Summary of Product Characteristics
OPTIVATE® High Purity Factor VIII and von Willebrand factor concentrate

1. Name of the Medicinal Product:
Optivate (human factor VIII) 100 IU/ml, a powder for solution for injection.

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 43 IU/mg of protein.

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

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 factor VIII 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:

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 hours.	20-40	Repeat every 12 to 24. 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 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 8-24 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 adult 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 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 on demand use in children, including those less than 6 years of age. There are insufficient data to recommend the use of Optivate in children less than 6 years of age for routine prophylaxis.

In the clinical study in children less than 6 years of age with severe haemophilia A, the median dose to treat a bleed was 25.8 IU/kg (range 17.1 to 58.2 IU/kg) but the majority of bleeds were categorised as minor. The target factor VIII concentrations for different types of bleeds in the table above should also be applied to children and adolescents.

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 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/Mix2Vial should be used for each vial because sterile filter needles/Mix2Vials are intended to filter the contents of a single vial of Optivate.

4.3 Contra-indications
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.
This product is made from human blood and may carry a risk for transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.
Appropriate vaccination (hepatitis A and B) for patients in receipt of plasma-derived factor VIII concentrates is recommended.

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

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

4.8 Undesirable effects

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.

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 (including shock).

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.

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 factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using modified assay. The risk of developing inhibitors is correlated to the exposure to anti-haemophilic factor VIII, the risk being highest within the first 20 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.
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 : 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.

For doses in children see section 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 results were as follows:

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

Powder

Sodium chloride
Trisodium citrate
Calcium chloride
Polysorbate 20
Trehalose dihydrate
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)

Solvent
Sterilised water for injections

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.

The diluent, Sterilised Water for Injections, Ph. Eur., is presented in either 5 ml Type I, Ph. Eur., glass vials (for the 2.5 ml and 5 ml fill volumes) or 10 ml Type I, Ph. Eur., glass vials with Type I halobutyl rubber stoppers or plastic ampoules (5 ml).

6.6 Special precautions for disposal and other handling
The reconstitution is performed as follows:
Optivate should only be reconstituted with Sterilised Water for Injections, Ph. Eur. 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 Sterilised Water for Injections, Ph. Eur. 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 swap.
Either of the following methods of reconstitution can then be used:
Filter Needle or Mix2Vial – only one of either will be supplied with the product.

Using a Filter Needle (where supplied):

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 the 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 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 discolouration 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.

Using a Mix2Vial (where supplied):

	Step 1 •Remove the cap from the product vial and clean the top of the stopper with an alcohol swab. •Repeat this step with the sterile water vial. •Peel back the top of the Transfer Device package but leave the device in the package.
	Step 2 •Place the blue end of the Transfer Device on the water vial and push straight down until the spike penetrates the rubber stopper and snaps into place. •Remove the plastic outer packaging from the Transfer Device and discard it, taking care not to touch the exposed end of the device.
	Step 3 •Turn the water vial upside down with the device still attached. •Place the clear end of the Transfer Device on the product vial and push straight down until the spike penetrates the rubber stopper and snaps into place.
	Step 4 •The sterile water will be pulled into the product vial by the vacuum contained within it. •Gently swirl the vial to make sure the product is thoroughly mixed. Do not shake the vial. •A clear or slightly pearl-like solution should be obtained, usually in about 2 to 2 ½ minutes (5 minutes maximum).
	Step 5 •Separate the empty water vial and blue part from the clear part by unscrewing anti-clockwise. •Draw air into the syringe by pulling the plunger to the required volume of water added. •Connect the syringe to the white filter. •Push the air in the syringe into the vial.

	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'.

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.

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

7. Marketing Authorisation Holder:
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8. Marketing Authorisation Number(s):
SIN13191P

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27th May 2010

10. Date of revision of text
December 2019