Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Optivate 250 IU, powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Optivate is presented as a powder and solvent for solution for injection containing nominally 250 IU human coagulation factor VIII per vial.

Optivate contains approximately 100 IU/mL human coagulation factor VIII when reconstituted with 2.5 mL sterilised water for injections.

The potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of Optivate is approximately 43 IU/mg of protein.

Optivate also contains human von Willebrand factor (VWF by ristocetin cofactor activity) at a concentration of approximately 430 IU per vial respectively for the 250 IU presentations.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Product vial containing white or pale yellow powder.
Solvent vial containing clear colourless liquid.

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.

Posology

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.

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.

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 2.2% - 2.7% of normal activity (2.2-2.7 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 to 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 surgery Including tooth extraction	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 population

Children under 6 years of age

The recommended 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.

Children over 6 years of age

There are very limited data on the use of Optivate in children aged 6 to 12 years

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.

Method of administration
Dissolve the preparation as described in section 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).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hypersensitivity

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 shock-treatment should be observed.

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 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 section 4.8 Undesirable effects.

If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII 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. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.

Cardiovascular events
In patients with existing cardiovascular risk factors, substitution therapy with FVIII may increase the cardiovascular risk.

Catheter-related complications

If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered.

Prevention of infection transmission

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. 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 factor VIII products.

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.

Paediatric population
The listed warnings and precautions apply both to adults and children.

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 Fertility, 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.

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 (≥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).

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 conditions	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.

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 safety information with respect to transmissible agents, see section 4.4.

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 via the Yellow Card Scheme:
Website: www.mhra.gov.uk/yellowcard
:

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: 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 section 4.2.

5.2 Pharmacokinetic properties

The pharmacokinetics of Optivate have been evaluated in 15 patients (≥ 12 years old) with severe haemophilia A (<2% activity) after bolus doses of 50 IU/kg. The mean initial half-life was 2.2 hours and the mean elimination half-life was 12.6 hours. An overall mean FVIII in vivo incremental recovery was 2.5 IU/dl per IU/kg. The mean residence time (MRT) was found to be 17.5 hours (a range of 13.4 – 23.4), mean area under the curve (AUC 0-48) was 16.1 h.IU/ml (a range of 11.4 – 22.5) and the mean clearance was 3.1 mL/kg/hr.

Pharmacokinetic data are not available in Children younger than 12 years old.

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, von Willebrand factor.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium citrate
Calcium chloride
Polysorbate 20
Trehalose
Sodium Hydroxide (for pH-adjustment)
Hydrochloric Acid (for pH-adjustment)

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

Product sealed in vial - 3 years.

Reconstituted product - 1 hour.

6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze.
Keep the vial in the outer carton to protect from light.
Following reconstitution, use as soon as possible and certainly within 1 hour.

6.5 Nature and contents of container

1 package of Optivate contains:

1 vial with powder containing 250 IU, 500 IU or 1000 IU human coagulation factor VIII. Vials are Type I, Ph.Eur. glass stoppered with a halobutyl rubber stopper, oversealed with a snap-off polypropylene cap and aluminium lacquered skirt.

1 vial with solvent (sterilised water for injections), 2.5 mL, 5 mL or 10 mL. Vials are Type 1, Ph. Eur. glass sealed with a halobutyl rubber stopper and an overseal.

1 Transfer Device called Mix2Vial™ to allow needle-free, easy and safe reconstitution of the product with the sterilised water for injections

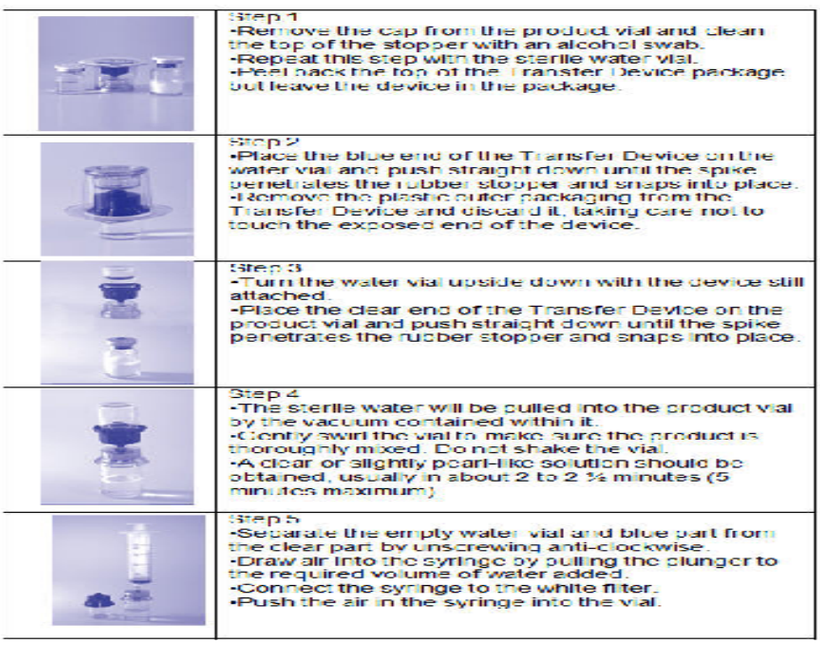
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Optivate should only be reconstituted with sterilised 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, respectively (see diagram on next page).

The containers of Optivate and 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.

The reconstitution is performed as follows:



Step 6
-Immediately invert the vial of solution which will be drawn into the syringe.
-Disconnect the filled syringe from the device.
-The product is now ready for administration. Follow the normal safety practices for administration. Use the product immediately after reconstitution, the product must not be stored.

Note: If you have more than one vial to make up your dose, repeat Steps 1 through 6 withdrawing the solution in the vial into the same syringe.

The Transfer Device supplied with the product is sterile and cannot be used more than once. When the reconstitution process is complete, dispose of in the 'sharps box'.

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

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 discolouration prior to administration. Infuse the product as soon as possible after reconstitution and certainly within one hour.

7 MARKETING AUTHORISATION HOLDER

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Elstree
Hertfordshire WD6 3BX
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8 MARKETING AUTHORISATION NUMBER

PA0763/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 31st July 2015

10 DATE OF REVISION OF THE TEXT

March 2017