13. PART VI: SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY PRODUCT

13.1. VI.1 Elements for summary tables in the EPAR

Not applicable

13.2. VI.2 Elements for a Public Summary

13.2.1. VI.2.1. Overview of disease epidemiology

Von Willebrand's Disease (VWD) is a congenital bleeding disorder caused by a deficiency or dysfunction of von Willebrand factor (VWF), a plasma protein that stimulates platelet aggregation and acts as a carrier for factor VIII to protect it from premature destruction. There is aslo a secondary deficiency of factor VIII, because of its dependence on VWF. There are 3 main phenotypes of VWD:

- Type 1 is the most common and is characterized by mild to moderate deficiencies of VWF and factor VIII.
- Type 2 results in qualitative abnormalities of VWF, and is further divided into subtypes according to the defect.
- Type 3 is rare but is a severe bleeding disorder due to very low or undetectable plasma levels of VWF, with low but usually detectable concentrations of factor VIII.

The clinical presentation of VWD includes easy bruising and bleeding from mucosal surfaces, such as epistaxis; severely affected patients may have spontaneous soft-tissue bleeding resulting in haematomas and haemarthroses. Excessive and prolonged bleeding can occur after surgery and women may have excessive bleeding during menstruation and childbirth.

The prevalence of VWD in the general population is estimated at between 0.1 and 1% (including all forms) depending on the study, but the prevalence of symptomatic VWD that requires specific treatment is estimated at between 1/50,000 and 1/8,500. Age of onset varies, with earlier onset being associated with more severe VWF deficiency.

13.2.2. VI.2.2. Summary of treatment benefits

WILLFACT® is a medicine, used to stop bleeding, that contains human von Willebrand factor (VWF) as active ingredient.

WILLFACT® is indicated in the prevention and treatment of surgical or other bleeding in patients with von Willebrand disease when desmopressin (DDAVP) treatment alone is ineffective or contra-indicated.

Patients are usually only treated at the time of spontaneous bleeding or given prophylaxis before invasive procedures.

Management depends on the type of VWD:

- Desmopressin is generally an effective preventative or curative treatment for abnormal bleeding in type 1 VWD.
- In patients with type 2 disease, the response to desmopressin is variable and substitution therapy with purified human VWF is often required.
- Desmopressin does not constitute an effective treatment for patients with type 3 disease, and thus these individuals require substitution therapy with purified human VWF associated, at least for the first injection, with FVIII. For patients managed within specialized hemostasis and thrombosis hospital centers, the prognosis is favorable, even for those with the most severe forms of the disease.

13.2.3. VI.2.3. Summary of safety concerns

- **Important identified risks**

Not applicable

- **Important potential risks**

Risk	What is known (Including reason why it is considered a potential risk)
Severe allergic reactions	As with every protein medicine for intravenous use derived from human blood or plasma, **hypersensitivity reactions in the form of an allergy** may occur. During your injection, you will be monitored specifically to determine whether you experience any early signs of hypersensitivity, *e.g.* stinging, hives (generalised urticaria), tightness of the chest, wheezing , drop in blood pressure (hypotension) and allergic severe reactions (anaphylaxis). If these symptoms occur, the injection will be interrupted immediately.
Thrombotic events	Blood vessels may also become blocked by blood clots (thromboses). This risk exists particularly if your previous medical history or laboratory results indicate that you present certain risk factors. In this case you will be monitored very carefully for the early signs of thrombosis, and a preventative treatment (prophylaxis) against vein blockages by blood clots should be introduced. When using a Factor VIII containing VWF product, your physician should be aware that the treatment may cause an excessive rise in FVIII:C. If you receive such FVIII containing VWF product, your physician should monitor your FVIII:C plasma level regularly. This ensures that your FVIII:C plasma level is not sustained excessive, which may increase the risk of thrombotic events.
Limited effectiveness	It is possible that, in patients with von Willebrand disease, especially type 3 patients, proteins may be formed that neutralise the effect of VWF. These proteins are called antibodies or inhibitors. If the laboratory results give corresponding indications, or if the bleeding does not stop despite a sufficient dose of Willfact, your physician will check whether VWF inhibitors are being formed in your body. If these inhibitors are present in high concentration, treatment with VWF may not be effective, and other treatment options should be considered. The new treatment will be provided by a physician who has experience in the treatment of haemostatic disorders.
Safety of the raw material in Willfact (plasma)	The use of medicines derived from human blood or plasma is by definition associated with the risk of infections. Various standard measures are taken to counter this, including the targeted selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, the possibility of transmitting of infective agents cannot be totally excluded when medicinal products prepared from human blood or plasma are administered. This also applies to unknown or emerging viruses and other pathogens. The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV). The measures taken may be of limited value against non enveloped viruses such as hepatitis A virus and parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or certain forms of anaemia.

- **Important missing information**

Not applicable

13.2.4. VI.2.4. Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them.

An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures

13.2.5. VI.2.5. Planned post-authorisation development plan

13.2.5. 1. List of studies in post authorisation development plan

Not applicable

13.2.5. 2. Studies which are a condition of the marketing authorisation

Not applicable

13.2.6. VI.2.6. Summary of changes to the Risk Management Plan over time

Not applicable