CSL Behring

Voncento

Human Coagulation Factor VIII (FVIII)/ Von Willebrand Factor (VWF) Complex

Swiss Summary of Risk Management Plan

Version number of RMP: 7.1

Marketing Autorisation Holder: CSL Behring AG

Date: 27-Mar-2020

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 risks as well as to prevent or minimize them.
The RMP summary of Voncento 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 Voncento in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. CSL Behring AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Voncento.

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The medicine and what it is used for

Human coagulation FVIII/VWF Complex is authorized for prophylaxis and treatment of non-surgical and surgical bleeding in patients with von Willebrand disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or contraindicated and for prophylaxis and treatment of bleeding in patients with haemophilia A (congenital FVIII deficiency) (see SmPC ["Arzneimittelinformation/ Information sur le médicament"] for the full indication). It contains Human Coagulation Factor VIII (FVIII)/von Willebrand Factor (VWF) Complex as the active substance and it is given by injection.

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

Important risks of Human coagulation FVIII/VWF Complex, together with measures to minimize such risks and the proposed studies for learning more about Human coagulation FVIII/VWF Complex'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 ("Arzneimittelinformation/ Information sur le médicament") 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.

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If important information that may affect the safe use of Human coagulation VIII/VWF Complex is not yet available, it is listed under 'missing information' below.

List of important risks and missing information

Important risks of Human coagulation FVIII/VWF Complex 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 Human coagulation FVIII/VWF Complex. 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	• Development of FVIII/VWF inhibitors • Embolic and thrombotic events
Important potential risks	• Transmission of infectious agents
Missing information	• Not applicable

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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 previously untreated patients (PUPs). Inhibitors to FVIII occur in approximately 30% of PUPs with hemophilia A (Hashemi et 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 over-all depends on the titer of the inhibitor, with low titer inhibitors (0.6 to < 5 Bethesda Unit (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).
Risk factors and risk groups	Risk factors for FVIII inhibitor formation include both patient and treatment related factors (Coppola et al, 2010; Chambost, 2010): **Patient related**: - Ethnic group (African ancestry) - FVIII gene mutations - Family history of inhibitors - 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) - Recent pro-inflammatory conditions such as bleeds, infections, vaccinations, etc., called danger signals **Treatment Related**: - Number of FVIII exposure days - Highest risk is within the first 50 exposures to FVIII (average age of 1 to 2 years after 9 to 12 treatments). - Severity of disease - Severe haemophilia A population are more at risk of inhibitor development than mild or moderate haemophilia. - Intensive exposure and surgical procedures due to administration of high amounts of FVIII concentrates. - Risk factors for development of anti-VWF alloantibodies include Type 3 VWD patients who receive multiple transfusions (Federici, 2009; Mannucci, 2001). **Ethnicity** The proportion of hemophilia A patients developing FVIII inhibitors was reported in literature in a range of 13.3 to 27.4% among

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Important Identified Risk: Development of FVIII/VWF inhibitors	
	Caucasians, 1.0 to 55.6% among black patients and 24.5 to 27.9% among Hispanics (Astermark et al, 2001; Carpenter et al, 2012; Dimichele, 2002; Gouw et al, 2007; Miller et al, 2012). In studies reporting comparative analysis, the results have shown that black and Hispanic patients have an increased risk for inhibitors compared to Caucasians, although not all studies have been statistically significant and many burdened with small numbers (Astermark et al, 2001; Carpenter et al, 2012; Dimichele, 2002; Gouw et al, 2007, Kempton et al, 2010; Mclean et al, 2011; Ragni et al, 2009). The odds ratio for black vs Caucasians have been reported at 1.6 (95% CI 1.3 to 1.9) and 1.9 (95% CI 0.6 to 6.1). The odds ratio for Hispanic vs Caucasian people has been estimated at 1.4 (95% CI 1.1 to 1.7) and noncaucasian vs caucasian at 5.8 (95% CI 1.7 to 19.9) (Carpenter et al, 2012; Gouw et al, 2007; Mclean et al, 2011). Reports on Asian patients as a separate group is scarce. One study was found that reported a 7% inhibitor proportion among Asians, which translated into an odds ratio of 0.3 (95% CI 0.4 to 2.4) compared to white patients (Gouw et al, 2007; Mclean et al, 2011). Risk factors for development of anti-VWF alloantibodies include Type 3 VWD patients who receive multiple transfusions (Federici, 2009; Mannucci, 2001).
Risk minimization measures	Routine risk minimization measures SmPC section 4.4 and 4.8 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Participation in EUHASS

Important Identified Risk: Embolic and thrombotic events	
Evidence for linking the risk to the medicine	Data obtained from literature and the company safety database. Thromboembolic events are a known class effect of FVIII-VWF plasma derived products. There have been reported cases with Human coagulation FVIII/VWF complex, which provided evidence of a causal association. The evidence sources indicate that thromboembolic events have impact on patients in terms of severity/seriousness. Although these events primarily occur in patients with underlying risk factors, embolic and thrombotic events are considered an important identified risk for Human coagulation FVIII/VWF complex.
Risk factors and risk groups	Patients with VWD or haemophilia A who are receiving high levels of FVIII/VWF concentrate. Additional risks factors for embolic and thrombotic events in the

	targeted population are the same in the general population. Patients with Haemophilia and VWD now have a better long term survival, therefore the risks are the same as in the general population and include (Geerts et al, 2008; Previtali et al, 2011): **Venous Thrombosis risks:** - Pregnancy - Hormone replacement therapy - Surgery - Immobilization - Trauma - Cancer **Arterial thrombosis risks**: - Smoking - Hypertension - Hypercholesterolaemia - Peripheral vascular disease - Diabetes - Obesity
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4, 4.8 and 4.9 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Participation in EUHASS

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 Human coagulation FVIII/VWF complex; 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 Human coagulation FVIII/VWF complex. The evidence sources indicate that the potential for transmission of infectious agents has an impact on patients in terms of severity/seriousness. Potential for transmission of infectious agents is considered an important potential risk for Human coagulation FVIII/VWF complex.
Risk factors and risk groups	Infectious agents such as HCV and HIV are transmitted by (Shepard et al, 2005; UNAIDS report, 2010): - Exposure to other blood products

Important Potential Risk: Transmission of infectious agents	
	– IV drug abuse – Sexual contact – Maternal-infant exposure Parvovirus B19 is a common infectious pathogen in humans, and is acquired during childhood.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Participation in EUHASS

Post-authorization development plan

Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligations for Human coagulation FVIII/VWF Complex.

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 (including hypersensitivity and inhibitor development).

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Summary of changes to the Swiss RMP Summary over time

Version	Date	Safety concerns	Comment
01	15-Nov-2016	Initial document	Initial document
02	11-Oct-2017	No changes to safety concerns	Inclusion of post marketing study Biostate 4001
03	15-Oct-2018	No changes to safety concerns	Update of planned final study report date of Biostate_4001 and of CSLCT-BIO-12-83
04	06-Sep-2021	- Removal of *important identified risks* 'Lack of Drug Effect', 'Hypersensitivity Reaction'; - Removal of *important potential risks* 'Safety in the home therapy setting, including risk of errors in handling and maladministration', 'Medication errors', 'Off label use including immune tolerance induction (ITI) therapy'; - Removal of *missing information* 'Patients with a current or known history of an inhibitor to FVIII or VWF', 'Treatment and inhibitor formation in previously untreated patients (PUPs), 'Pregnant and lactating women' and 'Elderly patients above 65 years of age'.	- The EU PASS Biostate_4001 has been removed. - Modification of the important identified risk 'Hypersensitivity reactions, including anaphylaxis' to the important identified risk 'Anaphylaxis'. - Version based on EU Risk Management Plan Version 7.1, 27-Mar-2020 - Required changes due to usage of new EU-RMP template as per GVP Module V Rev. 2.