



Optivate
(Human Factor VIII, von Willebrand Factor)

PL 08801/0055

UKPAR

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Optivate
(Human Factor VIII, von Willebrand Factor)

PL 08801/0055

LAY SUMMARY

The MHRA granted Bio Products Laboratory (BPL) a Marketing Authorisation for the medicinal product Optivate 100 IU/mL powder for solution (PL 08801/0055) on 27th May 2010. This medicine is subject to restricted medical prescription and is indicated for treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

Optivate is a concentrate of human coagulation factor VIII with associated von Willebrand Factor (the natural stabiliser for factor VIII). There are no added proteins as stabilisers. The product is obtained from blood from screened donors selected from the USA.

This application was submitted as an abridged simple national application under Article 10(a) according to Directive 2001/83/EC, as amended; a well-established use application.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Optivate outweigh the risks, hence a Marketing Authorisation has been granted.

Optivate
(Human Factor VIII, von Willebrand Factor)

PL 08801/0055

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of data on quality, safety and efficacy the UK granted a Marketing Authorisation to BPL for the medicinal product Optivate 100 IU/mL powder for solution (PL 08801/0055) on 27th May 2010. This product is a restricted prescription only medicine.

This application was a line-extension to the original Optivate application (PL 08801/0051) submitted as an abridged complex national application under Article 10(a) according to Directive 2001/83/EC, as amended; a well-established use application. The only change is the applicant reverting to their previously licensed method of hydration of the freeze dried product using a sterile syringe and a bottle of water, instead of the Mix2 rehydration kit.

Optivate is a concentrate of human coagulation factor VIII with associated von Willebrand Factor (the natural stabiliser for factor VIII) and is indicated for treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

Optivate has been developed from a current BPL product, 8Y (PL 08801/0021), a complex of factor VIII with its natural carrier protein, von Willebrand factor. This product is an intermediate purity factor VIII with only one specific antiviral step in its manufacture. Optivate was developed in order to produce a high purity factor VIII and von Willebrand factor complex and to add an extra specific antiviral step to the manufacturing process.

Optivate is presented as a lyophilised product for reconstitution with sterilised water for injections Ph.Eur., which is supplied with the product. There are three presentations: a vial containing a nominal 250 IU of factor VIII, one containing a nominal 500 IU of factor VIII and the third containing a nominal 1,000 IU of factor VIII. To reconstitute the lyophilised powder for infusion, 2.5 ml, 5 ml or 10 ml, respectively, of the sterilised water for injections Ph.Eur. is added. The resulting solutions have identical concentrations of constituents.

No new data were submitted nor were they necessary for this application as the data are identical to that of the original product. As the original product was granted prior to the introduction of current legislation, no PAR was generated for this.

QUALITY ASSESSMENT

The application is an exact copy of the existing license (PL 08801/0051). The only change is the applicant reverting to their previously licensed method of hydration of the freeze dried product using a sterile syringe and a bottle of water, instead of the Mix2 rehydration kit.

The mix2 rehydration kit (introduced in September 2009) is used to rehydrate the product before use and this is the format which is marketed in Europe. The sterile syringe and a bottle of water, instead of the Mix2 rehydration kit is designated primarily for non-European markets.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.

CLINICAL ASSESSMENT REPORT

No new clinical data have been supplied with these applications and none are required for applications of this type.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for these applications are consistent with that previously assessed for the originator product and as such have been judged to be satisfactory.

PRE-CLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

These applications are identical to the previously granted application for Optivate (PL 08801/0051).

No new or unexpected safety concerns arose from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the originator product (PL 08801/0051).

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the originator product. Extensive clinical experience with Optivate is considered to have demonstrated the therapeutic value of the product. The risk: benefit is, therefore, considered to be positive.

Optivate

(Human Factor VIII, von Willebrand Factor)

PL 08801/0055

STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the marketing authorisation application 15th March 2010
- 2 Following standard checks the MHRA informed the applicant that its application was considered valid on 26th March 2010
- 3 Following assessment of the submitted data, the application was finalised on 27th May 2010

Optivate

(Human Factor VIII, von Willebrand Factor)

PL 08801/0055

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Optivate[®], 100 IU/mL human factor VIII, a powder for solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

Each vial contains nominally 250 IU, 500 IU or 1000 IU of human coagulation factor VIII. One mL of Optivate contains approximately 100 IU of human coagulation factor VIII after reconstitution with 2.5 mL (250 IU), 5 mL (500 IU) or 10 mL (1000 IU) of Sterilised Water for Injections, Ph.Eur..

The factor VIII potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The factor VIII specific activity of Optivate is approximately 800 IU/mg protein when VWF is discounted and approximately 43 IU/mg protein when the presence of VWF is considered in the calculation.

The product contains approximately 172 IU VWF:RCo per mL when reconstituted with Sterilised Water for Injections as described above.

The specific activity of Optivate is approximately 75 IU of VWF:RCo/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 label on each vial states the assayed amounts of factor VIII and VWF Ristocetin Cofactor activities.

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Powder for solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital 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.

The dosage and duration of the substitution therapy depend on the severity of the FVIII deficiency, on the location and extent of the bleeding and the patient's clinical condition.

Posology

On demand treatment

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 IU factor VIII per kg body weight raises the plasma factor VIII activity by 2.2% - 2.7% of normal activity (2.2-2.7 IU/dL). The required dosage is determined using the following formula:

$$\text{Required units} = \text{body weight (kg)} \times \text{desired factor VIII rise (\% (IU/dL))} \times 0.4$$

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 to 24 hours for 3 to 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 surgery <i>Including tooth extraction.</i>	30-60	Every 24 hours, at least 1 day, until healing is achieved.
Major surgery	80-100 (pre- and postoperative)	Repeat infusion every 8 to 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).

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, 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.

Paediatric patients

Optivate is indicated for use in children, including those less than 6 years of age. The usual dose is 17 to 30 IU/kg. This can be given up to 3 times a week to prevent bleeding. In the clinical trials the median doses in children ≤ 6 years of age were 24.7 IU/kg for routine prophylaxis and 27.6 IU/kg to treat a bleed.

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 in 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 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 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, standard medical treatment for shock should be implemented.

Standard measures are implemented 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 HIV, HBV and HCV, and for non-enveloped viruses HAV and parvovirus B19.

It is strongly recommended that every time that Optivate 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.

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.

Cases of recurrent inhibitor (low titre) have been observed after switching from one FVIII 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 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.

See also 4.8 Undesirable effects.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor VIII products with other medicinal products have been reported.

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

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

4.8 Undesirable effects

Hypersensitivity or allergic reactions (which may include angioedema, flushing, generalised urticaria, hives, hypotension, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed infrequently, and may in some cases progress to severe anaphylaxis.

The following adverse reactions have been reported from 96 patients in clinical studies. Approximately 10% of patients can be expected to experience adverse reactions on long-term treatment. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$):

MedDRA Standard System Organ Class	Adverse Reactions	Frequency
Nervous System Disorders	Headache	Common
	Somnolence	Common
Ear and Labyrinth Disorders	Vertigo (dizziness)	Common
Skin and Subcutaneous Tissue Disorders	Rash	Common
	Pruritus	Common
Musculoskeletal and Connective Tissue Disorders	Muscle and joint stiffness	Common
General Disorders and Administration Site Disorders	Infusion site erythema, rash, or pain	Common
	Oedema peripheral	Common
	Shivering (rigors)	Common
	Fever (pyrexia)	Common

In post-marketing experience, the following additional undesirable effects have been reported: sneezing, cough, throat irritation, abdominal pain and malaise.

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 and wheezing) have been observed infrequently, and may in some cases progress to severe anaphylaxis.

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. One previously untreated patient (PUP) has been treated in the clinical development programme. Neither he nor any of the 95 previously treated patients (PTPs) in the clinical trials has developed inhibitors. The median number of exposure days in these patients was 97 days (range 2 to 408 days).

For information on viral safety see 4.4.

4.9 Overdose

No case of overdose has 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 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 factor VIII protecting protein, von Willebrand Factor mediates platelet adhesion to sites of vascular injury and plays a role in platelet aggregation.

From clinical trial experience, young children using prophylactic Optivate experienced less bleeds than those only using it on demand. For doses in children see 4.2.

5.2 Pharmacokinetic properties

The pharmacokinetics of Optivate have been evaluated in 15 patients with severe haemophilia A after bolus doses of 50 IU/kg. The mean results were as follows:

Non-compartmental terminal half-life	12.4 hours
Non-compartmental terminal half-life 95%CI	12.4 hours 10.94-13.83 hours
Mean Residence Time 95%CI	17.5 hours 15.99-18.92 hours

Clearance	3.1 mL/kg/h
95%CI	2.71-3.51 mL/kg/h
Area under curve (AUC _{0-48h})	16.1 h.IU/mL
95%CI	13.97-18.28 h.IU/mL
Area under curve (AUC _{0-inf})	17.31 h.IU/mL
95%CI	14.98-19.65 h.IU/mL
Volume of distribution	53.4 mL/kg
95%CI	46.2-60.52 mL/kg
Alpha half-life	2.2 hours
95%CI	1.48-2.88 hours
Beta half-life	12.6 hours
95%CI	11.33-13.92 hours
Incremental recovery	2.5 IU/dL per IU/kg
95%CI	2.22-2.74 IU/dL per IU/kg

During the clinical trials, there were 309 assessments of incremental recovery, all based on the maximum FVIII:C in the first hour (ISTH 2001). These assessments have involved 27 batches of Optivate and 70 adults with severe haemophilia A. The overall values of incremental recovery were as follows:

Mean: 2.7 IU/dL per IU/kg
95%CI 2.53-2.80 IU/dL per IU/kg
Median: 2.6 IU/dL per IU/kg.

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 mice 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:

Sodium chloride
Sodium citrate
Calcium chloride
Polysorbate 20
Trehalose

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 250 IU, 500 IU or 1000 IU 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 Special precautions for disposal

The reconstitution is performed as follows:

Optivate should only be reconstituted with Water for Injections provided with the product. The 250 IU, 500 IU and 1000 IU presentations should be reconstituted using 2.5 mL, 5 mL and 10 mL Sterilised Water for Injections, (Ph.Eur.), respectively.

The container of Optivate and 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.

Either of the following methods of reconstitution can then be used:

a) Carefully, open the container of water then, using a sterile disposable needle and syringe, draw up the required volume of Sterilised Water for Injections, Ph.Eur., and transfer to the vial of the factor VIII. On piercing the seal of the factor VIII vial, the water will be drawn into the vial, which is under vacuum. NB: THE FILTER NEEDLE PROVIDED MUST NOT BE USED TO DRAW UP THE WATER FOR INJECTIONS.

or

b) Remove the cover guard from one end of a double-ended transfer needle and insert through the stopper into the vial of Sterilised Water for Injections, Ph.Eur., Remove the other end of the needle guard, invert the water vial over the product vial and insert the free end of the needle through the stopper into the vial of factor VIII. On piercing the seal of the product vial, the water will be drawn into the vial, which is under vacuum. A small amount of water will remain in the water vial.

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 2½ 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.

When dissolved, draw up the solution using the **filter needle** attached to a syringe. Use a new filter needle for each vial of Optivate if the dose is more than one vial; but the contents of all vials can be drawn up into the same syringe.

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
Tel: +44 (0) 20 8957 2200
Email: info@bpl.co.uk

8 MARKETING AUTHORISATION NUMBER(S)

PL 08801/0055

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/05/2010

10 DATE OF REVISION OF THE TEXT

27/05/2010

Leaflet

Optivate

(Human Factor VIII, von Willebrand Factor)

PL 08801/005



**OPTIVATE® 250 IU, 500 IU, 1000 IU
POWDER FOR SOLUTION FOR INJECTION
HIGH PURITY FACTOR VIII AND VON WILLEBRAND FACTOR CONCENTRATE**

Please read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet you may need to read it again.
- If you have any further questions, please ask your doctor.
- This medicine has been prescribed for you personally. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. What Optivate is and what it is used for
2. Before you use Optivate
3. How to use Optivate
4. Possible side effects
5. How to store Optivate
6. Further information

1. WHAT OPTIVATE IS AND WHAT IT IS USED FOR

Optivate is a high purity factor VIII and von Willebrand Factor concentrate from human blood plasma obtained from screened donors. It is a white sterile powder, supplied with sterile water (Sterilised Water for Injections, Ph.Eur.).

Optivate is given by injection into a vein (intravenously) and is used to prevent and treat bleeding in patients with Haemophilia A (congenital factor VIII deficiency in the blood). Your doctor will explain further why this medicine has been given to you.

2. BEFORE YOU USE OPTIVATE

Do not use this medicine and speak to your doctor if you think you could be allergic (hypersensitive) to the active substance(s) or to any of the other ingredients (See section 6 for a list of these).

- Your doctor will advise you as to which vaccinations you should be given as a routine precaution, because you are receiving a blood plasma product.

Blood Tests

- **If you have a larger or longer bleed than usual and the bleeding does not stop after an injection of Optivate, speak to your doctor.** Some patients with a shortage of factor VIII may develop inhibitors (antibodies) to factor VIII during treatment. This could mean that the treatment will not work properly. Your doctor will check regularly for the development of these antibodies, and especially before an operation.

Both before and after treatment with this medicine, particularly for your first course of treatment, your doctor will probably carry out tests to check the level of factor VIII in your blood.

- This medicine may contain small amounts of blood group antibodies originally present in the plasma from the donors. This is normal and, in most cases, these antibodies do not cause any problems. However, if you need **large** doses of Optivate, for example during surgery, and are **blood group A, B, or AB**, your doctor may need to do a blood test to check if the medicine has had any effect on your red blood cells.

Taking other medicines

These injections must **not** be mixed with other medicinal products in the same syringe.

Please tell your doctor if you are taking or have recently taken **any** other medicines, **including** medicines obtained without a prescription.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are breast-feeding, tell your doctor. Your doctor will tell you if this product is necessary for you to take at this time.

Driving and using machines

There are no known effects of this product on the ability to drive or operate machinery.

Please note:

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus and for the non-enveloped hepatitis A and parvovirus B19 viruses.

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

3. HOW TO USE OPTIVATE

Before injecting this medicine at home, you will have received training at your Haemophilia Centre on how to do so. Use only the recommended injection equipment provided with your medicine.

How much Optivate to give

Always use this medicine exactly how your doctor has told you. You should check with your doctor if you are not sure.

- Your doctor will explain to you how much you should use and when you should use it.
- Your doctor will usually tell you your dose in terms of the number of full vials nearest to the dose most suited to you.
- If further treatment is needed, doses may be repeated at intervals of 8, 12 or 24 hours, as required. Your doctor will advise you if this is necessary.

The table gives the approximate doses of factor VIII which are needed to stop bleeding in various conditions:

Adults

Condition	Initial dose of Optivate (IU/kg body weight)
Minor spontaneous bleeding in joints and muscles.	8 – 16
Severe bleeding in joints and muscles, haematoma (swelling caused by collection of blood) in potentially serious situations, blood in the urine.	12 – 24
Major surgery.	See below

How much do adults require to prevent bleeding?

20 to 40 IU/kg every 2 or 3 days is usually enough.

Children

For children under the age of 6 years, your doctor will recommend the appropriate dose but the usual dose is 17 to 30 IU/kg. This can be given up to 3 times a week for prevention of bleeding.

When to inject Optivate

- The medicine should be injected when the first sign of bleeding occurs.
- The injection should be repeated as necessary to stop the bleeding.
- Each individual bleed should be judged on its own severity.
- If you are using this product for the first time, your doctor will supervise you.

Dissolving your medicine before use

Your medicine must only be dissolved in the sterile water provided with the product.

Quantity of Optivate	Volume of Water Supplied
250 IU	5 mL
500 IU	5 mL
1000 IU	10 mL

1. Before you remove the "flip-off" top, make sure that the vial of Optivate and the container of water supplied with it are both at room temperature (between 20°C and 30°C).
3. Sterile water for use with Optivate is provided in an ampoule with a "snap-off" cap or a glass vial with a stopper.
4. Keep all injection equipment sterile.
6. Do not use any solution if any small bits can be seen in the vials.

There are two ways (A or B) of continuing to make up the Optivate for injection:

A. Using a needle and syringe

- If the Water for Injections is in a plastic ampoule, break open the top and draw up the volume of water needed with a sterile needle and syringe (not the filter needle).
- If the Water for Injections is in a glass vial remove the "flip-off" top and clean the top of the stopper with an alcohol swab.
- Transfer the water to the vial of Optivate by pushing the needle through the stopper of the vial. The water in the syringe will be drawn into the vial, which is under vacuum, so there is no need to push the plunger of the syringe.

Note: The filter needle provided must not be used to draw up the Water for Injections.

- Gently swirl the Optivate vial (do not shake) and then remove the syringe from the needle to release the vacuum in the vial.
- Continue to swirl the Optivate vial gently until the powder is dissolved (usually in about 2 to 2½ minutes).
- When dissolved, draw up the solution using the filter needle attached to a syringe. Use a new filter needle for each vial of Optivate if your dose is more than one vial.

B. Using a double spiked needle (only suitable if the Water for Injections is in a glass vial)

- If the Water for Injections is in a glass vial, remove the "flip-off" top and clean the top of the stopper with a alcohol swab.
- Remove the cover guard from one end of a double-ended transfer needle (which your doctor can provide) and insert the needle through the stopper into the vial of water.
- Remove the other end of the needle guard, turn it upside down over the vial of Optivate and push the needle through the Optivate stopper.
- On piercing the stopper of the Optivate vial, the water will be drawn in as the vial is sealed under vacuum. A small amount of water will remain in the water vial, which can be discarded.
- Gently swirl the Optivate vial (do not shake) and then remove the water vial from the double spiked needle to release the vacuum in the Optivate vial.
- Continue to swirl the Optivate vial gently until the powder is dissolved (usually in about 2 to 2½ minutes).
- When dissolved, draw up the solution using the filter needle attached to a syringe. Use a new filter needle for each vial of Optivate if your dose is more than one vial.

Do not use this medicine if:

- the water is not pulled into the product vial (this indicates a loss of vacuum in the vial, so the product must not be used).
- the dissolved product and Sterilised Water for Injections forms a gel or a clot (if this happens, please tell Bio Products Laboratory, reporting the batch number printed on the vial). Do not use solutions which are cloudy or have bits in them.

Injecting the medicine

After the medicine is dissolved inject the medicine and attach a suitable needle to the syringe.

The dose, especially your first, should be given slowly (no more than 3 mL per minute) into your vein.

Remember

- the solution must not be stored after reconstitution.
- you must finish injecting the dose into a vein within one hour of dissolving the medicine.
- the solution must not be added to any other fluids, blood or any other medicine.
- you should only use the sterile water supplied to make up the solution. Never inject the water on its own, without first dissolving the powder in it.

How much is given before, during and after major surgery?

1. Major surgery should only be performed when levels of factor VIII can be tested.
2. Your blood should be tested for factor VIII inhibitors (antibodies).
3. If antibodies are not present, a dose of 32 to 40 IU per kg of body weight is given before the operation.
4. During the first few days after the operation, the plasma factor VIII concentration is usually checked at regular periods.
5. A dose of Optivate is usually given every 8 to 24 hours, as needed.
6. After the first few days, the number of times the dose is given may be reduced.
7. Treatment will be continued for as long as recommended by your doctor.
8. If the factor VIII concentration does not reach the expected level (this will be tested by your doctor), or if it decreases quicker than expected (within 12 hours), an inhibitor to factor VIII may be present, which stops factor VIII from working properly. Your doctor is likely to have the appropriate laboratory tests done to see if there is such an inhibitor present.

If you use more Optivate than you should

If you think you may be using too much, stop the injection and tell your doctor. If you know you have used too much, tell your doctor as soon as possible.

If you forget to use Optivate

Do not use a double dose to make up for a forgotten dose. Inject your normal dose as soon as you remember and then continue as instructed by your doctor or Haemophilia nurse.

If you stop using Optivate

Always consult your doctor before deciding to stop your treatment.

4. POSSIBLE SIDE EFFECTS

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

Stop the infusion and tell your doctor immediately or go to the emergency department of your nearest hospital, if you get any of the following symptoms:

- Swelling around the throat
- Flushing
- Hives (nettle rash)
- Feeling lightheaded or dizzy (low blood pressure)
- Rapid heart beat

These symptoms may worsen into severe shock. The above allergic-type reactions are very rare (fewer than 1 patient in every 10,000 patients treated get them).

- Feeling sick or being sick
- Restlessness
- Tightness in the chest or wheezing
- Tingling sensation

Other known side effects are:

Adults and Children

Common (more than 1 in every 100 patients treated):

- Headache
- Other skin rashes
- Feeling that everything is moving, spinning round or tilting (vertigo)
- Cough
- Sneezing
- Redness of the skin (rashes) or pain at the place where the medicine was injected
- Swelling in the extremities of the body
- Itching
- Raised temperature (fever)
- Sudden shivering and feeling cold and rapid rise in temperature
- Stiffness in muscles and joints
- Sleepiness, lethargy or feeling unwell

5. HOW TO STORE OPTIVATE

- Keep out of the reach and sight of children.
- You should store the powder in its container and carton, in the dark, either in a refrigerator or at room temperature (2°C to 25°C), but no higher. Do not freeze.
- The vial of sterilised water that comes with the medicine should also be stored, either in a refrigerator or at room temperature, (up to 25°C, but no higher). Do not freeze.
- Neither the medicine nor the water should be used after the expiry date which is stated as "EXPIRY" on the containers. The expiry date refers to the last day of that month.
- Do not use any solution if any small bits can be seen in it.
- Once reconstituted, Optivate must be used within one hour.

Disposal

After injection of the correct dose, dispose of any solution that remains, any used syringes and needles and empty containers. Your treatment centre will provide a special container ('sharps box') for this purpose. Medicines should not be disposed of via wastewater or household waste.

6. FURTHER INFORMATION

What Optivate contains

The active substances are human coagulation factor VIII with associated von Willebrand Factor (VWF), the natural stabiliser for factor VIII. The other ingredients are: sodium chloride, calcium chloride, sodium citrate, polysorbate 20 and trehalose.

What Optivate looks like and contents of the pack

Optivate, in the form of a white or yellow, crumbly powder, comes in quantities of 250 IU (International Units), 500 IU and 1000 IU in glass vials. These vials are closed with a synthetic rubber stopper under vacuum, held with a tamper-evident cap.

Optivate should only be reconstituted with Sterilised Water for Injections which is supplied with Optivate in plastic ampoules or clear glass bottles.

Marketing Authorisation Holder and Manufacturer

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

Marketing Authorisation Number

PL 08801/0055

This leaflet was last approved in

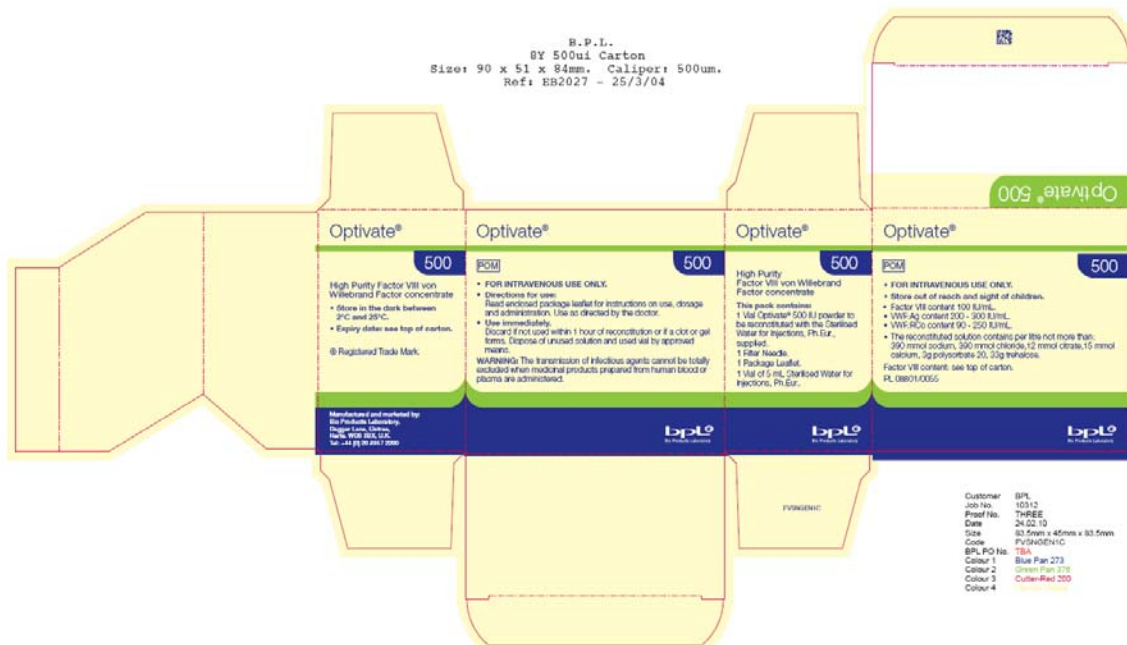
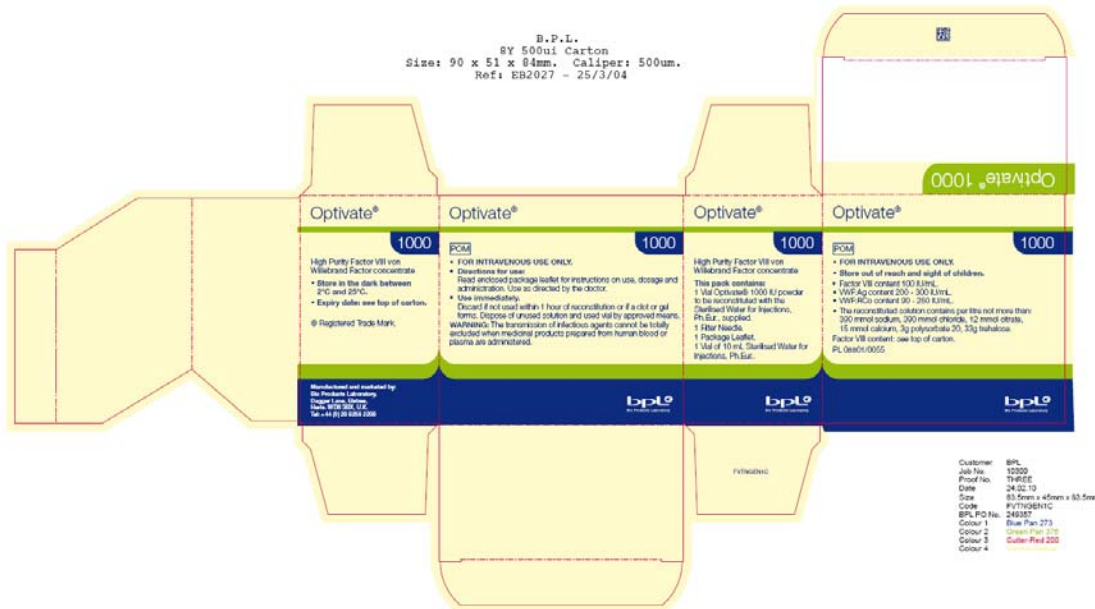
For further information or if you have any questions about the use of this product, please contact BPL via the Marketing Department at the address above or through info@bpl.co.uk.

Labelling

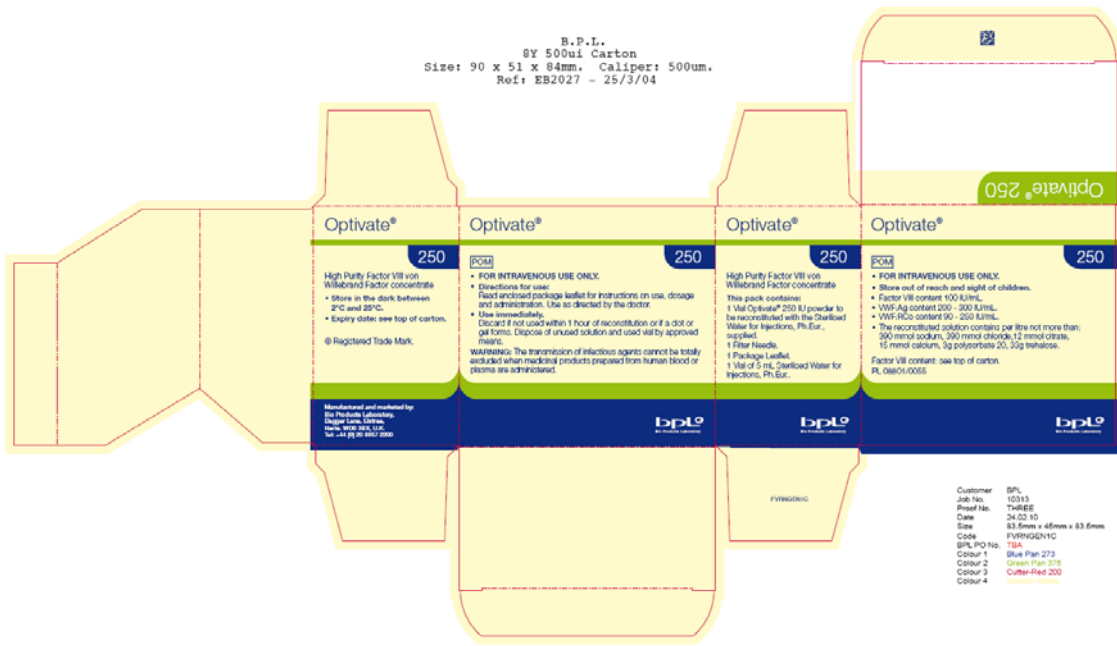
Optivate

(Human Factor VIII, von Willebrand Factor)

PL 08801/0055



B.P.L.
 8Y 500ui Carton
 Size: 90 x 51 x 84mm. Caliper: 500um.
 Ref: EB2027 - 25/3/04



Customer BPL
 Job No. 10313
 Proof No. THREE
 Date 24.03.10
 Size 83.5mm x 48mm x 83.5mm
 Code FVTNGEN1C
 BPL PO No. TBA
 Colour 1 Blue Pan 273
 Colour 2 Green Pan 375
 Colour 3 Cutter Pan 200
 Colour 4

Optivate® 1000 IU
BATCH:

Factor VIII content (IU):

VWF: (RCo):

BATCH:

EXPIRY:

Optivate® High Purity Factor VIII & VWF

1000 IU

FOR INTRAVENOUS USE ONLY.

• Directions for use: Read enclosed leaflet for instructions on use, dosage and administration.

• Use immediately. Discard if not used within one hour of reconstitution or if a clot or gel forms.

Store in the dark between 2°C and 25°C

FVTNGEN1L

PL 08801/0055

bpl

Dispose of unused solution and used vial by approved means.

The reconstituted solution contains per litre not more than: 390 mmol sodium, 390 mmol chloride, 12 mmol citrate, 15 mmol calcium, 3 g polysorbate 20, 33 g trehalose.

Factor VIII content: see first panel.

Warning: The transmission of infectious agents cannot be totally excluded when medicinal products prepared from human blood or plasma are administered.

Bio Products Laboratory,
 Dagger Lane, Silsbee, Herts. WD9 3BX, U.K.
 Tel: +44 (0) 20 8967 2200

bpl

Customer BPL
 Job No. 10316
 BPL PO No. TBA
 Proof No. FOUR
 Date 09.02.10
 Size 110x33mm
 Code FVTNGEN1L
 Colour 1 Blue Pan 273C
 Colour 2 Pantone 376C
 Colour 3 Cutter Pan 200
 Colour 4 Grey Pan 430

Optivate® 500 IU
BATCH:

Factor VIII content (IU):
VWF: (IU/g):

BATCH:
EXPIRY:

Optivate® High Purity Factor VIII & VWF **500**

• FOR INTRAVENOUS USE ONLY. POM

• Directions for use: Read enclosed leaflet for instructions on use, dosage and administration.
• Use immediately. Discard if not used within one hour of reconstitution or if a clot or gel forms.

Store in the dark between 2°C and 25°C

PL 08801/0055 **bpl**® FVNGEN1L

Dispose of unused solution and used vial by approved means. The reconstituted solution contains per litre not more than: 300 mmol sodium, 300 mmol chloride, 12 mmol citrate, 15 mmol calcium, 3 g polysorbate 20, 33 g trehalose.
Factor VIII content: see first panel.
Warning: The transmission of infectious agents cannot be totally excluded when medicinal products prepared from human blood or plasma are administered.

Bio Products Laboratory,
Dräger Linn, Dönne,
Herts. WC6 3BX, U.K.
Tel: +44 (0) 20 8977 2000

bpl®

Customer BPL
Job No. 10315
BPL PO No. TBA
Proof No. TWO
Date 09.02.10
Size 77x31mm
Code FVNGEN1L
Colour 1 Blue Pan 273C
Colour 2 Pantone 376C
Colour 3 Cutter Pan 200
Colour 4 Grey Pan 430

Optivate® 250 IU
BATCH:

Factor VIII content (IU):
VWF: (IU/g):

BATCH:
EXPIRY:

Optivate® High Purity Factor VIII & VWF **250**

• FOR INTRAVENOUS USE ONLY. POM

• Directions for use: Read enclosed leaflet for instructions on use, dosage and administration.
• Use immediately. Discard if not used within one hour of reconstitution or if a clot or gel forms.

Store in the dark between 2°C and 25°C

PL 08801/0055 **bpl**® FVNGEN1L

Dispose of unused solution and used vial by approved means. The reconstituted solution contains per litre not more than: 300 mmol sodium, 300 mmol chloride, 12 mmol citrate, 15 mmol calcium, 3 g polysorbate 20, 33 g trehalose.
Factor VIII content: see first panel.
Warning: The transmission of infectious agents cannot be totally excluded when medicinal products prepared from human blood or plasma are administered.

Bio Products Laboratory,
Dräger Linn, Dönne,
Herts. WC6 3BX, U.K.
Tel: +44 (0) 20 8977 2000

bpl®

Customer BPL
Job No. 10314
BPL PO No. TBA
Proof No. TWO
Date 09.02.10
Size 77x31mm
Code FVNGEN1L
Colour 1 Blue Pan 273C
Colour 2 Pantone 376C
Colour 3 Cutter Pan 200
Colour 4 Grey Pan 430

10 ml STERILIZED
WATER FOR INJECTIONS Ph. Eur.
Do not freeze

Warning: Contains no preservatives; if only part used, remainder must be discarded.
Do not use unless contents are free from deposit.

Supplied to BPL ELSTREE
by Phoenix Pharma Ltd, Gloucester, U.K.
Manufactured at hameln pharmaceuticals gmbh, Germany
Product Licence 1502/0003R

44332/09/03

314005
MAR. 2007

Batch No.
Expiry Date