Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Haemate P 500 IU Powder and solvent for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Haemate P 500 is prepared as a powder and solvent for solution for injection
The product reconstituted with 20ml of water for injection contains approximately 500 IU human coagulation factor VIII and 1200 IU of vWF:RCof per vial. Each vial contains 510-960 mg of dried substance and has a total protein content of 100-220 mg.

The potency (IU) for human coagulation factor VIII is determined using the European Pharmacopoeia chromogenic assay against the World Health Organisation (WHO) international standard.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection or infusion

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Prophylaxis and treatment of bleeding in haemophilia A (congenital factor VIII deficiency).
- Prophylaxis and treatment of bleeding in von Willebrand's disease.

4.2 Posology and method of administration

4.2.1. Posology

Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia.

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 International Units (relative to an International Standard for factor VIII in plasma).

One International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in one ml of normal human plasma. The calculation of the required dosage of factor VIII is based on the empirical finding that 1 International Unit (IU) factor VIII per kg body weight raises the plasma factor VIII activity by 1.5 to 2% of normal activity (1.5-2 IU/dL). 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) in 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 bleed or oral bleed	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 bleed 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 to 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 post-operative)	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 to 60% or IU/dL

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, 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.

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.

Patients should be monitored for the development of factor VIII inhibitors. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a factor VIII inhibitor is present. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of patients with haemophilia. See also section 4.4.

<u>von Willebrand's disease:</u>
The dosage should be adjusted according to the extent and source of the bleeding. As a rule, 20 IU to 40 IU

factor VIII: C per kilogram body weight (corresponds to approximately 48-96 IU vWF:RiCof per kilogram body weight) are administered every 8 to 12 hours. It has to be considered that postoperative and postpartum bleeds may occur 10 to 12 days after surgery or delivery.

Administration of 1 IU vWF:RCof per kilogram body weight can be expected to lead to a rise in vWF:RCof activity of approx. 1.5% of the norm.

The amount administered should always be adjusted individually according to the clinical effect achieved; under certain circumstances larger amounts than those calculated can be required especially in the case of the initial dose.

In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis is essential.

Method of administration
Dissolve the preparation as described at 6.6. The product should be administered via the intravenous route. The injection or infusion rate should not exceed 4 ml per minute (approx. 100 IU).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. The product contains traces of human proteins other than factor VIII. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

If these symptoms occur, they should be advised to discontinue use of the product immediately and contact their physician.

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

There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors. Therefore, patients at risk must be monitored for early signs of thrombosis. Prophylaxis against venous thromboembolism should be instituted, according to current recommendations.

When medicinal product prepared from human blood or plasma are administered, infectious diseases due to the transmission of infective agents cannot be totally excluded. This also applies to pathogens of hitherto unknown nature. The risk of transmission of infective agents is however reduced by:

- Selection of donors by a medical interview and screening of individual donations and plasma pools for HbsAg and antibodies to HIVand HCV.
- Testing of plasma pools for HCV genomic material.
- Inactivation/removal procedures included in the production process that have been validated using model viruses. These procedures are considered effective for HIV, HCV and HBV.

The viral inactivation/removal procedures may be of limited value against non-enveloped viruses such as HAV or parvovirus B19.

Appropriate vaccination (hepatitis A and B) for patients in receipt of plasma-derived factor VIII concentrates is recommended.

Parvovirus B19 infection may be serious for pregnant women (foetal infection and for individuals with immunodeficiency or increased red cell production (e.g. in haemolytic anaemia).

The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are invariably IgG immunoglobulins directed against the factor VIII pro-coagulant 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 anti-haemophilic factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days. Patients treated with human coagulation factor VIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. See also 4.8 Undesirable effects.

In the interest of patients, it is recommended that, whenever possible, every time that Haemate-P is administered to them, the name and batch number of the product is registered.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor VIII products with other medicinal products are known.

4.6 Pregnancy and lactation

Animal reproduction studies have not been conducted with Haemate P. Based on the rare occurrence of haemophilia A in women, experience regarding the use of Haemate P during pregnancy and breast-feeding is not available. Therefore, Haemate P should be used during pregnancy and lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

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 infrequently, and may in some cases progress to severe anaphylaxis (including shock).

On rare occasions, fever has been observed.

Patients with haemophilia A may 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.

Haemolysis in patients who are not blood group compatible and hypervolaemia have rarely been observed after administration of high doses of factor VIII.

There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors.

In patients receiving FVIII-containing vWF products, sustained excessive FVIII:C plasma levels may increase the risk of thrombotic events.

For information on viral safety see 4.4.

4.9 Overdose

No symptoms of overdose with human coagulation factor VIII have been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: antihemorrhagics: blood coagulation factor VIII. ATC code: B02BD06.

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

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:C 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 levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

In addition to its role as a FVIII protecting protein, vWF mediates platelet adhesion to sites of vascular injury, plays a role in platelet aggregation and is indispensable for substitution therapy in patients with von Willebrand's disease. The activity of vWF is measured as von Willebrand factor:ristocetin cofactor (vWF:RCof). In severe cases of von Willebrand's disease the factor VIII activity is also considerably reduced.

5.2 Pharmacokinetic properties

After injection of the product approximately two thirds to three quarters of the factor VIII remain in the circulation. The factor VIII recovery should be between 80% and 120%.

Plasma factor VIII activity decreases by a two-phase exponential decay. In the initial phase, distribution between the intravascular and other compartments (body fluids) occurs with a half-life of elimination from the plasma of 3 to 6 hours. In the subsequent phase the half-life varies between 8-20 hours, with an average of 12 hours. This corresponds to the physiological half-life.

In a clinical study in patients with haemophilia A the *in-vivo* recovery of F VIII was determined to be 101.5%. With reference to the administration of 1 IU Factor VIII:C/kg body weight, the mean F VIII increase was 2.3% of the norm. The biological half-life was determined to be 15.3 +/- 5.5 hours. In individual cases the biological half-life may vary.

In a clinical study in patients with von Willebrand's disease the mean vWF:RCof *in-vivo* recovery was 63% in type I, 87% in type lla and 72% in type III of vWD. On administration of 1 IU/kg body weight the mean vWf:RCof increase was 1.5 +/- 0.3% of the norm. The mean biological half-life proved to range between 7 hours (type III) and 13.8 +/- 2.1 hours (type 1).

Following the substitution with Haemate P a quite normal multimeric structure is seen in the patient plasma lasting over several hours.

5.3 Preclinical safety data

5.3.1 Toxicological properties

Human plasma coagulation factor VIII (from the concentrate) is a normal constituent of the human plasma and acts like the endogenous factor VIII.

Repeated dose animal toxicity testing is impracticable due to the development of antibodies to heterologous protein.

Even doses of several times the recommended human dosage per kilogram body weight show no toxic effects on laboratory animals.

Since clinical experience provides no hint for tumorigenic and mutagenic effects of human plasma coagulation factor VIII, experimental studies, particularly in heterologous species, are not considered imperative.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin
Glycine
Sodium chloride
Sodium citrate
Water for injections

6.2 Incompatibilities

Haemate P must not be mixed with other medicinal products.

6.3 Shelf Life

36 months.
Reconstituted preparations should be used within 8 hours.

6.4 Special precautions for storage

Haemate P should be stored at +2 to +8 °C.
Haemate P may also be stored at room temperature for up to 6 months during the expiry period, but not at or above 30 °C. The revised expiry date (date removed from refrigerator + 6 months) should be written on the carton. If the product is not used by the revised expiry date, it should be discarded.
Do not freeze.

6.5 Nature and contents of container

Vials:
- Injection vial of colourless type II glass sealed with rubber infusion stopper, plastic disc and aluminium cap.

1 vial (hermetically sealed under vacuum) with dried substance.
1 vial with 20 ml water for injections.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Do not use after the expiry date given on the label.

Preparation of the solution:
1. Bring the solvent to 20 to 37 °C.
2 Remove the caps from the vials of dried substance and solvent.
3. Disinfect the surface of both rubber stoppers.
4. Insert the needle at the corrugated side of the transfer set into the solvent vial. Remove the protective sheath from the other end of the transfer set. Invert the solvent vial and insert the needle into the preparation vial without touching the needle. The solvent is then suctioned into

the preparation vial by the vacuum. Finally, remove solvent vial and transfer set.

5. Slowly swirl the vial to dissolve the dried substance completely. Avoid vigorous shaking. A clear to slightly opalescent solution is obtained. Do not use solutions which are cloudy or have deposits.

The reconstitution time is approx. 2 minutes.

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

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA 800/2/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 17 August 2004

10 DATE OF REVISION OF THE TEXT

March 2006