References

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Haemate® P, poeder en oplosmiddel voor oplossing voor injectie of infusie.

Name of the medicinal product: Haemate® P 1200 IU vWF/500 IU FVIII, Haemate® P 2400 IU vWF/1000 IU FVIII. Powder and solvent for solution for injection or infusion. **Qualitative and quantitative composition:** Each vial Haemate® P 1200 IU vWF/500 IU FVIII contains nominally 500 IU human coagulation factor VIII (FVIII) and 1200 IU human von Willebrand factor (vWF). After reconstitution with 10 ml water for injections, the solution contains 50 IU/ml of FVIII and 120 IU/ml of vWF. Each vial Haemate® P 2400 IU vWF/1000 IU FVIII contains nominally 1000 IU human coagulation factor VIII (FVIII) and 2400 IU human von Willebrand factor (vWF). After reconstitution with 15 ml water for injections, the solution contains 66,6 IU/ml of FVIII and 160 IU/ml of vWF. The FVIII potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The specific FVIII activity of Haemate P is approximately 2 - 6 IU of FVIII/mg protein The vWF potency (IU) is measured according to ristocetin cofactor activity (vWF:RCo) compared to the International Standard for von Willebrand factor concentrate (WHO)The specific vWF activity of Haemate P is approximately 5 - 17 IU of vWF:RCo/mg protein. Excipient with known effect: Sodium: Haemate P 1200 IU vWF/ 500 IU FVIII: approximately 113 mmol/l (2.6 mg/ml). Haemate P 2400 IU vWF/1000 IU FVIII: approximately 150 mmol/l (3,5 mg/ml). for the full list of excipients, see summary of product characteristics. **Therapeutic indications: Von Willebrand Disease (VWD)** Prophylaxis and treatment of haemorrhage or surgical bleeding, when desmopressin (DDAVP) treatment alone is ineffective or contra-indicated. **Haemophilia A (congenital factor VIII deficiency)** Prophylaxis and treatment of bleeding in patients with haemophilia A. This product may be used in the management of acquired factor VIII deficiency and for treatment of patients with antibodies against factor VIII. **Posology:** Treatment of VWD and Haemophilia A should be supervised by a physician experienced in the treatment of haemostatic disorders. **Von Willebrand's disease:** It is important to calculate the dose using the number of IU of vWF:RCo specified. Generally, 1 IU/kg vWF:RCo raises the circulating level of vWF:RCo by 0.02 IU/ml (2 %). Levels of vWF:RCo of > 0.6 IU/ml (60%) and of FVIII:C of > 0.4 IU/ml (40%) should be achieved. Usually 40 - 80 IU/kg of von Willebrand factor (vWF:RCo) and 20 - 40 IU FVIII:C/kg of body weight (BW) are recommended to achieve haemostasis. An initial dose of 80 IU/kg von Willebrand factor may be required, especially in patients with type 3 von Willebrand disease where maintenance of adequate levels may require greater doses than in other types of von Willebrand disease. Prevention of haemorrhage in case of surgery or severe trauma: For prevention of excessive bleeding during or after surgery the injection should start 1 to 2 hours before the surgical procedure. An appropriate dose should be re-administered every 12 - 24 hours. The dose and duration of the treatment depend on the clinical status of the patient, the type and severity of bleeding, and both vWF:RCo and FVIII:C levels. When using a FVIII-containing von Willebrand factor product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII:C. After 24 - 48 hours of treatment, in order to avoid an uncontrolled rise in FVIII:C, reduced doses and/or prolongation of the dose interval should be considered. Paediatric population: Dosing in children is based on body weight and is therefore generally based on the same guidelines as for adults. The frequency of administration should always be oriented to the clinical effectiveness in the individual case. **Haemophilia A:** Treatment monitoring: During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. In the case of major surgical interventions in particular, a precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable.Individual patients may vary in their response to factor VIII, achieving different levels of in vivo recovery and demonstrating different half-lives. Patients should be monitored for the development of factor VIII inhibitors. See also summary of product characteristics.The dosage and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding and on the patient's clinical condition. It is important to calculate the dose using the number of IU of FVIII:C specified. The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or preferably in IU (relative to an International Standard for factor VIII in plasma). One IU of factor VIII activity is equivalent to that quantity of factor VIII in one ml of normal human plasma. On demand treatment: The calculation of the required dosage of factor VIII is based on the empirical finding that 1 IU factor VIII per kg body weight raises the plasma factor VIII activity by about 2 % (2 IU/dl) of normal activity. The required dosage is determined using the following formula: Required units = body weight [kg] x desired factor VIII rise [% or IU/dl] x 0.5. The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. In the case of the following haemorrhagic events, the factor VIII activity should not fall below the given plasma activity level (in % of normal or IU/dl) within the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

MedDRA SOC	Adverse reaction	Frequency
Blood and Lymphatic System Disorders	Hypervolemia Haemolysis vWF inhibition FVIII inhibition	Unknown Unknown Very rare Uncommon (PTPs)* Very common (PUPs)*
General Disorders and Administration Site Conditions	Fever	Very rare
Immune System Disorders	Hypersensitivity (allergic reactions)	Very rare
Vascular Disorders	Thrombosis Thromboembolic events	Very rare Very rare

Prophylaxis: For long term prophylaxis against bleeding in patients with severe haemophilia A, the usual doses are 20 to 40 IU of factor VIII per kg body weight at intervals of 2 to 3 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary. Paediatric population: There are no data available from clinical studies regarding the dosage of Haemate P in children. **Method of administration:** For intravenous use. Reconstitute the product as described in the summary of product characteristics. The reconstituted preparation should be warmed to room or body temperature before administration. Inject slowly intravenously at a rate comfortable for the patient. Once the product is transferred into the syringe it should be used immediately. In case larger amounts of the factor have to be administered, this can also be done by infusion. For this purpose transfer the reconstituted product into an approved infusion system. The injection or infusion rate should not exceed 4 ml per minute. Observe the patient for any immediate reaction. If any reaction takes place that might be related to the administration of Haemate P, the rate of infusion should be decreased or the application should be stopped, as required by the clinical condition of the patient. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Undesirable effects:** The following adverse reactions are basing on postmarketing experience. Summary of the safety profile: During treatment with Haemate P in adults and adolescents the following adverse reactions may occur: hypersensitivity or allergic reactions, thromboembolic events and pyrexia. Furthermore patients may develop inhibitors to FVIII and vWF. Tabulated list of adverse reactions: The table presented below is according to the MedDRA system organ classification. Frequencies have been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Degree of haemorrhage / Type of surgical procedure	Factor VIII level required (% or IU/dl)	Frequency of doses (hours) / Duration of therapy (days)
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20 - 40	Repeat every 12 - 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleeding or haematoma	30 - 60	Repeat infusion every 12 - 24 hours for 3 - 4 days or more until pain and acute disability are resolved.
Life-threatening haemorrhages	60 - 100	Repeat infusion every 8 - 24 hours until threat is resolved.
Surgery		
Minor including tooth extraction	30 - 60	Every 24 hours, at least 1 day, until healing is achieved.
Major	80 - 100 (pre- en postoperative)	Repeat infusion every 8 - 24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor VIII activity of 30% - 60% (IU/dl).

* Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs = previously-treated patients. Blood and lymphatic system disorders: When very large or frequently repeated doses are needed, or when inhibitors are present or when pre- and post- surgical care is involved, all patients should be monitored for signs of hypervolemia. In addition, those patients with blood groups A, B and AB should be monitored for signs of intravascular haemolysis and/or decreasing haematocrit values. General disorders and administration site conditions: on very rare occasions, fever has been observed. Immune system disorders: Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed very rarely, and may in some cases progress to severe anaphylaxis (including shock). **Von Willebrand Disease:** Blood and lymphatic system disorders: Patients with vWD, especially type 3 patients, may very rarely develop neutralizing antibodies (inhibitors) to vWF. If such inhibitors occur, the condition will manifest itself as an inadequate clinical response. Such antibodies are precipitating and may occur concomitantly to anaphylactic reactions. Therefore, patients experiencing anaphylactic reaction should be evaluated for the presence of an inhibitor. In all such cases, it is recommended that a specialised haemophilia centre be contacted. Vascular disorders: Very rarely, there is a risk of thrombotic/thromboembolic events (including pulmonary embolism). An accurate monitoring of doses and time of administration is necessary, especially in patients with a high risk of thromboembolism (old age, obesity and concomitant use of oral contraceptives). In addition, a clinical evaluation on thrombosis should be performed in patients undergoing surgery. In patients receiving vWF products with FVIII, sustained excessive FVIII:C plasma levels may increase the risk of thrombotic events (see also summary of product characteristics). **Haemophilia A:** Blood and lymphatic system disorders: Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with Haemate P. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. Experience from clinical trials with Haemate P in previously untreated patients (PUPs) is very limited. For safety with respect to transmissible agents, see summary of product characteristics. Reporting of suspected adverse reactions: Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Federal agency for medicines and health products – Department Vigilance - EUROSTATION II – Victor Hortaplein, 40/ 40 -B-1060 Brussels - Website: www.fagg.be e-mail: adversedrugreactions@fagg-afmps.be **Marketing authorisation holder:** CSL Behring GmbH, Emil-von-Behring-Strasse 76, 35041 Marburg, Duitsland, Haemate® P 1200 IU vWF/500 IU FVIII: BE179015, Haemate® P 2400 IU vWF/1000 IU FVIII: BE179024. **Date of revision of the text:** 01/2020. **On medical prescription.**

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Built on data **Haemate® P**

Von Willebrand factor/factor VIII

CSL Behring

Your partner in the treatment of von Willebrand disease

THE RELIABLE CHOICE

- For the treatment of **every type** of von Willebrand disease[1]
- For **every age group**[1]

AWARENESS CAMPAIGN TO IMPROVE DIAGNOSIS

- Gynecologist
- Pediatrician

More then 35 years experience

The reliable choice in the treatment of von Willebrand disease[1-5]

- **Highly active** von Willebrand Factor (vWF) concentrate
  - High content of von Willebrand Factor (Ratio vWF/FVIII = 2.4/1)[2,3,4] minimizes the risk of factor VIII accumulation[2,3,5]
  - High content of High Molecular Weight (HMW) von Willebrand Factor multimers, similar as in human plasma[2,3,4,5]
- **Highly effective** in treatment on demand[3,4], in prophylaxis[4,5,6] and surgical[7] procedures
  - High efficacy, rated excellent / good in 95-100% of patients treated for von Willebrand disease (VWD)
- **High level of confidence** based on
  - > 35 years of clinical experience
  - Excellent safety record[4,5,8]
- **High level of convenience**
  - Reconstitution with Mix2Vial[1]
  - Storage < 25°C for the complete shelf life[1]

2 Vial sizes

- Haemate P 2400/1000 (vWF/FVIII) 10ml
- Haemate P 1200/500 (vWF/FVIII) 15ml

Mix2Vial

- included for reconstitution

Built on data **Haemate® P**

Von Willebrand factor/factor VIII