Product Data Sheet

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

## 1. NAME OF THE MEDICINAL PRODUCT:

Optivate 500 IU, powder for solution for injection
Optivate 1000 IU, 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.

Optivate 500 IU
Each vial contains nominally 500 IU human coagulation factor VIII.
Optivate contains approximately 100 IU/ml of human coagulation factor VIII after reconstitution.

Optivate 1000 IU
Each vial contains nominally 1000 IU human coagulation factor VIII.
Optivate contains approximately 100 IU/ml of human coagulation factor VIII after reconstitution.

The factor VIII potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The 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 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.
Produced from the plasma of human donors.

Excipient with known effect:
Optivate contains approximately 320 mmol/1 (7.4 mg/ml) sodium.
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM:

Powder and solvent for solution for injection.
Powder: White or pale yellow powder.
Solvent: 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.

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 on 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:

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|---|
| ***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 surgery*<br>Including tooth extraction | 30-60 | Every 24 hours, at least<br>1 day, until healing is achieved. |
| *Major surgery* | 80-100<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). |

*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 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 listed in section 6.1.

## 4.4 Special warnings and precautions for use

*Traceability*
In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

*Hypersensitivity*
Allergic type hypersensitivity reactions are possible with Optivate. The product contains traces of human proteins other than factor VIII and VWF.
If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.
In case of shock, standard medical treatment for shock should be implemented.

*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 severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 50 exposure days but continues throughout life although the risk is uncommon.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre posing less of a risk of insufficient clinical response than high titre inhibitors.

In general, all patients treated with human coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests.

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 factor VIII 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.

*Transmissible agents*
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 (foetal 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 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 (see section 4.8).

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 have been reported.

## 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

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

## 4.8 Undesirable effects

Summary of the safety profile

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

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including Optivate. If such inhibitors occur, the condition may manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

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

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: 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). The table lists adverse reactions reported from 96 patients in clinical studies. Approximately 10% of patients can be expected to experience adverse reactions on long-term treatment.

| **MedDRA Standard System Organ Class** | **Adverse reactions** | **Frequency** |
|---|---|---|
| **Blood and lymphatic system disorders** | Factor VIII inhibition | Uncommon (PTPs)*<br>Very common (PUPs)* |
| **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 |

* Frequency is based on studies with all factor VIII products which included patients with severe haemophilia A. PTPs = previously-treated patients, PUPs = previously-untreated patients.

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

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il
Additionally, you should also report to Kamada LTD to email address:
pharmacovigilance@kamada.com

## 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.

Mechanism of action
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.

Of note, annualised bleeding rate (ABR) is not comparable between different factor concentrates and between different clinical studies.

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.

Paediatric population

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 results are presented in the table below:

| **Parameter** | **Mean** | **95% CI** |
|---|---|---|
| Non-compartmental terminal half-life (hours) | 12.4 | 10.94-13.83 |
| Mean residence time (hours) | 17.5 | 15.99-18.92 |
| Clearance (ml/hour/kg) | 3.1 | 2.71-3.51 |
| Area under curve ($AUC_{0-48h}$) (IU.h/ml) | 16.1 | 13.97-18.28 |
| Area under curve ($AUC_{0-inf}$) (IU.h/ml) | 17.31 | 14.98-19.65 |
| Volume of distribution (ml/kg) | 53.4 | 46.2-60.52 |
| Initial (Alpha) half-life (hours) | 2.2 | 1.48-2.88 |
| Elimination (Beta) half-life (hours) | 12.6 | 11.33-13.92 |
| Incremental recovery (IU/dl per IU/kg) | 2.5 | 2.22-2.74 |

CI = Confidence Interval

Paediatric population

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

Powder
Trehalose dihydrate
Sodium chloride
Trisodium citrate dihydrate
Calcium chloride dihydrate
Polysorbate 20
Sodium hydroxide
Hydrochloric acid
Solvent
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 provided 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 - the expiry date of the product is indicated on the packaging materials.
Reconstituted product – 1 hour.

**6.4 Special precautions for storage**

Store at 2°C -25°C.
Do not freeze.
Keep the vials in the outer carton in order to protect from light.
Following reconstitution, use immediately and certainly within 1 hour.

**6.5 Nature and contents of container**

Optivate 500 IU powder and solvent for solution for injection
- 500 IU powder in a 10 ml vial (type 1 glass) with a stopper (halobutyl rubber), with an overseal (aluminium) and tamper evident flip-off cap (polypropylene)
- 5 ml solvent in a 5 ml vial (type 1 glass) for reconstitution
- One Mix2Vial™ transfer device

Optivate 1000 IU powder and solvent for solution for injection
- 1000 IU powder in a 30 ml vial (type 1 glass) with a stopper (halobutyl rubber), with an overseal (aluminium) and tamper evident flip-off cap (polypropylene)
- 10 ml solvent in a 10 ml vial (type 1 glass) for reconstitution
- One Mix2Vial™ transfer device

Not all pack sizes may be marketed.

An Administration User Kit is provided, which includes:

**Winged infusion set:** a butterfly No. 23 needle for administration of the product.
**20 mL syringe:** the dissolved solution is withdrawn into the syringe. The size of syringe is provided to enable more than one vial to be administered using one syringe (see following instructions).

### 6.6 Special precautions for disposal and other handling

Optivate should only be reconstituted with water for injections provided with the product. The 500 IU and 1000 IU presentations should be reconstituted using 5mL and 10mL water for injections, respectively (see diagram on next page).

The containers of Optivate and water for injections should be brought to between 20°C and 30°C prior to the removal of the flip-off cap from the product vial.

Reconstituted medicinal product should be inspected visually for particulate matter and discolouration prior to administration. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Use the product immediately after reconstitution or within 1 hour.

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

Instructions for reconstitution:

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<tr>
<td>  </td>
<td>Step 1<br>• Remove the cap from the product vial and clean the top of the stopper with an alcohol swab.<br>• Repeat this step with the water vial.<br>• Peel back the top of the Mix2Vial™ transfer device package but leave the device in the package.</td>
<td>  </td>
<td>Step 4<br>• The water will be pulled into the product vial by the vacuum contained within it.<br>• Gently swirl the vial to make sure the product is thoroughly mixed. Do not shake the vial.<br>• A clear or slightly pearl-like solution should be obtained, usually in about 2 to 2½ minutes (5 minutes maximum).</td>
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<td>  </td>
<td>Step 2<br>• Place the blue end of the Mix2Vial™ transfer device on the water vial and<br>push straight down until the spike penetrates the rubber stopper and snaps into place.<br>• Remove the plastic outer packaging from the Mix2Vial™ transfer device and discard it, taking care not to touch the exposed end of the device.</td>
<td>  </td>
<td>Step 5<br>• Separate the empty water vial and blue part from the clear part by unscrewing anti-clockwise.<br>• Draw air into the syringe by pulling the plunger to the required volume of water added.<br>• Connect the syringe to the clear part of the Mix2Vial™.<br>• Push the air in the syringe into the vial.</td>
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|---|---|---|---|
|  | **Step 3**<br>• Turn the water vial upside down with the device still attached.<br>• Place the clear end of the Mix2Vial™ transfer device on the product vial and push straight down until the spike penetrates the rubber stopper and snaps into place. |  | **Step 6**<br>• Immediately invert the vial of solution which will be drawn into the syringe.<br>• Disconnect the filled syringe from the Mix2Vial™ transfer device.<br>• The product is now ready for administration. Follow the normal safety practices for administration.<br>Use the product immediately after reconstitution, the product must not be stored. Discard if not used within 1 hour of reconstitution. |

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

The Mix2Vial™ transfer device supplied with the product is sterile and cannot be used more than once.

**7. Manufacturer:**

Bio Products Laboratory Limited (BPL)
Dagger Lane, Elstree, Hertfordshire, WD6 3BX, United Kingdom

**8. License holder:**

Kamada Ltd. Beit Kama, Israel

**License number:**
140-02-31686-00
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