdFVIII within the first 50 EDs. Of note, the clinical relevance of inhibitor development overall, depends on the titer of the inhibitor, with low titer inhibitors (0.6 to < 5 BU/mL) which are transiently present or remain consistently low titer posing less of a risk of insufficient clinical response than high titer inhibitors (≥

	5 BU/mL) (EMA PRAC, Referral under Article 31 of Directive 2001/83/EC Factor VIII 2017). Alloantibodies against VWF are a rare complication, the prevalence in type 3 VWD is 6 to 10%. It is important to highlight that all reported cases have occurred in severe or type 3 VWD; there are no reports of VWF alloantibody development in either type 1 or type 2 VWD. Recently, the first results of the 3 WINTER-IPS-project, which included a large cohort of 260 type 3 VWD patients, showed a 6% prevalence of alloantibodies in type 3 VWD patients (Stufano et al, 2019). It is thought that this occurs in about 10 to 15% of patients with type 3 VWD, who have received multiple transfusions (Federici, 2009, Mannucci, 2001). A recent case-report of a 6-year-old girl with type 3 von Willebrand disease, in whom inhibitors were sought due to ineffective haemostasis in addition to a lower than expected VWF recoveries after a surgical procedure, provides further evidence that alloantibodies develop in severe or type 3 VWD (Faganel Kotnik et al, 2020). In 2015 Baaij et al reported the first case of alloantibodies in a 35-year-old woman with type 2B VWD (Baaij et al, 2015). Although the pathophysiological mechanism is not fully understood, this case clearly demonstrates that antibody formation should be considered in non-type 3 VWD as well, when insufficient recovery of VWF:RCo is observed after administration of VWF concentrate.
Risk factors and risk groups	Risk factors for FVIII inhibitor formation include both patient and treatment-related factors (Coppola et al, 2010; Chambost, 2010; Collins et al, 2013; EMA PRAC Rapporteur's Updated Assessment Report, Referral under Article 31 of Directive 2001/83/EC Factor VIII, 2017): **Patient related:** • Ethnic group: 2 to 5-fold increase associated with patients of Hispanic

	and African origin compared to Caucasians • Host-related high risk gene mutations: such as null mutations, larger deletions, intron 1 and 22 inversion, and small missense mutations • Age: inhibitors are likely to develop in patients < 5 years and > 60 years • Major histocompatibility complex genotype (human leukocyte antigen Class I type) • Polymorphisms of immune response genes (interleukin-10, tumor necrosis factor, cytotoxic T-lymphocyte-associated protein-4) • Severity of disease: severe HA population are more at risk of inhibitor development than mild or moderate hemophilia • Previous history of inhibitors • Recent pro-inflammatory conditions such as bleed, infections, vaccinations, etc., called danger signals **Treatment Related:** • Treatment-related EDs: risk is highest during early exposure, with a median time of inhibitor presentation at approximately 10 to 15 EDs, and risk subsequently falling after 50 EDs and intensive exposure and surgical procedures due to administration of high amounts of FVIII concentrates. • Early FVIII treatment exposure • Switching FVIII products • Risk factors for development of anti-VWF alloantibodies include Type 3 VWD patients who receive multiple transfusions (Federici, 2009; Mannucci, 2001)
Risk minimization measures	<u>Routine risk minimization measures:</u> SmPC Section 4.2 SmPC Section 4.8

	SmPC Section 4.4 where advice is given on monitoring for development of neutralizing antibodies and management of patients with high levels of inhibitor to be directed by physicians with experience in the care of hemophilia and FVIII inhibitors, and information is given about risk factors and clinical relevance of inhibitors <u>Additional risk minimization measures:</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Participation in EUHASS

BU=Bethesda Unit; ED=Exposure Day; EUHASS=European Haemophilia Safety Surveillance System; FVIII=Coagulation Factor VIII; HCV= Hepatitis C Virus; HIV=Human Immunodeficiency Virus; pdVWF= plasma derived von Willebrand Factor; SmPC=Summary of Product Characteristics; TEE=Thromboembolic Event; VWD= von Willebrand Disease, VWF= von Willebrand Factor

Important identified risk: Embolic and Thrombotic events (TEEs)	
Evidence for linking the risk to the medicine	Data obtained from literature and the company safety database. TEEs are known class effects of FVIII/VWF plasma derived products. There have been reported cases with Haemate P providing evidence of a causal association. The evidence source indicate that thromboembolic events have impact on patients in terms of severity/seriousness. Although these events primarily occur in patients with underlying risk factors, thromboembolic events are considered an important identified risk for Haemate P.
Risk factors and risk groups	Patients with VWD or HA who are receiving high levels of FVIII/VWF concentrate. Additional risk factors for TEEs in the targeted population are the same as in the general population. Patients with hemophilia and VWD now have better long-term survival, therefore, the risks are similar as in the general population and include (Geerts et al, 2008); Previtali et al, 2011):

	<u>Venous thrombosis risks:</u> • Pregnancy • Hormone replacement therapy • Surgery • Immobilization • Trauma • Cancer <u>Arterial thrombosis risks:</u> • Smoking • Hypertension • Hypercholesterolemia • Peripheral vascular disease • Diabetes • Obesity
Risk minimization measures	<u>Routine risk minimization measures:</u> SmPC Section 4.8 and 4.9 SmPC Section 4.4 where advice is given on monitoring patients at risk for early signs of thrombosis, that prophylaxis against venous thromboembolism should be instituted and on monitoring plasma levels of FVIII:C and considering antithrombotic measures. <u>Additional risk minimization measures:</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Participation in EUHASS

BU=Bethesda Unit; ED=Exposure Day; EUHASS=European Haemophilia Safety Surveillance System; FVIII=Coagulation Factor VIII; HCV= Hepatitis C Virus; HIV=Human Immunodeficiency Virus; SmPC=Summary of Product Characteristics; TEE=Thromboembolic Event; VWD= von Willebrand Disease, VWF= von Willebrand Factor

Important potential risk: Transmission of infectious agents	
Evidence for linking the risk to the medicine	Data obtained from literature and the company safety database. The potential for transmitting infectious agents is a known class effect of all blood/plasma-driven products. There have been reported cases with Haemate P; none of them provided evidence of confirmed cases of transmission of infectious agents. For these reasons, potential for transmission of infectious agents is considered an important potential risk for Haemate P.
Risk factors and risk groups	Infectious agents such as HCV and HIV can be transmitted by exposure to other blood products, intravenous drug abuse, sexual contact and maternal-infant exposure (Shepard et al, 2005; UNAIDS report, 2010). Parvovirus B19 is a common infectious pathogen in humans and is acquired during childhood.
Risk minimization measures	<u>Routing risk minimization measures:</u> SmPC Section 4.4 where advice is given on considering appropriate vaccination (hepatitis A and B) and recording the name and batch number of the product and on standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma including: • Selection of donors • Screening of individual donations and plasma pools for specific markers of infection • Inclusion of effective manufacturing steps for the inactivation/removal of viruses <u>Additional risk minimization measures:</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Participation in EUHASS

BU=Bethesda Unit; ED=Exposure Day; EUHASS=European Haemophilia Safety Surveillance System; FVIII=Coagulation Factor VIII; HA=Hemophilia A; HCV= Hepatitis C Virus; HIV=Human Immunodeficiency Virus; SmPC=Summary of Product Characteristics; TEE=Thromboembolic Event; VWD= von Willebrand Disease, VWF= von Willebrand Factor

II.C Post-authorization development plan

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

There are no studies which are conditions of the marketing authorization or specific obligation of Haemate P.

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

Haemophilia Network Registry: EUHASS

Purpose of the study: CSL Behring participates in this ongoing pharmacovigilance program monitoring the safety of treatments for people with inherited bleeding disorders in Europe to obtain long-term post-marketing safety data.