Manufacturer

CSL Behring

Distributor

DKSH

Contents

Conc of human coagulation factor VIII & von Willebrand factor.

Indications / Uses

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.

Dosage / Direction for Use

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

Posology: **von Willebrand's disease:** 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: 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: (See equation.)

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: (See Table 1.)

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. See Precautions.
Previously untreated patients: The safety and efficacy of Haemate in previously untreated patients have not yet been established.
Paediatric population: There are no data available from clinical studies regarding the dosage of Haemate in children.
Method of administration: For intravenous use.
Reconstitute the product as described in Special precautions for disposal and other handling: Reconstitution under Cautions for Usage. 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, the rate of infusion should be decreased or the application should be stopped, as required by the clinical condition of the patient (see Precautions).

Overdosage

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

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Description.

Special Precautions

Hypersensitivity: Allergic type hypersensitivity reactions are possible. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis.

In case of shock, the current medical standards for shock treatment should be observed.

Haemate contains up to 70 mg sodium per 1000 IU. To be taken into consideration by patients on a controlled sodium diet.

Von Willebrand Disease: There is a risk of occurrence of thrombotic events including pulmonary embolism, particularly in patients with known clinical or laboratory risk factors (e.g. in the perioperative period without conduct of thromboprophylaxis, no early

mobilization, obesity, overdose, cancer). Therefore, patients at risk must be monitored for early signs of thrombosis. Prophylaxis against venous thromboembolism should be instituted, according to the current recommendations.

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.

Patients with VWD, especially type 3 patients, may develop neutralising antibodies (inhibitors) to VWF. If the expected VWF:RCo activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an appropriate assay should be performed to determine if a VWF inhibitor is present. In patients with high levels of inhibitor, therapy may not be effective and other therapeutic options should be considered.

Haemophilia A: Inhibitors: The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the exposure to factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

In general, all patients treated with human coagulation factor VIII should be carefully

monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for FVIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. The management of such patients should be directed by physicians with experience in the care of haemophilia A patients and those with factor VIII inhibitors. See Adverse Reactions.

Virus safety: Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include 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, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. 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) and hepatitis C virus (HCV) and for the non-enveloped hepatitis A virus (HAV).

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 (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived FVIII/VWF products.

It is strongly recommended that every time that Haemate is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

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

Use In Pregnancy & Lactation

Animal reproduction studies have not been conducted with Haemate.

von Willebrand disease: The situation is different in von Willebrand disease because of its autosomal heredity. 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 treatment and prevention of acute bleedings can be recommended. There are no clinical studies available on substitution therapy with VWF in pregnant or lactating women.

Haemophilia A: Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breastfeeding is not available. Therefore, VWF and FVIII should be used during pregnancy and lactation only if clearly indicated.

Adverse Reactions

The following adverse reactions are basing on postmarketing experience.

Summary of the safety profile: During treatment with Haemate 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). (See Table 2.)

Description of selected adverse reactions: *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 neutralising 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).

In patients receiving VWF products sustained excessive FVIII:C plasma levels may increase the risk of thrombotic events (see Precautions).

Haemophilia A: Blood and lymphatic system disorders: Patients with haemophilia A may very rarely develop neutralising antibodies (inhibitors) to factor VIII. 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.

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

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.

Interactions

No interaction of VWF and FVIII with other medicinal products have been studied.

Preg Safety (US)

A B **C** D X

Category C: Either studies in animals have revealed adverse effects on the foetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the foetus.

Caution For Usage

Special precautions for disposal and other handling: General instructions: The solution should be clear or slightly opalescent. After filtering/withdrawal (see as follows) 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.

Reconstitution and withdrawal must be carried out under aseptic conditions.

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. Open the Mix2Vial package by peeling off the lid. Do not remove the Mix2Vial from the blister package.
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. 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. 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. 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. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.
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.
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. 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 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 Dosage & Administration), 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.
Incompatibilities: This medicinal product must not be mixed with other medicinal products, diluents and solvents except those mentioned in Description.

Storage

Do not store Haemate above 25°C.
Do not freeze. Keep container in the outer carton.
Shelf-Life: 3 years.
After reconstitution the physico-chemical stability has been demonstrated for 48 hours at room temperature (max. +25°C). From a microbiological point of view and as Haemate contains no preservative, the reconstituted product should be used immediately. If it is not administered immediately, storage shall not exceed 8 hours at room temperature.
Once the product is transferred into the syringe it should be used immediately.

Description

One vial contains nominally: 250/500/1000 IU human coagulation factor VIII (FVIII). 600/1200/2400 IU human von Willebrand factor (VWF).
After reconstitution with 5/10 ml Haemate P 250/500 contains 50 IU/ml of FVIII and 120 IU/ml of VWF. After reconstitution with 15 ml Haemate P 1000 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 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 is approximately 5-17 IU of VWF:RCo/mg protein.

Haemate is produced from the plasma of human donors.

Excipients/Inactive Ingredients: *Excipient with known effect:* Sodium: 250/500 IU- approximately 113 mmol/l (2.6 mg/ml).

1000 IU- approximately 150 mmol/l (3.5 mg/ml).

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

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

Mechanism of Action

Pharmacotherapeutic Group: Antihaemorrhagics: Blood coagulation factors, von Willebrand factor and coagulation factor VIII in combination. **ATC code:** B02BD06.

Pharmacology: ***Pharmacodynamics:*** Von Willebrand Factor: Haemate behaves in the same way as endogenous VWF.

In addition to its role as a factor VIII protecting protein, von Willebrand factor mediates platelet adhesion to sites of vascular injury and plays the main role in platelet aggregation.

Administration of VWF allows correction of the haemostatic abnormalities exhibited by patients who suffer from VWF deficiency (VWD) at two levels: VWF re-establishes platelet adhesion to the vascular sub-endothelium at the site of vascular damage (as it binds both to the vascular sub-endothelium and to the platelet membrane), providing primary haemostasis as shown by the shortening of the bleeding time. This effect occurs immediately and is known to depend to a large extent to the high content of high molecular weight VWF-multimers.

VWF produces delayed correction of the associated FVIII deficiency. Administered intravenously, VWF binds to endogenous FVIII (which is produced normally by the patient), and by stabilising this factor, avoids its rapid degradation.

Because of this, administration of pure VWF (VWF product with a low FVIII level)

restores the FVIII:C level to normal as a secondary effect after the first infusion with a slight delay.

Administration of a FVIII:C containing VWF preparation restores the FVIII:C level to normal immediately after the first infusion.

Factor VIII: Haemate behaves in the same way as endogenous FVIII.

The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions.

When infused into a haemophiliac patient, factor VIII binds to von Willebrand factor in the patient's circulation.

Activated factor VIII acts as a cofactor for activated factor IX accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma level of factor VIII is increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendency.

Pharmacokinetics: Von Willebrand Factor: The pharmacokinetics of Haemate has been evaluated in 28 VWD patients [type 1 n=10; type 2A n=10; type 2M n=1, type 3 n=7] in the non-bleeding state. The median terminal half-life of VWF:RCo (two compartment model) was 9.9 hours (range: 2.8 to 51.1 hours). The median initial half-life was 1.47 hours (range: 0.28 to 13.86 hours). The median in vivo recovery for VWF:RCo activity was 1.9 (IU/dL)/(IU/kg) [range: 0.6 to 4.5 (IU/dL)/(IU/kg)]. The median AUC was 1664 IU/dL*h (range 142 to 3846 IU/dL*h), the median MRT was 13.7 hours (range 3.0 to 44.6 hours) and the median clearance was 4.81 ml/kg/h (range 2.08 to 53.0 ml/kg/h).

Peak plasma levels of VWF usually occur at around 50 min after injection. Peak FVIII

level occur between 1 and 1.5 h after injection.

Factor VIII: After intravenous injection, there is a rapid increase of plasma Factor VIII activity (FVIII:C) followed by a rapid decrease in activity and a subsequent slower rate of decrease in activity. Studies in patients with haemophilia A have demonstrated a median half-life of 12.6 hours (range: 5.0 to 27.7 hours). An overall median FVIII in vivo recovery of 1.73 IU/dL per IU/kg (range 0.5-4.13) was obtained. In one study the median residence time (MRT) was found to be 19.0 hours (range 14.8 to 40.0 hours), the median area under the curve (AUC) was 36.1 (%*hours)/(IU/kg) (range 14.8 to 72.4 (%*hours)/(IU kg)), the median clearance 2.8 mL/h/kg (range 1.4 to 6.7 mL/h/kg).

Paediatric population: No pharmacokinetic data are available in patients younger than 12 years.

Toxicology: *Preclinical safety data:* Haemate contains factor VIII and von Willebrand factor as active ingredients which are derived from human plasma and act like endogenous constituents of plasma. Single dose applications of Haemate to various animal species did not reveal toxic effects. Preclinical studies with repeated dose applications (chronic toxicity, cancerogenicity and mutagenicity) cannot be reasonably performed in conventional animal models due to the development of antibodies following the application of heterologous human proteins.

MIMS Class

Intravenous & Other Sterile Solutions

ATC Classification

B02BD06 - von Willebrand factor and coagulation factor VIII in combination ; Belongs to the class of blood coagulation factors. Used in the treatment of hemorrhage.

Presentation / Packing

Powd for inj (white powder and clear, colourless solvent in vial) 250 IU x 1's, 500 IU x 1's, 1,000 IU x 1's.