# SUMMARY OF PRODUCT CHARACTERISTICS

## OPTIVATE®
## High Purity Factor VIII and von Willebrand factor concentrate

## 1. NAME OF THE MEDICINAL PRODUCT
Optivate®, 100IU/ml powder for solution for injection,

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION
The product Optivate® is a concentrate of human coagulation factor VIII with associated von Willebrand factor (VWF) (the natural stabiliser for FVIII). There are no added proteins as stabilisers.
The product is obtained from blood from screened donors. These donors are selected from the USA.

Optivate® contains 100IU/ml human coagulation factor VIII (Ph.Eur. chromogenic FVIII assay) when reconstituted in sterilised water for injection.

The VWF content is 200 to 320 IU/ml (ELISA antigen method). The ratio of FVIII to VWF is approximately 1IU:2.5IU. The factor VIII specific activity of Optivate® is calculated as 800 IU/mg protein when VWF is discounted and not less than 30 IU/mg protein when the presence of VWF is considered in the calculation.
The label on each vial states the assayed amounts of factor VIII and VWF antigen.

For excipients, see 6.1.

## 3. PHARMACEUTICAL FORM
Powder for solution for injection.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications
Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

This product may be used in the management of acquired factor VIII deficiency.

### 4.2 Posology and method of administration
Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia.

**Posology**
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 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 IU factor VIII per kg body weight raises the plasma

factor VIII activity by 2.5% of normal activity 2.5 IU/dl. The required dosage is determined using the following formula:

| | | | | | |
|---|---|---|---|---|---|
| **Required units =** | **body weight (kg)** | **x** | **desired factor VIII rise (%) (IU/dl)** | **x** | **0.4** |

The amount to be administered and the frequency of administration should always be orientated 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; 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 (%) (IU/dl) | Frequency of doses (hours)/Duration of therapy (days) |
|---|---|---|
| **Haemorrhage** | | |
| Early haemarthrosis, muscle bleeding or oral bleeding | 20-40 | Repeat every 12 to 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 to 24 hours until threat resolved. |
| **Surgery** | | |
| *Minor*<br>Including tooth extraction | 30-60 | Every 24 hours, at least 1 day, until healing is achieved. |
| *Major* | 80-100<br><br>(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% to 60% (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 *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.

There are insufficient data to recommend use of Optivate® in children less than 6 years of age.

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 4.4.

**Method of administration**
Dissolve the preparation as described at 6.6. The product should be administered via the intravenous route at a rate not exceeding 3 ml per minute (note that increasing the rate of administration may result in side effects).

If it is necessary to receive more than one vial, the contents of all the vials may be drawn up into a syringe of appropriate size. A separate sterile filter needle should be used for each vial because sterile filter needles are intended to filter the contents of a single vial of the Optivate®.

## 4.3 Contra-indications
Hypersensitivity to the active substance or to any of the excipients.

## 4.4 Special warnings and special 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 and VWF. 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 shock-treatment should be observed.

When medicinal products 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 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 HIV and 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 include Solvent / Detergent treatment and terminal heating at 80°C for 72 hours. These procedures are considered effective for HIV, HCV HAV, parvovirus B19 and HBV.

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

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 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 Optivate® is administered to them, the name and batch number of the product is registered.

**4.5 Interaction with other medicaments 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 factor VIII. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breast-feeding is not available. Therefore, factor VIII 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.

There is no clinical experience in treating previously untreated patients (PUPS)

None of the previously treated patients (PTPs) in the clinical trials has developed inhibitors.

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 :
Antihaemorrhagics: blood coagulation factor VIII. ATC code: B02BD02.

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:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as results 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 factor VIII protecting protein, von Willebrand mediates platelet adhesion to sites of vascular injury and plays a role in platelet aggregation.

### 5.2 Pharmacokinetic properties

The pharmacokinetics of Optivate® have been evaluated in patients with severe haemophilia A after bolus doses of 50 IU/kg. The results were as follows:
Incremental recovery 2.5 IU/dL per IU/kg; $T_{0.5}$ alpha 2.7 hours; $T_{0.5}$ beta 12.0 hours; Mean Residence Time 11.5 hours; Clearance 2.16 dL/hour; $AUC_{0-48}$ 1,808 h.IU/dL.

### 5.3 Preclinical safety data

The factor VIII and von Willebrand factor in Optivate® are normal constituents of human plasma and act in the same way as the endogenous proteins, therefore, safety testing is not relevant.

However an acute toxicity study and a repeated dose toxicity study in the mouse indicated that the Optivate formulation was not toxic, even at levels up to 20 times that likely to be used in man. In these studies, the various constituents of the product were administered to the test animals in different, greater, amounts for each excipient, compared to that in a clinical dose.

It is scientifically inappropriate to conduct genotoxicity or carcinogenicity studies with plasma coagulation factor VIII with or without its natural stabiliser, VWF.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

**The reconstituted solution contains not more than**

| | | |
|---|---|---|
| Sodium | 390 | mmol/l |
| Chloride | 390 | mmol/l |
| Citrate | 12 | mmol/l |
| Calcium | 17 | mmol/l |
| Polysorbate 20 | 2.7 | g/L |
| Trehalose as dihydrate | 33 | g/L |

### 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
Only the recommended injection/infusion sets should be used because treatment failure can occur as a consequence of human plasma coagulation factor VIII adsorption to the internal surfaces of some infusion equipment.

### 6.3 Shelf life

Unopened (at 2°C - 25°C, in the dark) 3 years.

### 6.4 Special precautions for storage

Store below 25°C. Do not freeze. Protect from light.

### 6.5 Nature and contents of container

The product is presented as a 500IU or 1000IU presentation in Type I, Ph.Eur. glass vials. These vials are stoppered with a halobutyl rubber freeze-drying stopper under vacuum and then oversealed with a snap-off polypropylene cap and aluminium lacquered skirt.

### 6.6 Instructions for use and handling, and disposal

The reconstitution is performed as follows :
Optivate® should only be reconstituted with Sterilised Water for Injections (Ph.Eur.) provided with the product. The 500IU and 1000IU presentations should be reconstituted using 5ml and 10ml WFI respectively.
The container of Optivate® and the Sterilised Water for Injections should be brought to between 20°C and 30°C prior to the removal of the flip-off closure from the product vial. Remove the cap from the vial of Optivate® and clean the stopper with a spirit swab. Carefully, break open the ampoule of water.

Using a sterile disposable needle and syringe draw up the required volume of Sterilised Water for Injections and transfer to the vial containing the factor VIII concentrate. On piercing the seal of the Optivate® vial, the water will be drawn into the vial, which is under vacuum.
THE FILTER NEEDLE PROVIDED MUST NOT BE USED TO DRAW UP THE WATER FOR INJECTIONS

If the water to be used for reconstitution is not drawn into the vial containing factor VIII this indicates loss of vacuum. If the vial does not contain a vacuum or if reconstituted factor VIII is turbid or forms a gel or a clot the vial must not be used.
The container should be agitated to wet the product and the vacuum then released by removing the syringe from the needle before removing the needle from the Optivate® vial.

Continue to agitate gently until dissolution is complete. A clear or slightly opalescent solution should usually be obtained within 2 to 2 ½ minutes up to a maximum of 5 minutes**.** The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration. Infuse the product as soon as possible after reconstitution and certainly within one hour.

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

## 7. MARKETING AUTHORISATION HOLDER

BPL, Bio Products Laboratory
Dagger Lane, Elstree, Herts, WD6 3BX
United Kingdom

## 8. MARKETING AUTHORIZATION NUMBER(S)

PL08801/0051

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

***Not available yet***

## 10. DATE OF REVISION OF TEXT

March 2004. Item code: OptSmPC 1