REPLENINE-VF

1. NAME OF THE MEDICINAL PRODUCT

Replenine-VF 500, powder for solution for injection
Replenine-VF 1000, powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Replenine-VF contains high purity human coagulation factor IX.

500 IU

Each vial contains nominally 500 IU human coagulation factor IX.

Replenine-VF contains approximately 50 IU/ml of human coagulation factor IX after reconstitution at full volume.

1000 IU

Each vial contains nominally 1000 IU human coagulation factor IX.

Replenine-VF contains approximately 50 IU/ml of human coagulation factor IX after reconstitution at full volume.

One ml of Replenine-VF contains approximately 100 IU human coagulation factor IX after reconstitution at half volume (see section 6.6).

The potency (IU) is determined using the European Pharmacopoeia one stage clotting test. The specific activity of Replenine-VF is approximately 100 IU/mg protein.

Produced from the plasma of human donors.

Excipient with known effect:
This medicinal product contains up to 83 mg sodium per vial, equivalent to 4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
Powder: White or slightly coloured powder.
Solvent: Clear colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

4.2 Posology and method of administration

Treatment should be under the supervision of a physician experienced in the treatment of haemophilia.

Treatment monitoring
During the course of treatment, appropriate determination of factor IX levels is advised to guide the dose to be administered and the frequency of repeated infusions. Individual patients may vary in their response to factor IX, demonstrating different half-lives and recoveries. Dose based on body weight may require adjustment in underweight or overweight patients.

In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor IX activity) is indispensable.

When using an in vitro thromboplastin time (aPTT)-based one stage clotting assay for determining factor IX activity in patients' blood samples, plasma factor IX activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. This is of importance particularly when changing the laboratory and/or reagents used in the assay.

Posology

Dose and duration of the substitution therapy depend on the severity of the factor IX deficiency, on the location and extent of the bleeding and on the patient's clinical condition.

The number of units of factor IX administered is expressed in International Units (IU), which are related to the current WHO standard for factor IX products. Factor IX 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 IX in plasma).

One International Unit (IU) of factor IX activity is equivalent to that quantity of factor IX in one ml of normal human plasma.

On demand treatment
The calculation of the required dose of factor IX is based on the empirical finding that 1 International Unit (IU) of factor IX per kg body weight raises the plasma factor IX activity by 1.16% of normal activity. The required dose is determined using the following formula:

Required units = body weight (kg) x desired factor IX rise (%) or (IU/dl) x 0.85

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 IX activity should not fall below the given plasma activity level (in 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 IX level required (%) or (IU/dl)**	**Frequency of doses (hours)/ Duration of therapy (days)**
Haemorrhage		
Early haemarthrosis, muscle bleed or oral bleeding	20-40	Repeat every 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.

More extensive haemarthrosis, muscle bleed or haematoma.	30-60	Repeat infusion every 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 is 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 post-operative)	Repeat infusion every 8 to 24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a Factor IX activity of 30% to 60% (IU/dl).

Prophylaxis
For long term prophylaxis against bleeding in patients with severe haemophilia B, the usual doses are 20 to 40 IU of factor IX per kilogram of body weight at intervals of 3 to 4 days.

In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

Continuous infusion
Prior to surgery, a pharmacokinetic analysis should be performed to obtain an estimate of clearance.

The initial infusion rate can be calculated as follows:

Clearance x desired steady state level = infusion rate (IU/kg/hr)

After the initial 24 hours of continuous infusion, the clearance should be calculated again every day using the steady state equation with the measured level and the known rate of infusion (see section 5.2).

Paediatric population

Children under 12 years of age
There are limited data on the use of Replenine-VF in children under 12 years of age (see section 5.1). The recommended dose and dosing frequency in adolescents (aged 12-17 years) are as recommended for adults.

Method of administration

Intravenous use
Replenine-VF should be administered via the intravenous route at a rate not exceeding 3 ml per minute.
For instructions on reconstitution of the medicinal product before administration, see section 6.6.

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 Replenine-VF. The product contains traces of human proteins other than factor IX. 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

After repeated treatment with human coagulation factor IX products, patients should be monitored for the development of neutralising antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

There have been reports in the literature showing a correlation between the occurrence of a factor IX inhibitor and allergic reactions. Therefore, patients experiencing allergic reactions should be evaluated for the presence of an inhibitor. It should be noted that patients with factor IX inhibitors may be at an increased risk of anaphylaxis with subsequent challenge with factor IX.

Because of the risk of allergic reactions with factor IX products, the initial administrations of factor IX should, according to the treating physician's judgement, be performed under medical observation where proper medical care for allergic reactions could be provided.

Thromboembolism

Because of the potential risk of thrombotic complications, clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with appropriate biological testing when administering this product to patients with liver disease, to patients post-operatively, to new-born infants, or to patients at risk of thrombotic phenomena or DIC. In each of these situations, the benefit of treatment with Replenine-VF should be weighed against the risk of these complications.

Cardiovascular events

In patients with existing cardiovascular risk factors, substitution therapy with factor IX 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.

<u>Transmissible agents</u>

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 (HBV) and hepatitis C (HCV), and for the non-enveloped hepatitis A and parvovirus B19 viruses.

It is strongly recommended that every time that Replenine-VF 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.

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived factor IX products.

Paediatric population

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

4.5 Interaction with other medicinal products and other forms of interactions

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

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with factor IX. Based on the rare occurrence of haemophilia B in women, experience regarding the use of factor IX during pregnancy and breast-feeding is not available. Therefore, factor IX should be used during pregnancy and lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines

Replenine-VF 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. In some cases, these reactions have progressed to severe anaphylaxis (including shock), and they have occurred in close temporal association with development of factor IX inhibitors (see section 4.4). Nephrotic syndrome has been reported following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors and a history of allergic reaction.

Patients with haemophilia B may develop neutralising antibodies (inhibitors) to factor IX. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

There is a potential risk of thromboembolic episodes following the administration of factor IX products, with a higher risk for low purity preparations. The use of low purity factor IX products has

been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. The use of high purity factor IX is rarely associated with such adverse reactions.

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 patients in clinical studies and from post-marketing experience.

MedDRA Standard System Organ Class (SOC)	**Adverse reactions**	**Frequency**
Nervous system disorders	Headache	Common
General disorders and injection site changes	Injection site reaction	Common

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

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 case of overdose with human factor IX has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics: blood coagulation factor IX, ATC code: B02BD04.

Factor IX is a single chain glycoprotein with a molecular mass of about 68,000 Dalton. It is a vitamin- K dependent coagulation factor and it is synthesised in the liver.
Factor IX is activated by factor XIa in the intrinsic coagulation pathway and by the factor VII/tissue factor complex in the extrinsic pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot is formed.

Haemophilia B is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor IX 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 IX

is increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

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

In a multicentre, non-randomised, open-label clinical study, 22 patients aged 17-76 years with severe haemophilia B (≤2% activity) were treated either prophylactically (n=6) or on demand (n=16) for a median duration of 44 weeks. Patients on the prophylactic regimen (mean dose of 163 IU/kg per month per patient) experienced 11 bleeds on average during the study and the mean dose used to treat them was 49 IU/kg. Patients treated on demand experienced a mean of 13.4 bleeds during the study and the mean dose used to treat them was 30.4 IU/kg.

Paediatric population

In a multicentre, non-randomised, open-label clinical study in 15 children under 6 years of age (range 0.2-5.6 years) with severe haemophilia B (≤2% activity) for a median duration of 28 weeks. The mean number of bleeds per subject per month was 0.2 bleeds for patients in the prophylaxis group (n=10) and 1.2 bleeds in the on-demand group (n=6).

The mean dose of Replenine-VF for prophylaxis was 29 IU/kg (range: 20-37 IU/kg) given up to twice weekly; the mean monthly dose was 194 IU/kg. The mean dose to treat a bleed was 27 IU/kg (range: 13-53 IU/kg).

Inhibitors
The paediatric trial enrolled three previously untreated patients, all of whom remained inhibitor negative after treatment with Replenine-VF for 6 months. Overall, of the 67 previously tested patients in clinical studies, one young child developed an inhibitor with a titre of 3.6 Bethesda Units.

5.2 Pharmacokinetic properties

In a clinical study of 15 adult patients with haemophilia B, the mean pharmacokinetic properties of Replenine-VF were as follows:

Parameter	**Mean**
Incremental recovery (IU/dl per IU/kg)	1.16
Area under curve (AUC_{0-56h}) (IU/ml/h)	15.2
Terminal half-life (hours)	19.0
Initial (Alpha) half-life (hours)	4.8
Elimination (Beta) half-life (hours)	20.9
Mean Residence time (hours)	24.9
Clearance (ml/hour/kg)	4.52
Volume of distribution (ml/kg)	122.1

From clinical studies in 48 adult patients with haemophilia B, most of whom had several assessments of incremental recovery, all based on the maximum FIX:C in the first 1 hour (ISTH, 2001), the overall results were as follows:

Mean	1.25 (95%CI 1.16 - 1.33) IU/dl per IU/kg
Median	1.17 IU/dl per IU/kg

In a clinical trial of Replenine-VF given by continuous infusion to cover for major surgery, an initial bolus dose was given to raise the factor IX activity to about 100 IU/dl. Continuous infusion was then started at 6 IU/kg/hour (given undiluted by syringe pump or syringe driver). Subsequently, the rate of infusion was adjusted according to the following formula:

$$\text{New rate (IU/kg/hour)} = \text{Latest rate (IU/kg/hour)} \times \frac{\text{Target FIX level (IU/ml)}}{\text{Recently recorded FIX level (IU/ml)}}$$

The median clearance was fastest during the first 24 hours peri-operatively (Day 1). Thereafter, median clearance declined as follows: Day 1, 7.3 ml/kg/h; Day 2, 4.2 ml/kg/h; Day 3, 4.4 ml/kg/h; Day 4, 3.4 ml/kg/h; Day 5, 3.2 ml/kg/h; Day 6, 1.3 ml/kg/h. The formula describing the reduction in clearance from post-operative Days 2 to 8 was as follows:

Factor IX clearance (ml/h/kg) = 5.05 – (0.36 x day)

There was inter-patient variability in clearance so, when covering surgery by continuous infusion, monitoring of plasma factor IX activity is required (see section 4.2).

Additional data from the study of continuous infusion in major surgery provided the following mean pharmacokinetic values for the period on continuous infusion (by one-compartment multidose analysis):

Half-life:	14.8 hours
Mean Residence Time:	31.3 hours
Clearance:	3.8 ml/hour/kg
Volume of Distribution:	107.0 ml /kg

5.3 Preclinical safety data

Human plasma coagulation factor IX (as contained in Replenine-VF) is a normal constituent of the human plasma and acts like the endogenous factor IX.

Repeat-dose toxicity testing in animals is impracticable due to interference with developing antibodies to heterologous protein. Since clinical experience provides no evidence for tumourigenic and mutagenic effects of human plasma coagulation factor IX, experimental studies, particularly in heterologous species, are not considered necessary.

Single dose toxicity studies in rats and mice have established greater than a 20-fold safety margin. Thrombogenicity testing in rabbits and rats showed no evidence of thrombogenicity at doses of 200-300 IU/kg body weight.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
L-lysine monohydrochloride

sodium chloride
trisodium citrate
glycine
disodium phosphate dihydrate
citric acid
polysorbate 80
tri-n-butyl phosphate.

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 factor IX adsorption to the internal surface of some injection/infusion equipment.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
After reconstitution, chemical and physical in-use stability has been demonstrated for 1 hour up to 25°C.
From a microbiological point of view, unless the method of opening/reconstitution precludes the risk of microbial contamination, the reconstituted medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 1 hour up to 25°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Can be stored up to 3 months at 25°C. Record date of removal from refrigerator on carton.
Keep the vials in the outer carton in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.
Do not use beyond the expiry date on the label.

6.5 Nature and contents of container

500 IU

-500 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 30 ml vial (type 1 glass) for reconstitution
-One Mix2Vial™ transfer device

1000 IU

-1000 IU powder in a 50 ml vial (type 1 glass) with a stopper (halobutyl rubber), with an overseal (aluminium) and tamper evident flip-off cap (polypropylene)
-20 ml solvent in a 50 ml vial (type 1 glass) for reconstitution

-One Mix2Vial™ transfer device

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Replenine-VF should only be reconstituted with water for injections provided with the product. The 500 IU presentation should be reconstituted using 10 ml solvent. The 1000 IU presentation should be reconstituted using 20 ml solvent.

The containers of Replenine-VF and water for Injections should be brought to between 20°C and 25°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:

You can reconstitute your product in two ways using the Transfer Device called Mix2Vial™:
(A) Reconstituting in Full Volume or
(B) Reconstituting with Half Volume

(A) Reconstituting in Full Volume

	**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 water vial. • Peel back the top of the Mix2Vial™ transfer device package but leave the device in the package.
	**Step 2** • Place the blue end of the Mix2Vial™ 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 Mix2Vial™ 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 Mix2Vial™ transfer device on the product vial and push straight down until the spike penetrates the rubber stopper and snaps into place.

	**Step 4** • The 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 Mix2Vial™ transfer 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 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.

B) Reconstituting with Half Volume

To use the Mix2Vial™ transfer device for reconstituting Replenine-VF in half volumes, it is first necessary to remove and discard half the water volume from the water for injections vial.

- Pierce the stopper of the water vial with a needle and syringe and draw up half the volume of water.
- Check that the correct amount is withdrawn. This needle and syringe, with its contents, should be safely disposed of.
- The remaining water in the vial will be used for reconstitution (half the original volume).
- To complete the dissolving process, follow steps 1 to 6 in Section A above.
- The product is then ready for administration.

Note: If you have more than one vial to make up your dose, repeat the above steps 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
122-97-29999-00
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