FULL PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

Haemate® P 250 IU FVIII / 600 IU VWF
Powder and solvent for solution for injection or infusion

Haemate® P 500 IU FVIII / 1200 IU VWF
Powder and solvent for solution for injection or infusion

Haemate® P 1000 IU FVIII / 2400 IU VWF
Powder and solvent for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial Haemate P 250 IU FVIII / 600 IU VWF contains nominally:
250 IU human coagulation factor VIII (FVIII).
600 IU human von Willebrand factor (VWF).
After reconstitution with 5 ml water for injections the solution contains
50 IU/ml of FVIII and 120 IU/ml of VWF.

One vial Haemate P 500 IU FVIII / 1200 IU VWF contains nominally:
500 IU human coagulation factor VIII (FVIII).
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.

One vial Haemate P 1000 IU FVIII / 2400 IU VWF contains
nominally: 1000 IU human coagulation factor VIII (FVIII).
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.

Haemate P is produced from the plasma of human donors.

Excipient with known effect:
Sodium:
Haemate P 250 IU FVIII / 600 IU VWF and Haemate P 500 IU FVIII / 1200 IU VWF – approximately 113 mmol/l (2.6 mg/ml)
Haemate P 1000 IU FVIII / 2400 IU VWF – approximately 150 mmol/l (3.5 mg/ml)

For the full list of excipients, see section 11 (Description).

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection or infusion.
White powder and clear, colourless solvent for solution for injection/infusion.

4 INDICATIONS AND USAGE

Congenital and acquired deficiency of blood clotting factor VIII:
severe or moderate haemophilia,
prophylaxis during operation.

Von Willebrand's disease.

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.

Von Willebrand Disease (VWD)
Prophylaxis and treatment of haemorrhage or surgical bleeding, when desmopressin (DDAVP) treatment alone is ineffective or contra-indicated.

5 DOSAGE AND ADMINISTRATION

Treatment of VWD and Haemophilia A should be supervised by a physician experienced in the treatment of haemostatic disorders.

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

It is important to calculate the dose using the number of IU of FVIII:C specified.

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.

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 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).

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.

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.

Previously untreated patients
The safety and efficacy of Haemate P in previously untreated patients have not yet been established.

Paediatric population
There are no data available from clinical studies regarding the dosage of Haemate P in children.

Method of administration

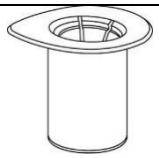
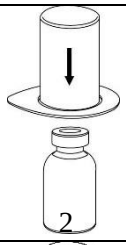
For intravenous use.
Reconstitute the product as described in section 5.1. The reconstituted preparation should be warmed to room or body temperature before administration. Inject slowly intravenously at a rate comfortable for the patient. Once the product is transferred into the syringe it should be used immediately.

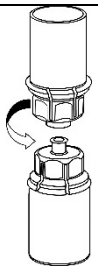
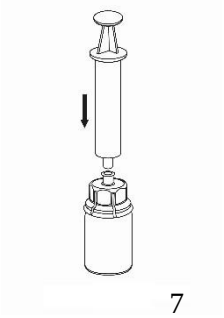
In case larger amounts of the factor have to be administered, this can also be done by infusion. For this purpose transfer the reconstituted product into an approved infusion system.

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.

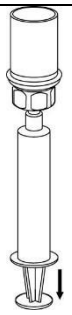
5.1 Reconstitution

Bring the solvent to room temperature. Ensure product and solvent vial flip caps are removed and the stoppers are treated with an antiseptic solution and allowed to dry prior to opening the Mix2Vial package.

 1	1. Open the Mix2Vial package by peeling off the lid. Do **not** remove the Mix2Vial from the blister package!
 2	2. Place the **solvent 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 **straight down** through the solvent vial stopper.
 3	3. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set.
 4	4. Place the **product 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 **straight down** through the product vial stopper. The solvent will automatically flow into the product vial.

 5	5. With one hand grasp the product-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 product. Discard the solvent vial with the blue Mix2Vial adapter attached.
 6	6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.
 7	7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial´s Luer Lock fitting. Inject air into the product vial.

Withdrawal and application

 8	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.
 9	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.

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.

Administer solution slowly intravenously (see section 5), taking care to ensure that no blood enters the syringe filled with product.

Any unused product or waste material should be disposed of in accordance with national requirements.

5.2 Administration

HAEMATE P is for intravenous use only.

- The solution should be clear or slightly opalescent. After filtering/withdrawal, 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.

- From a microbiological point of view and as Haemate P contains no preservative, the reconstituted product should be used immediately. If it is not administered immediately, storage shall not exceed 8 hours below 25°C. Once the product has been transferred into a syringe it should be used immediately.

- Discard the administration equipment and any unused HAEMATE P after use.

6 CONTRAINDICATIONS

HAEMATE P is contraindicated in individuals who have had an anaphylactic or severe systemic reaction to antihemophilic factor or von Willebrand factor preparations.

Hypersensitivity to the active substance or to any of the excipients listed in section 11 (Description).

7 WARNINGS AND PRECAUTIONS

7.1 Thromboembolic Events (VWD Patients)

Thromboembolic events have been reported in VWD patients receiving Antihemophilic Factor/von Willebrand Factor Complex replacement therapy, especially in the setting of known risk factors for thrombosis.[3,4] Early reports indicate a higher incidence may occur in females. Endogenous high levels of FVIII have also been associated with thrombosis, but no causal relationship has been established. Exercise caution and consider antithrombotic measures in all at-risk VWD patients who are receiving coagulation factor replacement therapy.

7.2 Monitoring for Intravascular Hemolysis

HAEMATE P contains blood group isoagglutinins (anti-A and anti-B). When doses are very large or need to be repeated frequently (for example, when inhibitors are present or when pre- and post-surgical care is involved), monitor patients of blood groups A, B, and AB for signs of intravascular

hemolysis and decreasing hematocrit values and treat appropriately.

7.3 Monitoring VWF:RCo and FVIII Levels

Monitor the VWF:RCo and FVIII levels of VWD patients receiving HAEMATE P using standard coagulation tests, especially in cases of surgery. It is advisable to monitor trough VWF:RCo and FVIII:C levels at least once a day in order to adjust the dosage of HAEMATE P as needed to avoid excessive accumulation of coagulation factors .

7.4 Transmission of Infectious Agents

Because HAEMATE P is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent . The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacturing.

Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Thus the risk of transmission of infectious agents cannot be eliminated completely.

Some viruses, such as Parvovirus B19 virus (B19V) or hepatitis A (HAV), are particularly difficult to remove or inactivate. B19V may most seriously affect pregnant women and immune-compromised individuals.

Although the overwhelming number of B19V and HAV cases are community acquired, reports of these infections have been associated with the use of some plasma-derived products. Therefore, physicians should be alert to the potential symptoms of B19V and HAV infections.

Symptoms of B19V may include low-grade fever, rash, arthralgia, and transient symmetric, nondestructive arthritis. Diagnosis is often established by measuring B19V-specific IgM and IgG antibodies. Symptoms of HAV include low-grade fever, anorexia, nausea, vomiting, fatigue, and jaundice. A diagnosis may be established by measuring specific IgM antibodies.

Physicians should strongly consider administration of hepatitis A and hepatitis B vaccines to individuals receiving plasma derivatives. Potential risks and benefits of vaccination should be weighed by the physician and discussed with the patient.

8 ADVERSE REACTIONS

The most serious adverse reaction observed in patients receiving HAEMATE P is anaphylaxis. Thromboembolic events have also been observed in patients receiving HAEMATE P for the treatment of VWD . Reports of thromboembolic events in VWD patients with other thrombotic risk factors receiving coagulation factor replacement therapy have been obtained from spontaneous reports, published literature, and a European clinical study. In some cases, inhibitors to coagulation factors may occur. However, no inhibitor formation was observed in any of the clinical studies.

In patients receiving HAEMATE P in clinical studies for treatment of VWD, the most commonly reported adverse reactions observed by >5% of subjects are allergic-anaphylactic reactions

(including urticaria, chest tightness, rash, pruritus, and edema). For patients undergoing surgery, the most common adverse reactions are postoperative wound and injection-site bleeding, and epistaxis.

8.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates obseved cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

Treatment of Bleeding Episodes in VWD

Allergic symptoms, including allergic reaction, urticaria, chest tightness, rash, pruritus, and edema, were reported in 6 of 97 (6%) subjects in a Canadian retrospective study. Four of 97 (4%) subjects experienced seven adverse events that were considered to have a possible or probable relationship to HAEMATE P. These included chills, phlebitis, vasodilation, paresthesia, pruritus, rash, and urticaria. All were mild in intensity with the exception of a moderate case of pruritus.

In a prospective, open-label safety and efficacy study of HAEMATE P in VWD subjects with serious life- or limb-threatening bleeding or undergoing emergency surgery, seven of 71 (10%) subjects experienced nine adverse reactions. These were one occurrence each of mild vasodilation and mild pruritis; two occurrences of mild paresthesia; and one occurrence each of moderate peripheral edema and extremity pain and severe pseudothrombocytopenia (platelet clumping with a false low reading). HAEMATE P was discontinued in the subject who experienced the peripheral edema and extremity pain.

Prevention of Excessive Bleeding During and After Surgery in VWD

Among the 63 VWD subjects who received HAEMATE P for prevention of excessive bleeding during and after surgery, including one subject who underwent colonoscopy without the planned polypectomy, the most common adverse events were postoperative hemorrhage (35 events in 19 subjects with five subjects experiencing bleeding at up to three different sites), postoperative nausea (15 subjects), and postoperative pain (11 subjects). Table 6 presents the postoperative hemorrhagic adverse events.

Table 6. Hemorrhagic Adverse Events in 63 Surgical Subjects

Adverse Event	Surgical Procedure Category	Number of Subjects/ Events	Onset* (Number of Events)		Severity (Number of Events)		
			On	Post	Mild	Mod	Severe
Wound/injection site bleeding	Major	8/11	7	4	9	–	2
	Minor	2/2	2	–	1	1	–
	Oral	2/6	–	6	3	3	–
Epistaxis	Major	4/4	2	2	3	1	–
	Minor	1/1	1	–	1	–	–
Cerebral hemorrhage/ subdural hematoma	Major	1/2	2†	–	–	2	–
Gastrointestinal bleeding	Major	1/3	3‡	–	–	2	1

Menorrhagia	Major	1/1	1§	–	–	1	–
Groin bleed	Oral	1/1	–	1	1	–	–
Ear bleed	Major	1/1	1	–	1	–	–
Hemoptysis	Major	1/1	1	–	1	–	–
Hematuria	Major	1/1	1	–	1	–	–
Shoulder bleed	Major	1/1	1	–	1	–	–

* On = on-therapy; onset while receiving HAEMATE P or within 1 day of completing HAEMATE P administration. Post = post-therapy; onset at least one day after completing HAEMATE P administration.
† Reported as serious adverse events following intracranial surgery.
‡ Two of these events were reported as serious adverse events following gastrojejunal bypass.
§ Reported as a serious adverse event requiring hysterectomy following hysteroscopy and dilation and curettage.

Table 7 lists the non-hemorrhagic adverse events reported in at least two subjects, regardless of causality, and the adverse events that were possibly related to HAEMATE P. Pulmonary embolus considered possibly related to HAEMATE P occurred in one elderly subject who underwent bilateral knee replacement.

Table 7. Non-Hemorrhagic and Possibly Related Adverse Events in 63 Surgical Subjects

Body System	Adverse Event (AE)	Number of Subjects with an AE Possibly Related to HAEMATE P	Number of Subjects with an AE Regardless of Causality*
Body as a whole	Pain	–	11
	Fever	–	4
	Abdominal pain	–	3
	Infection	–	3
	Surgery	–	3

Body System	Adverse Event (AE)	Number of Subjects with an AE Possibly Related to HAEMATE P	Number of Subjects with an AE Regardless of Causality*
	Back pain	–	2
	Facial edema	–	2
Cardiovascular	Chest pain	–	3
	Pulmonary embolus†	1	1
	Thrombophlebitis†	1	1
Digestive	Nausea	1	15
	Constipation	–	7
	Vomiting	1	3
	Sore throat	–	2
Hemic and lymphatic system	Anemia/decreased hemoglobin	–	2
Metabolic/nutritional	Increased SGPT	1	1
Nervous	Dizziness	1	5
	Headache	1	4
	Increased sweating	–	3
	Insomnia	–	2
Skin and appendages	Pruritus	–	3
	Rash	1	1
Urogenital	Urinary retention	–	4
	Urinary tract infection	–	2

* Events occurring in two or more subjects.
† Events occurring in separate subjects.

Eight subjects experienced 10 postoperative serious adverse events: one with subdural hematoma and intracerebral bleeding following intracranial surgery related to an underlying cerebrovascular abnormality; one with two occurrences of gastrointestinal bleeding following gastrojejunal bypass; and one each with sepsis, facial edema, infection, menorrhagia requiring hysterectomy following hysteroscopy and dilation and curettage, pyelonephritis, and pulmonary embolus.

8.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of HAEMATE P. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HAEMATE P exposure.

Adverse reactions reported in patients receiving HAEMATE P for treatment of VWD or hemophilia A are allergic-anaphylactic reactions (including urticaria, chest tightness, rash, pruritus, edema, and shock), development of inhibitors to FVIII, and hemolysis. Additional adverse reactions reported for VWD are thromboembolic complications, chills and fever, and hypervolemia.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/

and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

9 DRUG INTERACTIONS

None reported.

10 USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Animal reproduction studies have not been conducted with HAEMATE P. It is also not known whether HAEMATE P can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HAEMATE P should be given to a pregnant woman only if clearly needed.

10.2 Labor and Delivery

It is not known whether HAEMATE P can cause harm to the mother or the fetus when administered during labor and delivery. HAEMATE P should be given during labor and delivery only if clearly needed.

10.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HAEMATE P is administered to a nursing woman.

10.4 Pediatric Use

HemophiliaA

Adequate and well-controlled studies with long-term evaluation of joint damage have not been done in pediatric subjects. Joint damage may result from suboptimal treatment of hemarthroses.

VWD

The safety and effectiveness of HAEMATE P for the treatment of VWD was demonstrated in 26 pediatric subjects, including infants, children, and adolescents, but have not been evaluated in neonates. The safety of HAEMATE P for the prevention of excessive bleeding during and after surgery was demonstrated in eight pediatric subjects (ages 3 to 15) with VWD. Of the 34 pediatric subjects studied for either treatment of bleeding episodes in VWD or prevention of excessive bleeding during and after surgery, four were infants (1 month to under 2 years of age), 23 were children (2 through 12 years), and seven were adolescents (13 through 15 years).

As in adults, pediatric patients should be dosed based on body weight (kg).

10.5 Geriatric Use

Clinical studies of HAEMATE P did not include sufficient numbers of subjects 65 years of age

and older to determine whether they respond differently from younger subjects. As for all patients, dosing for geriatric patients should be appropriate to their overall situation.

11 DESCRIPTION

HAEMATE P, Antihemophilic Factor/von Willebrand Factor Complex (Human), is a purified, sterile, lyophilized concentrate of Factor VIII (FVIII) and von Willebrand Factor (VWF) (Human) for intravenous administration in the treatment of patients with classical hemophilia (hemophilia A) and VWD .

HAEMATE P is purified from the cold insoluble fraction of pooled human plasma. The pooled human plasma used to produce HAEMATE P is collected from licensed facilities in the United States (US). All source plasma used in the manufacture of HAEMATE P is tested by FDA-licensed Nucleic Acid Tests (NAT) for hepatitis C virus (HCV), human immunodeficiency virus-1 (HIV-1), hepatitis A virus (HAV), and hepatitis B virus (HBV) and found to be nonreactive (negative).

Each vial of HAEMATE P contains the labeled amount of von Willebrand Factor:Ristocetin Cofactor (VWF:RCo) and FVIII activity expressed in International Units (IU) , as defined by the current international standard established by the World Health Organization. One International Unit (IU) of VWF:RCo or FVIII is approximately equal to the amount of VWF:RCo or FVIII in 1.0 mL of fresh-pooled human plasma. The average ratio of VWF:RCo to FVIII is 2.4:1. Fibrinogen content in HAEMATE P is less than or equal to 0.2 mg/mL. HAEMATE P contains anti-A and anti-B blood group isoagglutinins .

When reconstituted with the volume of Sterile Water for Injection, USP provided, each mL of HAEMATE P contains 72 to 224 International Units (IU) VWF:RCo activity[*], 40 to 80 International Units (IU) FVIII activity, 15 to 33 mg of glycine, 3.5 to 9.3 mg of sodium citrate, 2 to 5.3 mg of sodium chloride, 8 to 16 mg of Albumin (Human), 2 to 4 mg of other proteins, and 10 to 20 mg of total proteins. HAEMATE P contains no preservative.

The manufacturing procedure for HAEMATE P includes multiple processing steps that reduce the risk of virus transmission. The virus inactivation/removal capacity consists of four steps:

- Cryoprecipitation
- $Al(OH)_3$ adsorption, glycine precipitation, and NaCl precipitation, studied in combination
- Heat treatment at 60°C for 10 hours in aqueous solution
- Lyophilization

[*] This correlates to a VWF:RCo to FVIII activity average ratio of 2.4:1, which is used to calculate the nominal values of VWF:RCo activity and is the average VWF:RCo activity.

The total cumulative virus reductions range from 6.0 to ≥11.7 $\log_{10}$ as shown in Table 8.

Table 8. Cumulative Virus Reduction Factors for HAEMATE P

Manufacturing Step	Virus Reduction Factor (log_{10})						
	Enveloped Viruses				Non-Enveloped Viruses		
	HIV-1	BVDV	PRV	WNV	HAV	CPV	B19V
Cryoprecipitation	ND	ND	1.6	ND	ND	1.9	ND
$Al(OH)_3$ Adsorption/ Glycine Precipitation/ NaCl Precipitation	3.8	2.8	3.9	ND	2.3	3.0	ND
Heat Treatment*	≥6.4	≥8.9	4.7	≥7.8	4.2	1.1	≥3.9†
Lyophilization	ND	ND	ND	ND	1.3	ND	ND
Cumulative Virus Reduction [log_{10}]	**≥10.2**	**≥11.7**	**10.2**	**NA**	**7.8**	**6.0**	**NA**

HIV-1, human immunodeficiency virus type 1, model for HIV-1 and HIV-2
BVDV, bovine viral diarrhea virus, model for HCV
PRV, pseudorabies virus, model for large enveloped DNA viruses
WNV, West Nile virus
HAV, hepatitis A virus
CPV, canine parvovirus, model for B19V
B19V, human parvovirus B19
ND, not determined
NA, not applicable
* At 60°C for 10 hours in aqueous solution.
† The virus evaluation studies for B19V employed a novel experimental infectivity assay using a clone of the cell line UT7 that contains erythropoietic progenitor cells; (residual) virus titer was determined using an immunofluorescence-based detection method.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The active components of HAEMATE P consist of two different noncovalently bound proteins (FVIII and VWF). FVIII is an essential cofactor in activation of factor X, leading ultimately to the formation of thrombin and, subsequently, fibrin. VWF promotes platelet aggregation and platelet adhesion on damaged vascular endothelium; activated platelets interact with clotting proteins to form a clot. VWF also serves as a stabilizing carrier protein for the procoagulant protein FVIII.[5,6] The activity of VWF is measured as VWF:RCo.

12.2 Pharmacokinetics

HemophiliaA

After infusion of HAEMATE P, a rapid increase of plasma FVIII:C is followed by a rapid decrease in activity and, subsequently, a slower rate of decrease in activity. Studies with HAEMATE P in subjects with hemophilia A have demonstrated a mean half-life of 12.2 (range: 8.4 to 17.4) hours.

VWD

The pharmacokinetics of HAEMATE P were studied in 41 subjects in a US study and in 28 subjects in a European study. In both studies, subjects were evaluated in the nonbleeding state prior to a surgical procedure. Table 9 summarizes the pharmacokinetics of HAEMATE P based on these

studies. Wide inter-subject variability was observed in pharmacokinetic values obtained from these studies.

Table 9. Pharmacokinetics of HAEMATE P in Two Studies of Subjects in the Non-Bleeding State Prior to Surgery

	US Study	European Study
Number of subjects Type 1 VWD Type 2A VWD Type 2B VWD Type 2M VWD Type 3 VWD	41 16 2 4 6 13	28 10 10 -- 1 7
Dosage of HAEMATE P	60 IU VWF:RCo/kg BW	80 IU VWF:RCo/kg BW
Median terminal half-life of VWF:RCo (range)	11 hours* (3.5-33.6)	10 hours† (2.8-28.3)
Median clearance (range)	3.1 mL/hr/kg (1-16.6)	4.8 mL/hr/kg (2.1-53)
Volume of distribution at steady state (range)	53 mL/kg (29-141)	59 mL/kg (32-290)
Median IVR for VWF:RCo activity (range)	2.4 IU/dL per IU/kg (1.1-4.2)	1.9 IU/dL per IU/kg (0.6-4.5)

IU = International Units.
BW = body weight.
* Excluding 5 subjects with a half-life exceeding the blood sampling time of 24 or 48 hours.
† Excluding 1 subject with a half-life exceeding the blood sampling time of 48 hours.

HAEMATE P has been demonstrated in several studies to contain the high molecular weight multimers of VWF. The presence of a multimeric composition of VWF in HAEMATE P is similar to that found in normal plasma and this component is considered to be important for correcting the coagulation defect in patients with VWD.[7,8]

The multimeric patterns of HAEMATE P in the US study were measured in 13 subjects with type 3 VWD; 11 had absent or barely detectable multimers at baseline. Of those 11 subjects, all had some high molecular weight multimers present 24 hours after infusion of HAEMATE P. In the European study, infusion of HAEMATE P corrected the defect of the multimer pattern in subjects with types 2A and 3 VWD. High molecular weight multimers were detectable until at least 8 hours after infusion.

Based on the small sample size evaluation, it appears that age, sex, and type of VWD have no impact on the pharmacokinetics of VWF:RCo.

13 CLINICAL STUDIES

Controlled clinical studies to evaluate the safety and efficacy of prophylactic dosing with HAEMATE P to prevent spontaneous bleeding have not been conducted in VWD subjects. Adequate data are not presently available on which to evaluate or to base dosing

recommendations in this setting.

13.1 Treatment of Bleeding Episodes in VWD

Clinical efficacy of HAEMATE P in the control of bleeding in subjects with VWD was determined by a retrospective review of clinical safety and efficacy data obtained from 97 Canadian VWD subjects who received product under an Emergency Drug Release Program. The dosage schedule and duration of therapy were determined by the medical practitioner.

There were 514 requests for product use for surgery, bleeding, or prophylaxis in the 97 subjects. Of these, HAEMATE P was not used in 151 cases, and follow-up safety and/or efficacy information was available for 303 (83%) of the remaining 363 requests. In many cases, HAEMATE P from a single request was used for several treatment courses in one subject. Therefore, there are more reported treatment courses than requests.

HAEMATE P was administered to 97 subjects in 530 treatment courses: 73 for surgery, 344 for treatment of bleeding, and 20 for prophylaxis of bleeding. The majority of the 93 "other" uses involved dental procedures, diagnostic procedures, prophylaxis prior to a procedure, or test doses.

Table 10 summarizes the dosing information (all subjects) for bleeding episodes.

Table 10. Dosing Information for Bleeding Episodes in VWD

		Type/Location of Bleeding Episode				
		Digestive System	**Nose+Mouth +Pharynx**	**Integument System**	**Female Genital System**	**Musculo-skeletal**
No. of Subjects		14	29	11	4	22
Loading Dose	Mean Dose (SD)* No. of Infusions†	62.1 (31.1) 37	66.9 (24.3) 127	73.4 (37.7) 22	88.5 (28.3) 7	50.2 (24.9) 107
Maintenance Dose	Mean Dose (SD)* No. of Infusions†	61.5 (38.0) 250	67.5 (22.4) 55	56.5 (63.3) 4	74.5 (17.7) 15	63.8 (28.8) 121
No. of Treatment Days per Bleeding Episode	Mean (SD) No. of Events	4.6 (3.6) 49	1.4 (1.2) 130	1.1 (0.4) 22	2.8 (2.9) 9	2.0 (1.9) 108
No. of Infusions by Treatment Day						
No. of Subjects		14	29	11	4	22

		Type/Location of Bleeding Episode				
		Digestive System	**Nose+Mouth +Pharynx**	**Integument System**	**Female Genital System**	**Musculo-skeletal**
Day 1‡	Mean (SD) No. of Events	1.2 (0.4) 49	1.1 (0.2) 130	1.0 (0.2) 22	1.0 (0.0) 9	1.0 (0.1) 108
No. of Subjects		13	9	3	1	15
Day 2	Mean (SD) No. of Events	1.2 (0.6) 41	1.3 (0.5) 12	1.0 (0.0) 3	1.0 (-) 1	1.2 (0.5) 26
No. of Subjects		12	6	-	2	10
Day 3	Mean (SD) No. of Events	1.5 (0.8) 25	1.4 (0.7) 9	- -	1.0 (0.0) 3	1.2 (0.4) 18

SD, standard deviation.
* IU VWF:RCo/kg.
† Number of infusions where the dose per kg body weight was available.
‡ Day 1, first treatment day.

13.2 Prevention of Excessive Bleeding During and After Surgery in VWD

Two prospective, open-label, non-controlled, multicenter clinical studies, one in the US and one in Europe, investigated the safety and hemostatic efficacy of HAEMATE P in subjects with VWD undergoing surgery.

- **US clinical study** – The primary objective of this study was to demonstrate the safety and hemostatic efficacy of HAEMATE P in preventing excessive bleeding in adult and pediatric subjects with VWD undergoing surgery. The 35 subjects (21 female and 14 male) ranged in age from 3 to 75 years (mean 32.9); seven were age 15 or younger and two were age 65 or older.

Twelve subjects had type 1 VWD, two had type 2A, three had type 2B, five had type 2M, and 13 had type 3. Twenty-eight of the surgical procedures were classified as major (e.g., orthopedic joint replacement, intracranial surgery, multiple tooth extractions, laparoscopic cholecystectomy), four as minor (e.g., placement of intravenous access device), and three subjects had oral surgery[*]. Seven of the 13 subjects with type 3 VWD had major surgery.

The first 15 subjects received a loading dose of HAEMATE P corresponding to 1.5 times the "full dose" (defined as the dose predicted to achieve a peak VWF:RCo level of 100 International Units (IU)/dL as determined by each subject's calculated IVR and baseline VWF:RCo level); the loading dose did not vary with the type of surgery performed (i.e., major, minor, or oral). The remaining 20 subjects were dosed based on individual pharmacokinetic assessments and target peak VWF:RCo levels of 80 to 100 International Units (IU)/dL for major surgery and 50 to 60 International Units (IU)/dL for minor or oral surgery, respectively. All 35 subjects received initial maintenance doses corresponding to 0.5 times the full dose at intervals of 6, 8, or 12 hours after surgery as determined by their individual half-lives for VWF:RCo; subsequent maintenance doses were adjusted based on regular measurements of trough VWF:RCo and FVIII:C levels. The median duration of treatment was 1 day (range: 1 to 2 days) for oral surgery, 5 days (range:

[*] Oral surgery is defined as extraction of fewer than three teeth, if the teeth are non-molars and have no bony involvement. Extraction of more than one impacted wisdom tooth is considered major surgery due to the expected difficulty of the

surgery and the expected blood loss, particularly in subjects with type 2A or type 3 VWD. Extraction of more than two teeth is considered major surgery in all patients.

3 to 7 days) for minor surgery, and 5.5 days (range: 2 to 26 days) for major surgery.

- **European clinical study** – The primary objective of this study was to assess the ability of HAEMATE P to effectively correct the coagulation defect in subjects with VWD undergoing elective surgery, as demonstrated by an increase in VWF:RCo and FVIII, a shortening of the prolonged bleeding time, and the prevention and/or cessation of excessive bleeding. This study did not have a pre-stated hypothesis to evaluate hemostatic efficacy. The 27 subjects (18 females and nine males) ranged in age from 5 to 81 years (median age: 46 years); one was age 5, and five were older than 65. Ten subjects had type 1 VWD, nine had type 2A, one had type 2M, and seven had type 3. Sixteen of the surgical procedures were classified as major (orthopedic joint replacement, hysterectomy, multiple tooth extractions, laparoscopic adnexectomy, laparoscopic cholecystectomy, and basal cell carcinoma excision). Six of the seven subjects with type 3 VWD had major surgery.

Dosing was individualized based on a pharmacokinetic assessment performed before surgery. The median duration of treatment was 3.5 days (range: 1 to 17 days) for minor surgery and 9 days (range: 1 to 17 days) for major surgery.

In both studies, assessments of the hemostatic efficacy of HAEMATE P in preventing excessive bleeding were performed at the end of surgery, 24 hours after the last infusion of HAEMATE P, and at the end of the study (14 days following surgery).

Table 11 summarizes the end-of-surgery hemostatic efficacy assessments in subjects participating in either the US or European study.

Table 11. Investigator's End-of-Surgery Hemostatic Efficacy Assessments for the US and European Surgical Studies

	Number of Subjects	End-of-Surgery Hemostatic Efficacy Assessments	
		Effective (Excellent / Good)*	95% Confidence Interval (CI) for Effective Proportion†
US study	35	32 (91.4%)	78.5-97.6%
European study	26‡	25 (96%)	82-99.8%

* Excellent: Hemostasis clinically not significantly different from normal.
Good: Mildly abnormal hemostasis in terms of quantity and/or quality (e.g., slight oozing).
† 95% CIs according to Blyth-Still-Casella.
‡ One subject with missing information.

Table 12 summarizes the overall hemostatic efficacy assessments in subjects participating in either the US or European study. HAEMATE P was effective in preventing excessive bleeding during and after surgery.

Table 12. Investigator's Overall Hemostatic Efficacy Assessments for the US and European Surgical Studies

	Number of Subjects	Overall Hemostatic Assessments	
		Effective (Excellent / Good)*	95% CI for Effective Proportion†
US study‡	35	35 (100%)	91.3-100%
European study§	27	26 (96.3%)	82.5-99.8%

* Excellent: Hemostasis clinically not significantly different from normal.
Good: Mildly abnormal hemostasis in terms of quantity and/or quality (e.g., slight oozing).
† 95% CIs according to Blyth-Still-Casella.
‡ Overall hemostatic efficacy was assessed 24 hours after the last HAEMATE P infusion or 14 days after surgery, whichever came earlier.
§ Overall hemostatic efficacy was not prospectively defined for the European study; the efficacy result displayed is the least efficacious ranking assigned by an investigator between surgery and Day 14.

In the US study, all efficacy assessments were reviewed by an independent Data Safety Monitoring Board (DSMB). The DSMB agreed with the investigators' assessments of the overall hemostatic efficacy for all but two subjects (neither of whom had type 3 VWD). Based on this, the DSMB judged hemostatic efficacy as "effective" in 33 (94.3%) (95% CI: 81.1% to 99.0%) of the 35 subjects.

In the US study, the median actual estimated blood loss did not exceed the median expected blood loss, regardless of the type of surgery. Table 13 shows the median expected and actual estimated blood loss during surgery in the US study.

Table 13. Expected and Actual Estimated Blood Loss During Surgery in the US Study

Estimated Blood Loss	Oral Surgery (n=3)	Minor Surgery (n=4)	Major Surgery (n=28)	Total (n=35)
Expected – Median (range) mL	10 (5-50)	8 (0-15)	50 (0-300)*	20 (0-300)*
Actual – Median (range) mL	3 (0-15)	3 (0-10)	26 (0-300)†	18 (0-300)†

* One subject with missing information
† Five subjects with missing information

In the US study, four subjects received transfusions, three due to adverse events and one due to pre-existing anemia. In the European study, one subject received transfusions to treat pre-existing anemia.

13.3 Virus Transmission Studies

Clinical evidence of the absence of virus transmission in HAEMATE P was obtained in additional studies.

In one study, none of the evaluable subjects (31 of 67) who received HAEMATE P developed HBV infection or showed clinical signs of non-A, non-B (NANB) hepatitis infection.

In another study, 32 lots of HAEMATE P were administered to 26 subjects with hemophilia or VWD who had not previously received any blood products. No subject developed any signs of an infectious disease, and the 10 subjects not previously vaccinated remained seronegative for markers of infection with HBV, HAV, cytomegalovirus (CMV), Epstein-Barr virus, and HIV.

In a retrospective study, 155 subjects evaluated remained negative for the presence of HIV-1 antibodies for time periods ranging from 4 months to 9 years from the initial administration of HAEMATE P. All 67 of the subjects tested for HIV-2 antibodies remained seronegative.

14 REFERENCES

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15 PHARMACEUTICAL PARTICULARS

- **List of excipients**

Human serum albumin
Glycine
Sodium chloride
Sodium citrate

sodium hydroxide or hydrochloric acid (in small amounts for pH adjustment)

Supplied solvent: Water for injections 5/10/15 ml

- **Incompatibilities**

This medicinal product must not be mixed with other medicinal products, diluents and solvents except those mentioned in section 15.

- **Shelf life**

The expiry date of the product is indicated on the packaging materials. From a microbiological point of view and as Haemate P contains no preservative, the reconstituted product should be used immediately. If it is not administered immediately, storage shall not exceed 8 hours below 25°C. Once the product has been transferred into a syringe it should be used immediately.

- **Special precautions for storage**

Do not store Haemate P above 25 °C.

Do not freeze. Keep container in the outer carton.

- **Nature and contents of container**

Immediate containers

Substance vials:

250 IU FVIII /600 IU VWF: Injection vials of colourless, tubular glass type I (Ph. Eur.), sealed with rubber infusion stopper (latex-free), plastic disc and aluminium cap.

500 IU FVIII /1200 IU VWF and 1000 IU FVIII /2400 IU VWF: Injection vials of colourless, moulded glass type II (Ph. Eur.) sealed with rubber infusion stopper (latex-free), plastic disc and aluminium cap.

Solvent vials (for water for injections):
Injection vials of tubular glass with inner surface treatment, glass Type I (Ph. Eur.), colourless, sealed with rubber infusion stopper (latex-free), plastic disc and aluminium cap.

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

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

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

16. MANUFACTURER

CSL Behring GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

17. REGISTRATION NUMBER(S)

HAEMATE-P 250 I.U. FVIII/ 600 IU VWF	113 53 22360
HAEMATE-P 500 I.U. FVIII/ 1200 IU VWF	113 51 22459
HAEMATE-P 1000 I.U. FVIII/ 2400 IU VWF	113 52 22460

18. REGISTRATION HOLDER

Genmedix, 12 Beit Harishonim St., Emek-Heffer Industrial Park, 3877701.

Revised in June 2021 according to MoH guidelines.