

**EU PACKAGE LEAFLET – EU-PI (PI/EU/ENGLISH)**

**HAEMATE P<sup>®</sup> 250/500/1000**

**Rev.: 30-JUN-2022** / revision of EU text to reduce stability after reconstitution

Supersedes previous versions

### Package Leaflet: Information for the user

#### **Haemate<sup>®</sup> P 250 IU FVIII / 600 IU VWF**

Powder and solvent for solution for injection or infusion

#### **Haemate<sup>®</sup> P 500 IU FVIII / 1200 IU VWF**

Powder and solvent for solution for injection or infusion

#### **Haemate<sup>®</sup> P 1000 IU FVIII / 2400 IU VWF**

Powder and solvent for solution for injection or infusion.

Human von Willebrand factor,  
Human coagulation factor VIII

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet:**

1. What Haemate P is and what it is used for
2. What you need to know before you use Haemate P
3. How to use Haemate P
4. Possible side effects
5. How to store Haemate P
6. Contents of the pack and other information

#### **1. What Haemate P is and what it is used for**

##### ***What is Haemate P?***

Haemate P is presented as powder and solvent. The made up solution is to be given by injection or infusion into a vein.

Haemate P is made from human plasma (this is the liquid part of the blood) and it contains human von Willebrand factor and human coagulation factor VIII.

##### ***What is Haemate P used for?***

As Haemate P contains both FVIII and VWF, it is important to know which factor you most need. If you have haemophilia A your doctor will prescribe you Haemate P with the number of units of

FVIII specified. If you have VWD your doctor will prescribe you Haemate P with the number of units of VWF specified.

#### Von Willebrand disease (VWD)

Haemate P is used for the prevention and treatment of bleedings or surgical bleeding caused by the lack of von Willebrand factor, when desmopressin (DDAVP) treatment alone is ineffective or contra-indicated.

#### Haemophilia A (congenital factor VIII deficiency)

Haemate P is used to prevent or to stop bleedings caused by the lack of factor VIII in the blood.

It may also be used in the management of acquired factor VIII deficiency and for treatment of patients with antibodies against factor VIII.

## 2. What you need to know before you use Haemate P

The following sections contain information that your doctor should consider before you are given Haemate P.

### **Do NOT use Haemate P:**

- if you are hypersensitive (allergic) to human von Willebrand Factor or human coagulation factor VIII or any of the other ingredients of Haemate P (see section 6.).

**Please inform your doctor if you are allergic to any medicine or food.**

### **Warnings and precautions**

#### ***Traceability***

It is strongly recommended that every time you receive a dose of Haemate P the name and batch number of the medicine are recorded in order to maintain a record of the batches used.

Talk to your doctor or pharmacist before using **Haemate P:**

- **in case of allergic or anaphylactic-type reactions** (a serious allergic reaction that causes severe difficulty in breathing or dizziness). Allergic hypersensitivity reactions are possible. Your doctor should inform you **of the early signs of hypersensitivity reactions**, such as hives, generalised skin rash, tightness of the chest, wheezing, fall in blood pressure and anaphylaxis (a serious allergic reaction that causes severe difficulty in breathing, or dizziness). **If these symptoms occur, you should stop the use of the product immediately and contact your doctor.**
- The formation of **inhibitors** (antibodies) is a known complication that can occur during treatment with all factor VIII medicines. These inhibitors, especially at high levels, stop the treatment working properly and you or your child will be monitored carefully for the development of these inhibitors. If your or your child's bleeding is not being controlled with Haemate P, tell your doctor immediately.

- if you have been told you have heart disease or are at risk for heart disease, tell your doctor or pharmacist.
- if for the administration of Haemate P you will require a central venous access device (CVAD), the risk of CVAD-related complications including local infections, bacteria in the blood (bacteremia) and the formation of a blood clot in the blood vessel (thrombosis) where the catheter is inserted should be considered by your doctor.

#### Von Willebrand disease

- In case you have a known risk of developing blood clots (thrombotic events including blood clots in the lung), particularly in case you have known clinical or laboratory risk factors (e.g. in the perioperative period without conduct of thromboprophylaxis, no early mobilization, obesity, overdose, cancer). In this case, you must be monitored for early signs of thrombosis. Prophylaxis against venous thrombosis should be instituted, according to the current recommendations.

Your doctor will consider carefully the benefit of treatment with Haemate P compared with the risk of these complications.

#### ***Virus safety***

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:

- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and
- the testing of each donation and pools of plasma for signs of virus/infections.
- the inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses.

Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV, the AIDS virus), hepatitis B virus and hepatitis C virus (inflammation of the liver) and for the non-enveloped hepatitis A virus (inflammation of the liver).

The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.

Parvovirus B19 infection may be serious

- for pregnant women (infection of the unborn child) and
- for individuals with a depressed immune system or with an increased production of red blood cells due to certain types of anaemia (e.g. sickle cell anaemia or haemolytic anaemia).

Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived von Willebrand factor and coagulation factor VIII products.

#### **Other medicines and Haemate P**

- Tell your doctor or pharmacist if you are taking, have recently taken or might take any medicines, including medicines obtained without a prescription.
- Haemate P must not be mixed with other medicinal products, diluents or solvents.

#### **Pregnancy, breast-feeding and fertility**

- If you are pregnant or breast-feeding, please ask your doctor or pharmacist for advice before taking any medicine.
- Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breastfeeding is not available.
- In case of von Willebrand disease women are even more affected than men, because of additional bleeding risks like menstruation, pregnancy, labour, child birth and gynecological complications. Based on post-marketing experience substitution of VWF in the prevention and treatment of acute bleedings can be recommended. There are no clinical studies available on substitution therapy with VWF in pregnant or lactating women.
- During pregnancy and breast-feeding Haemate P should be given only if it is clearly indicated.

#### **Driving and using machines**

Haemate P has no influence on the ability to drive and use machines.

#### **Haemate P contains sodium**

Haemate 250 IU FVIII / 600 IU VWF contain less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

Haemate P 500 IU FVIII / 1200 IU VWF contain 26 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 1.3% of the recommended maximum daily dietary intake of sodium for an adult.

Haemate P 1000 IU FVIII / 2400 IU VWF contain 52.5 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 2.6 % of the recommended maximum daily dietary intake of sodium for an adult.

### **3. How to use Haemate P**

Treatment should be started and supervised by a physician who is experienced in this type of disorder.

#### **Dosage**

The amount of von Willebrand factor and factor VIII you need and the duration of treatment will depend on several factors, such as your body weight, the severity of your disease, the site and

intensity of the bleeding or the need to prevent bleeding during an operation or investigation (see section “*The following information is intended for medical or healthcare professionals only*”). If you have been prescribed Haemate P to use at home, your doctor will make sure that you are shown how to inject it and how much to use.

**Follow the directions given to you by your doctor or haemophilia center nurse.**

***If you use more Haemate P than you should***

No symptoms of overdose with VWF and FVIII have been reported. However, the risk of developing blood clots (thrombosis) cannot be excluded in case of an extremely high dose, especially in the case of VWF products with a high FVIII content.

**Reconstitution and application**

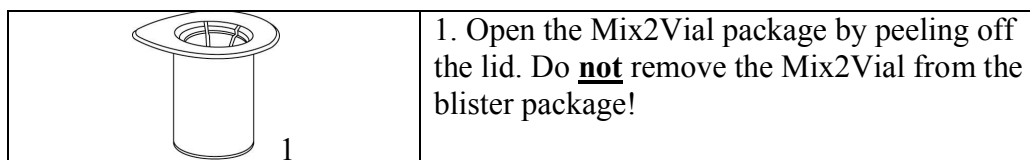
***General instructions***

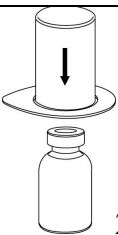
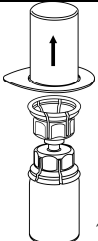
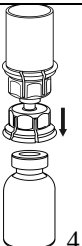
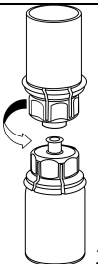

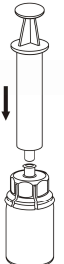
- The powder must be mixed (reconstituted) with the diluent (liquid) and withdrawn from the vial under aseptic conditions.
- The solution should be clear or slightly opalescent. After filtering/withdrawal (see below) the reconstituted product should be inspected visually for particulate matter and discoloration prior to administration. Even if the directions for use for the reconstitution procedure are precisely followed, it is not uncommon for a few flakes or particles to remain. The filter included in the Mix2Vial device removes those particles completely. Filtration does not influence dosage calculations.
- Do not use visibly cloudy solutions or solutions still containing flakes or particles after filtration.
- After administration any unused product or waste material should be disposed of in accordance with national requirements and as instructed by your doctor.

***Reconstitution:***

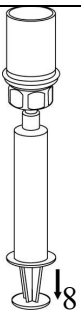
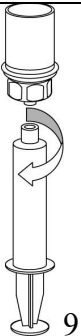
Without opening either vial, warm the Haemate P powder and the solvent to room temperature. This can be done either by leaving the vials at room temperature for about an hour, or by holding them in your hands for a few minutes. **DO NOT** expose the vials to direct heat. The vials must not be heated above body temperature (37°C).

Carefully remove the protective caps from the diluent vial and the Haemate P vial. Clean the exposed rubber stoppers of both vials with one alcohol swab each and allow them to dry. The diluent can now be transferred to the powder with the administration set (Mix2Vial) attached. Please follow the instructions given below.



 <p style="text-align: right;">2</p>	<p>2. Place the <b>solvent</b> vial on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the blue adapter end <b>straight down</b> through the solvent vial stopper.</p>
 <p style="text-align: right;">3</p>	<p>3. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling <b>vertically</b> upwards. Make sure that you only pull away the blister package and not the Mix2Vial set.</p>
 <p style="text-align: right;">4</p>	<p>4. Place the Haemate P vial on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the transparent adapter end <b>straight down</b> through the Haemate P vial stopper. The solvent will automatically flow into the Haemate P vial.</p>
 <p style="text-align: right;">5</p>	<p>5. With one hand grasp the Haemate P side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew the set carefully into two pieces to avoid excessive build up of foam when dissolving the Haemate P. Discard the solvent vial with the blue Mix2Vial adapter attached.</p>
 <p style="text-align: right;">6</p>	<p>6. Gently swirl the Haemate P vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.</p>
 <p style="text-align: right;">7</p>	<p>7. Draw air into an empty, sterile syringe. While the Haemate P vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting. Inject air into the Haemate P vial.</p>

***Withdrawal and application:***

	<p>8. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly.</p>
	<p>9. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe.</p>

### ***Application***

For intravenous use.

For injection of Haemate P the use of plastic disposable syringes is recommended as the ground glass surfaces of all-glass syringes tend to stick with solutions of this type.

The reconstituted solution should be administered slowly intravenously at a rate not more than 4 ml per minute. Take care that no blood enters the syringe filled with product. 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. Infusion should be carried out as instructed by your doctor.

Observe yourself for any immediate reaction. If any reaction takes place that might be related to the administration of Haemate P, the injection/infusion should be stopped. (see also section 2.).

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

### **4. Possible side effects**

Like all medicines, Haemate P can cause side effects, although not everybody gets them.

The following side effects have been observed very rarely (less than 1 of 10,000 patients):



- A sudden allergic reaction (such as 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).
- Increase in body temperature (fever).

#### *Von Willebrand disease*

- Very rarely, there is a risk of thrombotic/thromboembolic events including blood clots in the lung (risk of formation and migration of blood clots into the arterial/venous vessel system with a potential impact on organ systems).
- In patients receiving VWF products sustained excessive FVIII:C plasma levels may increase the risk of formation of blood clots (see also section 2.).
- Patients with VWD may very rarely develop inhibitors (neutralising antibodies) to VWF. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response leading to continuous bleeding. This happens especially in patients with a specific form of von Willebrand disease, the so-called type 3. 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 such cases, it is recommended that a specialised haemophilia centre be contacted.

#### *Haemophilia A*

- For children not previously treated with Factor VIII medicines, inhibitor antibodies (see section 2) may form very commonly (more than 1 in 10 patients); however patients who have received previous treatment with Factor VIII (more than 150 days of treatment) the risk is uncommon (less than 1 in 100 patients). If this happens your or your child's medicines may stop working properly and you or your child may experience persistent bleeding. If this happens, you should contact your doctor immediately.

#### **Side effects in children and adolescents**

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

#### **Reporting of side effects**

If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V [to be completed nationally]. By reporting side effects you can help provide more information on the safety of this medicine.

#### **5. How to store Haemate P**

- **Keep this medicine out of the sight and reach of children.**
- Do not use this medicine after the expiry date, which is stated on the label and carton.
- Do not store above 25°C.

- Do not freeze.
- Keep the vial in the outer carton, in order to protect from light.
- Haemate P does not contain a preservative so the made-up solution should preferably be used immediately.
- If the made-up solution is not administered immediately it must be used within 3 hours.
- Once the product is transferred into the syringe it should be used immediately.

## 6. Contents of the pack and other information

### What Haemate P contains

***The active substance is:***

human von Willebrand factor and human coagulation factor VIII.

***The other ingredients are:***

Human albumin, aminoacetic acid, sodium citrate, sodium chloride, sodium hydroxide or hydrochloric acid (in small amounts for pH adjustment)

*Solvent:* Water for injections

### What Haemate P looks like and contents of the pack

Haemate P is presented as a white powder and is supplied with water for injections as solvent. The made-up solution should be clear or slightly opalescent, i.e. it might sparkle when held up to the light but must not contain any obvious particles.

### ***Presentations***

*Pack with 250 IU FVIII / 600 IU VWF containing:*

- 1 vial with powder
- 1 vial with 5 ml water for injections
- 1 filter transfer device 20/20

Administration set (inner box):

- 1 disposable 5 ml syringe
- 1 venipuncture set
- 2 alcohol swabs
- 1 non-sterile plaster

*Pack with 500 IU FVIII / 1200 IU VWF containing:*

- 1 vial with powder
- 1 vial with 10 ml water for injections
- 1 filter transfer device 20/20

Administration set (inner box):

- 1 disposable 10 ml syringe
- 1 venipuncture set
- 2 alcohol swabs
- 1 non-sterile plaster

CSL Behring

Haemate® P 250/500/1000

PI/EU/English, Rev.: 30-Jun-2022 / revision of EU text to reduce stability after reconstitution

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*Pack with 1000 IU FVIII / 2400 IU VWF containing:*

1 vial with powder

1 vial with 15 ml water for injections

1 filter transfer device 20/20

Administration set (inner box):

- 1 disposable 20 ml syringe

- 1 venipuncture set

- 2 alcohol swabs

- 1 non-sterile plaster

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder and Manufacturer**

CSL Behring GmbH

Emil-von-Behring-Str. 76

35041 Marburg

Germany

**This leaflet was last revised in June 2022.**

### **Reg. No.:**

Haemate® P 250 I.E. FVIII / 600 I.E. VWF [To be completed nationally]

Haemate® P 500 I.E. FVIII / 1200 I.E. VWF [To be completed nationally]

Haemate® P 1000 I.E. FVIII / 2400 I.E. VWF [To be completed nationally]

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**The following information is intended for healthcare professionals only**

### **Posology**

#### ***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. Individual patients may vary in their response to factor VIII, achieving different levels of in vivo recovery and demonstrating different half-lives. Dose based on bodyweight may require adjustment in underweight or overweight patients. 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.

Patients should be monitored for the development of factor VIII inhibitors. See also section 2.

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 concentrate 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:

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- and 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).
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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.

**Special warnings and special precautions for use**

When using a VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII:C. In patients receiving FVIII-containing VWF products, plasma levels of FVIII:C should be monitored to avoid sustained excessive FVIII:C plasma levels which may increase the risk of thrombotic events, and antithrombotic measures should be considered.

For further information regarding for developing of antibodies in context of a therapy of haemophilia A or von Willebrand disease please refer to the expert information, section 4.4 and 4.8.

**Undesirable effects**

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.