Replenine-VF
(Human Factor IX)
PL 08801/0054

UKPAR

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The MHRA granted Bio Products Laboratory (BPL) a Marketing Authorisation for the medicinal product Replenine-VF, 50IU/ml human factor IX, powder for solution on 26th May 2010. This medicine is subject to restricted medical prescription and is indicated for treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency). Factor IX is a normal constituent of human plasma and its hereditary absence or deficiency usually results in a severe disorder of blood coagulation known as Haemophilia B.

Replenine-VF contains as its active, human factor IX of high specific activity with insignificant levels of human factor II, and human factor X.

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

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Replenine-VF outweigh the risks, hence a Marketing Authorisation has been granted.
Replenine-VF
(Human Factor IX)
PL 08801/0054

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of data on quality, safety and efficacy the UK granted a Marketing Authorisation to Bio Products Laboratory (BPL) for the medicinal product Replenine-VF, 50IU/ml human factor IX, powder for solution on 26th May 2010. This product is a restricted prescription only medicine.

This application was a line-extension to the original Replenine-VF licence (PL 08801/0028) submitted as an abridged complex national application under Article 10(a) according to Directive 2001/83/EC, as amended; a well-established use application. The only change is the applicant reverting to their previously licensed method of hydration of the freeze dried product using a sterile syringe and a bottle of water, instead of the Mix2 rehydration kit.

Replenine-VF contains as its active, human factor IX of high specific activity with insignificant levels of human factor II, and human factor X. Replenine-VF is a preparation of the human plasma coagulation factor IX, a single chain glycoprotein with a molecular mass of about 68,000 which is present in normal human plasma. The product Replenine-VF is a preparation of human factor IX, the VF denoting a virus filtered formulation.

Factor IX is a normal constituent of human plasma and its hereditary absence or deficiency usually results in a severe disorder of blood coagulation known as Haemophilia B. Replenine-VF, 50IU/ml human factor IX, sterile powder for solution contains human factor IX and is indicated for treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

Replenine-VF is presented as a sterile powder for solution, containing nominally 250, 500 or 1000 IU human coagulation factor IX per vial. The product contains approximately 50 IU/mL when reconstituted with either 5mL (250 IU vial), 10mL (500 IU vial) or 20mL (1000 IU Vial) of sterilised water for injections, Ph.Eur. Treatment with Replenine-VF should only be initiated under the supervision of a physician experienced in the treatment of haemophilia.

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

The application is an exact copy of the existing license (PL 08801/0028). The only change is the applicant reverting to their previously licensed method of hydration of the freeze dried product using a sterile syringe and a bottle of water, instead of the Mix2 rehydration kit.

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

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

No new clinical data have been supplied with these applications and none are required for applications of this type.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

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

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

EFFICACY
These applications are identical to the previously granted application for Replenine-VF (PL 08801/0028).

No new or unexpected safety concerns arose from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the originator product (PL 08801/0028).

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s product is identical to the originator product. Extensive clinical experience with Replenine-VF is considered to have demonstrated the therapeutic value of the product. The risk: benefit is, therefore, considered to be positive.
Replenine-VF
(Human Factor IX)
PL 08801/0054

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation application 19th February 2010
2. Following standard checks the MHRA informed the applicant that its application was considered valid on 26th February 2010
3. Following assessment of the submitted data, the application was finalised on 26th May 2010
Replenine-VF
(Human Factor IX)
PL 08801/0054

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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</table>
Replenine-VF
(Human Factor IX)
PL 08801/0054

SUMMARY OF PRODUCT CHARACTERISTICS
1 **NAME OF THE MEDICINAL PRODUCT**
REPLENINE®-VF, 50 IU/ml human factor IX, a powder for solution.

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**

2.1 **Qualitative composition**
REPLENINE®-VF is a high purity factor IX. This product is prepared from plasma from screened donors. Donors are selected from the USA.

2.2 **Quantitative composition**
REPLENINE®-VF is presented as a sterile powder for solution, containing nominally 250, 500 or 1000 IU human coagulation factor IX per vial. The product contains approximately 50 IU/mL when reconstituted with 5 mL (250 IU vial), 10mL (500 IU vial) or 20mL (1000 IU Vial) of Sterilised Water for Injections, Ph.Eur.
The potency (IU) is determined using the European Pharmacopoeia one stage clotting test. The specific activity of REPLENINE®-VF is approximately 100 IU per mg of protein.
For a full list of excipients, see section 6.1.

3 **PHARMACEUTICAL FORM**
REPLENINE®-VF is a powder for solution, it is a freeze-dried concentrate of factor IX for reconstitution with Sterilised Water for Injections, Ph.Eur. After reconstitution with the supplied sterile water diluent the product is administered intravenously.

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 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 factor IX deficiency, on the location and extent of the bleeding and on the patient’s clinical condition.

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

Required units = body weight (kg) x desired factor IX rise (%) (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. Factor IX products rarely require to be administered more than once daily.

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:

<table>
<thead>
<tr>
<th>Degree of haemorrhage/Type of surgical procedure</th>
<th>Factor IX level required (%) (IU/dl)</th>
<th>Frequency of doses (hours)/Duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td></td>
<td>Repeat every 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.</td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding</td>
<td>20-40</td>
<td>Repeat infusion every 24 hours for 3-4 days or more until pain and disability are resolved.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma.</td>
<td>30-60</td>
<td>Repeat infusion every 8 to 24 hours until threat is resolved.</td>
</tr>
<tr>
<td>Life threatening haemorrhages.</td>
<td>60-100</td>
<td>Repeat infusion every 8 to 24 hours until threat is resolved.</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td>Every 24 hours, at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Minor surgery</td>
<td>30-60</td>
<td>Repeat infusion every 8-24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a FIX activity of 30% to 60% (IU/dl).</td>
</tr>
<tr>
<td>Including tooth extraction</td>
<td>80-100 (pre- and postoperative)</td>
<td>Repeat infusion every 8-24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a FIX activity of 30% to 60% (IU/dl).</td>
</tr>
<tr>
<td>Major surgery</td>
<td></td>
<td>Repeat infusion every 8-24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a FIX activity of 30% to 60% (IU/dl).</td>
</tr>
</tbody>
</table>

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. 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. Individual patients may vary in their response to factor IX, achieving different levels of \textit{in vivo} recovery and demonstrating different half-lives.

\textit{Continuous infusion}

An initial pre-operative bolus injection is needed to raise the factor IX activity to about 100 IU/dL based on the formula in the text, above. A continuous infusion is usually started at 6 IU/kg/hour (given undiluted by syringe pump or syringe driver) and adjusted according to the factor IX activity in plasma monitored at least once daily. Adjust the rate of infusion according to the formula:

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

\textit{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. In a clinical study in children under six years of age, the median dose of REPLENINE\textsuperscript{®}-VF for prophylaxis was 29.3 IU/kg (95% confidence interval: 25.3 – 33.2 IU/kg) given up to twice weekly; the mean dose to treat a bleed was 26.8 IU/kg (95% confidence interval : 15.7 – 37.9 IU/kg).

Patients should be monitored for the development of factor IX inhibitors. If the expected factor IX 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 IX inhibitor is present. In patients with high levels of inhibitor, factor IX therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of patients with haemophilia.

See also 4.4.

\textit{Method of administration}

Reconstitute the product as described in 6.6. The product should be administered via the intravenous route. The dose, especially the first dose, should be given slowly (not more than 3 ml per minute).

For continuous infusion during and after major surgery, the undiluted product should be given intravenously by a syringe driver or syringe pump (see 4.2).

4.3 \textbf{CONTRAINDICATIONS}

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

4.4 \textbf{SPECIAL WARNINGS AND PRECAUTIONS FOR USE}

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. REPLENINE\textsuperscript{®}-VF contains traces of human proteins other than FIX. 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 treatment for shock-treatment should be observed.

- 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 HIV, HBV and HCV, and for the non-enveloped viruses HAV and parvovirus B19.

- 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) for patients in receipt of plasma-derived factor IX concentrates is recommended.

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 concentrates, 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.

Since the use of factor IX complex concentrates has historically been associated with the development of thromboembolic complications, the risk being higher in low purity preparations, the use of factor IX containing products may be potentially hazardous in patients with signs of fibrinolysis and in patients with disseminated intravascular coagulation (DIC). 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 thromboembolic phenomena or DIC. In each of these situations, the potential benefit of treatment with REPLENINE®-VF should be weighed against the risk of these complications.

In the interest of patients, it is recommended that, whenever possible, every time that REPLENINE®-VF is administered to them, the name and batch number of the product is registered.
4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
No interactions of human coagulation factor IX products with other medicinal products are known.

4.6 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, REPLENEINE\textsuperscript{®}-VF 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 patients in clinical studies experience.:

<table>
<thead>
<tr>
<th>MedDRA Standard System Organ Class</th>
<th>Adverse reactions</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>common ( \geq \frac{1}{100} ) to ( &lt;\frac{1}{10} )</td>
</tr>
<tr>
<td>General disorders and injection site changes</td>
<td>injection site reaction</td>
<td>common ( \geq \frac{1}{100} ) to ( &lt;\frac{1}{10} )</td>
</tr>
</tbody>
</table>

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 in patients treated with factor IX containing products. In some cases, these reactions have progressed to severe anaphylaxis, and they have occurred in close temporal association with development of factor IX inhibitors (see also 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.

On rare occasions, fever has been observed.

Patients with haemophilia B may develop antibodies (inhibitors) to factor IX. If such inhibitors occur, the condition will manifest as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. In a clinical study in 15 children aged less than six years, three previously untreated patients were enrolled and remained inhibitor negative after treatment with REPLENEINE\textsuperscript{®}-VF for six months. The median number of exposure days in these patients was 43 (range 26-54). Of the 67 PTP patients in clinical studies, one young child developed an inhibitor of 3.6 Bethesda Units.

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 side effects.

For information on viral safety see 4.4.

4.9  OVERDOSE
No symptoms of overdose with human factor IX have been reported.

5  PHARMACOLOGICAL PROPERTIES

5.1  PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Antihaemorrhagics: blood coagulation factor IX.
ATC code: B02B D04
Factor IX is a single chain glycoprotein with a molecular mass of about 68,000. It is a vitamin K-dependent coagulation factor and it is synthesised in the liver. Factor IX is activated by factor Xla 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 level of factor IX is increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

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

5.2  PHARMACOKINETIC PROPERTIES
In a clinical study of 15 adult patients with haemophilia B, the mean pharmacokinetic properties of REPLINEINE®-VF were as follows:

Incremental Recovery:  1.16  IU/dL per IU/kg
AUC_{0-56 hrs}:  15.2  IU.mL/hour
Terminal Half-life:  19.0  hours
Alpha Half-life:  4.8  hours
Beta-Half-life:  20.9  hours
Mean Residence Time:  24.9  hours
Clearance:  4.52  mL/hour/kg
Volume of Distribution:  122.1 mL/kg

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, when REPLENINE®-VF was given by continuous infusion to cover major surgery, 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:

\[
\text{Factor IX clearance (mL/h/kg)} = 5.05 - (0.36 \times \text{day})
\]

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. Repeated 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

REPLENINE®-VF solution contains the following excipients:
- glycine
- lysine
- sodium citrate
- sodium phosphate
- sodium chloride
- polysorbate 80
- tri-n-butyl phosphate.

#### 6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products. Only approved injection/infusion sets should be used with the reconstituted product because treatment failure may occur as a consequence of human factor IX adsorption to the internal surface of some unapproved infusion equipment.
6.3 SHELF LIFE
When unopened, shelf-life is 36 months at 2°C to 8°C, and up to 3 months at normal ambient temperature (25°C) within this period is not detrimental to the product. The expiry date is printed on the label.

When opened, store at 2°C to 25°C and use within one hour. Warm to ambient (25°C) before injection.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store REPLENINE®-VF in its carton to protect from light at the temperature specified on the packaging. DO NOT FREEZE. Do not use beyond the expiry date on the label. When the product is for home use a domestic refrigerator is suitable for storage.

Sterilised Water for Injections, Ph.Eur. should be stored between 2°C and 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER
REPLENINE®-VF is a freeze-dried plug of high purity factor IX supplied in a single ‘dose vial of either 250 IU, 500 IU or 1000 IU (nominal). The product is contained in glass (type I Ph.Eur.) bottles stoppered with a halobutyl stopper. The bung is over-sealed with a snap-off polypropylene cap and a clear lacquered aluminium skirt.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Reconstitute the product with the Sterilised Water for Injections, Ph.Eur. supplied (2.5 mL or 5 mL for 250 IU, 5 mL or 10 mL for 500 IU and 10 mL or 20 mL for 1000 IU). Do not use the water if beyond the expiry date or if signs of particulate matter are visible. Do not inject Sterilised Water for Injections, Ph.Eur. on its own.
Reconstitute REPLENINE®-VF as follows:
The container of concentrate and the Sterilised Water for Injections, Ph. Eur. should be brought to between 20°C and 30°C, prior to the removal of the ‘flip-off’ closures. Remove the caps from the concentrate and Sterilised Water for Injections, Ph.Eur., and clean stoppers with a spirit swab. Either of the following methods of reconstitution can then be used:
a) 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 IX. On piercing the seal of the factor IX vial, the water will be drawn into the vial which is under vacuum.
NB: THE FILTER NEEDLE PROVIDED MUST NOT BE USED TO DRAW UP THE WATER FOR INJECTIONS.
or
b) Remove the cover guard from one end of a double ended transfer needle and insert through the stopper into the vial of Sterilised Water for Injections, Ph.Eur. Remove the other end of the needle guard, invert the water vial over the product vial and insert the free end of the needle through the stopper into the vial of factor IX. 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. This method cannot be used to prepare the infusion at reduced volume (see above).
If the water to be used for reconstitution is not drawn into the vial containing factor IX, this indicates loss of vacuum. If the vial does not contain a vacuum or if the reconstituted factor IX 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 either:
a) Removing the syringe from the needle before removing the needle from the product vial.
or
b) Disconnecting the two vials by first removing the transfer needle from the water vial and then removing the transfer needle from the product vial.

REPLENINE®-VF dissolves rapidly and requires only very gentle agitation to ensure complete dissolution. A clear or slightly opalescent solution should be obtained within 5 minutes. If a gel or clot forms discard the vial.

The solution should be drawn from the vial into a plastic disposable syringe (approved syringes are made by Becton Dickinson) through the filter needle supplied with the product. For administration, a Number 23 "butterfly" needle (Abbott venisystems) is approved for use with this product.

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.

7 MARKETING AUTHORISATION HOLDER
Bio Products Laboratory
Dagger Lane
Elstree
Hertfordshire
WD6 3BX
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)
PL 08801/0054

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
26/05/2010

10 DATE OF REVISION OF THE TEXT
26/05/2010
Replenine-VF
(Human Factor IX)
PL 08801/0054

Patient Information Leaflet
Package Leaflet: Information for the User

REPLENINE®-VF 250 IU, 500 IU, 1000 IU POWDER FOR SOLUTION FOR INJECTION
HIGH PURITY FACTOR IX

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

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

In this leaflet:
1. WHAT REPLENINE-VF IS AND WHAT IT IS USED FOR
2. BEFORE YOU USE REPLENINE-VF
3. POSSIBLE SIDE EFFECTS
4. HOW TO STORE REPLENINE-VF
5. FURTHER INFORMATION

1. WHAT REPLENINE-VF IS AND WHAT IT IS USED FOR

Replenine-VF is a high purity factor IX from human blood plasma obtained from screened donors. It is a sterile, white, powdery, white, sterile, powder supplied with sterile water (Water for injections).

Replenine-VF is given by injection into a vein (intra-venously) and is used to prevent and treat bleeding in patients with haemophilia B (an inherited shortage of factor IX in the blood). Your doctor will explain further why this medicine has been given to you.

2. BEFORE YOU USE REPLENINE-VF

DO NOT USE this medicine if you:
• are allergic (hypersensitive) to factor IX or to any of the other ingredients (See Section 6 “Further Information”).

Take special care with Replenine-VF if you:
• suddenly have unusual bruising and feeling very unwell, which may need specialist medical attention
• have heart or liver disease, which may need specialist medical attention
• have a risk of blood clotting
• have had surgery
• have a high level of antibodies to factor IX

(Your doctor may give you an alternative treatment. He/she will check the level of factor IX and antibodies in your blood before and after treatment, especially for your first injections).

When injecting, take special care to keep all needles sterile.

If you develop an allergic reaction (see Section 4 “Possible side effects” for a list of these) stop the treatment and tell your doctor immediately.

Your doctor will advise you about any vaccinations you may need as a routine precaution when using a blood plasma product.

Your doctor will be extremely careful about using Replenine-VF in new-born infants.

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

These injections must not be mixed with other medicinal products.

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

Driving and using machines
There are no known effects of this product on your ability to drive or operate machinery.

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

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

It is strongly recommended that every time you receive a dose of Replenine-VF the name and batch number of the product are recorded in order to maintain a record of the batches used.
3. HOW TO USE REPLENINE-VF

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

**Adults**

Replenine-VF should be administered directly into a vein. Use only the recommended injection equipment.
- Your doctor will explain how much you should use.
- The dose, especially the first dose, should be given slowly (approximately 3 mL per minute).
- After reconstitution, the injection should be completed within one hour and the solution must not be stored.
- If further treatment is needed, doses may be repeated at intervals of 8 to 24 hours, as required. Your doctor will advise you if this is necessary.

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Initial dose of Replenine-VF (IU/kg body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor spontaneous bleeding in joints and muscles.</td>
<td>17 to 34</td>
</tr>
<tr>
<td>Severe bleeding in joints and muscles, bruising, minor surgery, e.g. tooth extraction, cartilage repair.</td>
<td>25 to 51</td>
</tr>
<tr>
<td>Life-threatening bleeding, major surgery.*</td>
<td>53 to 85</td>
</tr>
</tbody>
</table>

* In major surgery Replenine-VF may be given either as individual injections or by continuous infusion over several days (see also section How much is given before, during and after major surgery?).

**Children under 6 years of age**

Your doctor will recommend the appropriate dose for young children. Generally, the calculation of doses for children should follow that for adults.

**When to inject Replenine-VF**
- The medicine should be injected when the first sign of bleeding occurs.
- The injection should be repeated as necessary to stop the bleeding.
- Each individual bleed should be judged on its own severity.
- Replenine-VF can also be injected as part of treatment to prevent bleeding starting.
- If you are using this product for the first time, your doctor will supervise you.

**Dissolving your medicine before use**

<table>
<thead>
<tr>
<th>Vial of Replenine-VF</th>
<th>Quantity of Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 IU</td>
<td>2.5 or 5 mL</td>
</tr>
<tr>
<td>500 IU</td>
<td>5 or 10 mL</td>
</tr>
<tr>
<td>1000 IU</td>
<td>10 or 20 mL</td>
</tr>
</tbody>
</table>

1) Replenine-VF must only be dissolved in the sterile water provided with the product.
2) Before you remove its “flip-off” top, make sure that the vial of Replenine-VF and the container of water supplied with it are both at room temperature (between 20°C and 30°C).
3) Remove the cap from the Replenine-VF vial.
4) Clean the top of the medicine stopper with a spirit swab.
5) Sterile water for use with Replenine-VF is provided in two different types of container:
   - a plastic ampoule. Break open the top and draw up the required volume of water with a needle and syringe (not the single point filter needle with the connection for a syringe).
   - a glass vial with a stopper.
   - Pierce the stopper with a needle and syringe and draw up the required volume of water, or
   - If the glass vial is labelled with the precise volume of water you require, insert one end of a double-spike needle (which your doctor will provide) through the stopper into the water then invert the water vial and needle and insert the other end of this double needle into the product container.
6) Once you have pierced the Replenine-VF vial with the needle and syringe filled with water (or the double-ended needle attached to the water vial) water will flow into the container.
7) As the water enters the vial, swirl the vial gently around to wet the powder, but do not shake it.
8) Do not use this medicine if:
   - the water is not pulled into the vial (this indicates a loss of vacuum in the vial, so the powder must not be used).
   - the dissolved powder and sterile water form a gel or a clot (if this happens, please tell Bio Products Laboratory, reporting the batch number printed on the vial).
9) Remove the syringe or empty water container from the needle before removing the needle from the medicine vial.
10) Continue swirling the vial around gently until the powder is completely dissolved. A clear or slightly cloudy solution should be obtained, usually in about 2 to 2½ minutes (5 minutes maximum).
11) If you have to use more than one vial to make up your dose, you need to draw up the solution in each vial into one syringe for your injection, but you must use a new sterile filter needle to draw the contents of each vial up into the plastic syringe.
12) Do not use solutions which are cloudy or have bits in them.

**Injecting the medicine**

After the medicine is dissolved:

- Clean the stopper, with a spirit swab.
- Draw the medicine into a plastic, disposable syringe through the sterile filter needle provided (this will remove any tiny particles).
- To inject the medicine, attach a suitable needle or “Butterfly” to the syringe.
- The dose, especially the first dose, should be given slowly (no more than 3 mL per minute) into your vein.

**Remember:**
- The solution must not be stored after reconstitution.
- You must finish injecting the dose into a vein within one hour of dissolving the medicine.
- The solution must not be added to any other fluids, blood or any other medicine.
- You should only use the sterile water for injections to make up the solution, but you must never inject the water on its own without the powder.

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

(See also the table on page 2.)

**Before:** Major surgery should only be performed when levels of factor IX and factor IX inhibitors (antibodies) in your blood can be tested. If antibodies are not present, a dose is given before the operation to increase the level in your blood to between 80 and 100 IU/dL, usually about 65-85 IU per kg of body weight.

**After:** During the first few days after the operation, the plasma factor IX concentration will be checked at regular periods. A dose of Replene-VF (factor IX) is usually given every 8-24 hours, as needed.

After the first few days, the number of doses may be reduced.

Treatment is usually continued for 7 days or longer, depending on the type of operation.

If the factor IX concentration does not reach the expected level (this will be tested by your doctor), or if it decreases faster than expected (within 12 hours), an inhibitor of factor IX may be present which stops it from working properly. Your doctor will arrange for the appropriate laboratory tests to see if there is such an inhibitor present.

**If you use more Replene-VF than you should**

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

**If you forget to use Replene-VF**

- Do not use a double dose to make up for a forgotten dose.

**If you stop using Replene-VF**

- Always consult your doctor before deciding to stop your treatment.

4. **POSSIBLE SIDE EFFECTS**

As with all medicines, Replene-VF may cause side effects, although not everybody gets them.

**Hypersensitivity or allergic reactions** have been observed infrequently in patients treated with factor IX containing products. If you get any of the following symptoms, stop the infusion and tell your doctor immediately:

- Swelling around the face and throat
- Burning and stinging at the infusion site
- Chills
- Flushing
- Nettle rash (urticaria)
- Headache
- Hives
- Low blood pressure
- Lethargy
- Nausea or vomiting
- Restlessness
- Rapid heart beat
- Tightness of the chest or wheezing
- Tingling

**Kidney problems** (such as nephrotic syndrome) have been reported in some haemophilia B patients who have inhibitors (antibodies) to factor IX and a history of allergic reaction to factor IX containing products.

Inhibitors (antibodies) may develop to factor IX during treatment. This could mean that the treatment does not work properly. If bleeding does not stop after an injection, then speak to your doctor.

On rare occasions, fever has been observed (in fewer than 1 in 1,000 people).

The use of low purity factor IX products has been associated with **heart attack, thrombosis and blood coagulation**. The use of high purity factor IX, such as Replene-VF, is rarely associated with such side effects.

In clinical trials with Replene-VF, the following side effects have been reported in fewer than 1 in 10 people:

- Reaction at the injection site, e.g. irritation, inflammation, suddenly have unusual bruising and feeling very unwell.
- Headache.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.
5. HOW TO STORE REPLENINE-VF

- Keep out of the reach and sight of children.
- You should store the powder in its container and carton, in the dark in the refrigerator. Do not freeze. Short periods of storage at room temperature, in the dark, will not damage the product.
- The container of sterilised water that comes with the medicine should also be stored in the refrigerator. Do not freeze.
- Do not use the medicine or the sterilised water after the expiry date, which is stated as "EXPIRY" on the containers. The expiry date refers to the last day of that month.
- Do not use the sterilised water if any small bits can be seen in it.
- Once reconstituted, Replenine-VF must be used within one hour.

Disposal

After injection of the correct dose, dispose of any solution that remains, along with used syringes, needles and containers. Ask your doctor for a special container for this purpose and take it back to the doctor or pharmacist when full.

Medicines should not be disposed of via wastewater or household waste.

6. FURTHER INFORMATION

What Replenine-VF contains

The active substance is human coagulation factor IX.

The other ingredients are: factor II, factor X, protein, glycine, lysine, sodium citrate, sodium phosphate, sodium chloride, polysorbate 80 and triethanol phosphate.

What Replenine-VF looks like and the contents of the pack

Replenine-VF is a white, crumbly, sterile powder and is packed in quantities of 250 international Units (IU), 500 IU or 1,000 IU in glass vials. These vials are closed with a synthetic rubber stopper under vacuum, held on by a tamper evident cap.

Replenine-VF should only be reconstituted with Sterilised Water for Injections. Sterilised Water for Injections is supplied with Replenine-VF in clear glass bottles.

Marketing Authorisation Holder and manufacturer

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

Marketing Authorisation Number
PL 08801/0054

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June 2007

For further information or if you have any questions about the use of this product, please contact BPL via the Marketing Department at the address above or through info@bpl.co.uk.
Replenine-VF
(Human Factor IX)
PL 08801/0054

Labelling