1. NAME OF THE MEDICINAL PRODUCT

Mononine 1000 , 1000 IU,
powder and solvent for solution for injection /infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains nominally:
1000 IU human coagulation factor IX (FIX).
Mononine contains approximately 100 IU/ml factor IX after reconstitution with 10 ml of water for injections.

The potency (IU) is determined using the European Pharmacopoeia one stage clotting test.
The mean specific activity of Mononine is not less than 190 IU/mg protein.

Produced from the plasma of human donors.

Excipient with a known effect:
Sodium approximately 66 mmol/l (1.5 mg /ml).
For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection /infusion.
White powder and clear, colourless solvent for solution for injection/infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the prevention and control of bleeding in Factor IX deficiency, also known as Hemophilia B or christmas disease.

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.

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 IU factor IX per kg body weight raises the plasma factor IX activity by 1.0 % of normal activity. The required dosage is determined using the following formula:

Required units = body weight [kg] × desired factor IX rise [% or IU/dl] × 1.0

The amount to be administered, the method as well as the frequency of administration should always be oriented 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 % of normal or IU/dl) in the corresponding period. The following tables can be used to guide dosing in bleeding episodes and surgery:

Table 1: Single Intravenous Injection		
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 bleeding 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 bleeding or haematoma	30 – 60	Repeat infusion every 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 is resolved.
Surgery		
Minor including tooth extraction	30 – 60	Every 24 hours, at least 1 day, until healing is achieved

Major	80 – 100 (pre- and postoperative)	Repeat infusion every 8 -24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor IX activity of 30 % to 60 % (IU/dl).

Table 2: Continuous Infusion in Surgery	
Desired levels of factor IX for haemostasis	40 – 100 % (or IU/dl)
Initial loading dose to achieve desired level	Single bolus dose 90 IU per kg (range 75-100 IU/kg) body weight or pK-guided dosing
Frequency of dosing	Continuous i.v. infusion, depending on clearance and measured factor IX levels
Duration of treatment	Up to 5 days, further treatment may be necessary depending upon nature of surgery

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 kg 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.

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 in vivo recovery and demonstrating different half-lives.

Patients should be monitored for the development of factor IX inhibitors.
See also section 4.4.

Previously untreated patients
The safety and efficacy of Mononine in previously untreated patients have not yet been established.

Paediatric population
Dosing in children is based on body weight and is therefore generally based on the same guidelines as for adults. The frequency of administration should always be oriented to the clinical effectiveness in the individual case.

Method of administration
For intravenous use.

Reconstitute the product as described in section 6.6. The preparation should be warmed to room or body temperature before administration. Mononine should be administered via the intravenous route at a slow rate, so as to observe the patient for any immediate reaction. If any reaction takes place that is thought to be related to the administration of Mononine the rate of infusion should be decreased or the infusion stopped, as required by the clinical condition of the patient (see also section 4.4).

Single intravenous injection
Perform venipuncture using the accompanying venipuncture set. Attach the syringe to the luer end of the device.

Inject slowly intravenously at a rate comfortable to the patient (max. 2 ml/min).

Continuous infusion
Mononine should be reconstituted with water for injections as described in section 6.6. After reconstitution, Mononine can be given by continuous infusion undiluted using a syringe pump.

The potency of undiluted, reconstituted Mononine is approximately 100 IU/ml.

A diluted solution is obtained as follows:
- Dilute the reconstituted, filtered solution by transferring the appropriate quantity of Mononine to the desired volume of normal saline using aseptic technique.
- In dilutions of up to 1:10 (concentration of 10 IU factor IX/ml) activity of factor IX remains stable for up to 24 hours.
- A reduction in factor IX activity may result at higher dilutions. Factor IX activity should be monitored to maintain the desired blood level.

  Example for diluting 1,000 IU of reconstituted Mononine:

Targeted Dilution Potency	10 IU/ml	20 IU/ml
Volume of reconstituted Mononine	10.0 ml	10.0 ml
Volume of normal saline needed	90.0 ml	40.0 ml
Achieved dilution	1:10	1:5

- The use of polyvinylchloride (PVC) IV bags and tubing is recommended.
- Mix thoroughly and check bag for leaks.
- It is recommended to replace the bags with freshly diluted Mononine every 12-24 hours.

The recommended rate for continuous infusion with Mononine to maintain a steady state factor IX level of approximately 80 % is 4 IU/kg b.w./hour, but will depend on the pharmacokinetic profile of the patient and the desired factor IX target level. In patients

where the clearance of factor IX is known, the infusion rate can be calculated for the individual patient.

Rate (IU/kg b.w./hr) = Clearance (ml/hr/kg b.w.) × desired factor IX increase (IU/ml)

The safety and efficacy in children have not been studied under continuous infusion (see section 4.4). Therefore, in children and adolescents, continuous infusion of Mononine should only be considered if pre-surgical pharmacokinetic data (i.e. incremental recovery and clearance) are obtained for the calculation of the dosage and levels are carefully monitored perioperatively.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Known allergic reaction to mouse protein.

High risk of thrombosis or disseminated intravascular coagulation (see also 4.4).

4.4 Special warnings and precautions for use

Hypersensitivity
Allergic type hypersensitivity reactions are possible with Mononine. The product contains traces of mouse protein (the murine monoclonal antibody used in its purification process). While the levels of mouse protein are extremely low (≤ 50 ng mouse protein/100 IU), infusion of such proteins might theoretically induce hypersensitivity responses.

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, the current medical standards for shock-treatment should be observed.

A standard dose of 2000 IU Mononine contains up to 30.36 mg sodium. To be taken into consideration by patients on a controlled sodium diet.

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 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.

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 Mononine should be weighed against the risk of these complications.

Cardiovascular events
In patients with existing cardiovascular risk factors, substitution therapy with FIX 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.

Virus safety

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 (HAV) and parvovirus B19 viruses.

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

It is strongly recommended that every time that Mononine is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

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

There is no safety and efficacy data for continuous infusion application in children, particularly the potential for development of inhibitors is unknown (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

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

Little data are available regarding the use of ε-aminocaproic acid following an initial infusion of Mononine for the prevention or treatment of oral bleeding following trauma or dental procedures such as extractions.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with factor IX.

Pregnancy and lactation
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.

Fertility
There are no data on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The following adverse reactions are based on post-marketing experience as well as scientific literature.

Summary of the safety profile

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the injection 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).
In some cases, they have occurred in close temporal association with development of factor IX inhibitors (see also 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 clinical 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 side effects.

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification.

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).

MedDRA SOC	**Adverse Reaction**	**Frequency**
Renal and urinary disorders	Nephrotic syndrome	Very rare
Vascular Disorders	Thromboembolic episodes	Not known
General Disorders and Administration Site Conditions	Fever	Rare
Immune System Disorders	Hypersensitivity (allergic reactions)	Rare
Blood and Lymphatic System Disorders	FIX inhibition	Very rare

Description of selected adverse reactions

In a clinical study 2 of 51 (4 %) previously untreated patients (PUPs) developed inhibitors, and in one of these patients, this was associated with an anaphylactoid reaction on two occasions.

For information on viral safety see section 4.4.

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:
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il
and emailed to the Registration Holder's Patient Safety Unit at:
drugsafety@neopharmgroup.com

4.9 Overdose

No symptoms of overdose with human coagulation 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 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 are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

When reconstituted as recommended (see section 6.6), the resulting solution is a clear, colourless, isotonic preparation of neutral pH, containing approximately 100 times the factor IX activity found in an equal volume of plasma.

5.2 Pharmacokinetic properties

Short term infusion of Mononine in 38 patients with haemophilia B (recovery study) revealed a mean incremental recovery of 1.71 IU/dl per IU/kg b.w. (range 0.85-4.66). Mean terminal half-life in a subgroup of 28 patients was 14.9 hours (range 7.2 to 22.7).

Pharmacokinetic data of Mononine was also determined in 12 patients (elective surgery) prior to treatment with continuous infusion of Mononine.

Parameter	Recovery study (n=38) Mean (range)	Elective surgery (n=12) Mean (range)
Incremental recovery (IU/dl per IU/kg)	1.71 (0.85-4.66)	1.21 (0.83-1.60)
Terminal half-life (h)	14.9 (7.2-22.7)++	16.4 (8.7-36.6)
Initial half-life+++ (h)	n.a.	2.46 (0.34-6.2)
Area under the curve+ (h × kg/ml)	n.a.	0.254 (0.147-0.408)
Volume at steady state (ml/kg)	n.a.	111 (77-146)
Clearance (ml/h/kg)	n.a.	4.27 (2.45-6.78)
Mean residence time (h)	n.a.	27.4 (17.7-42.6)

+ Standardized to 1 IU/kg of dose n.a.: not available

++ Based on a subgroup of 28 patients

+++ Data from only 4 of the 12 patients. The remaining 8 patients followed a simple one-compartment model. A distribution process of Mononine is thus observed only occasionally.

Paediatric population

No pharmacokinetic data are available in patients younger than 12 years.

5.3 Preclinical safety data

Human plasma coagulation factor IX is a normal constituent of human plasma and acts like endogenous factor IX. Single dose toxicity testing is of no relevance since higher doses may result in overloading.

Repeated dose toxicity testing in animals is impracticable due to the animals developing antibodies to heterologous (human) protein.

Since clinical experience provides no hint for tumorigenic or mutagenic effects of human plasma coagulation factor IX, experimental studies, particularly in heterologous species, are not considered meaningful.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine,
Mannitol,
Sodium chloride,
HCl or NaOH (in small amounts for pH adjustment)

Supplied solvent:
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, solvents and diluents, except those mentioned in section 6.1 and normal saline.

6.3 Shelf life

2 years.

The made up solution should be used immediately.
However, After reconstitution **or** *After dilution (up to 1:10) of the reconstituted Mononine 1000 solution,* the physico-chemical stability has been demonstrated for 24 hours at up to max +25ºC.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 ºC). Do not freeze. Keep the vial in the outer carton in order to protect from light.

During its shelf-life, the product (when kept in its outer carton) may be stored at ambient room temperature (up to 25 °C) for up to 1 month without being refrigerated again during this period. The date of transfer to room temperature and the end of the 1-month period should be recorded on the outer carton. At the end of this period the product has to be used or discarded.

6.5 Nature and contents of container

Immediate containers
1000 IU powder and 10 ml solvent in vials (Type I glass) with stoppers (chlorobutyl rubber).

Presentation
One pack with 1000 IU containing:
- 1 vial with powder

- 1 vial with 10 ml water for injections

One device pack containing:
- 1 filter transfer device 20/20
- 1 disposable 10 ml syringe
- 1 venipuncture set
- 2 alcohol swabs
- 1 non-sterile plaster

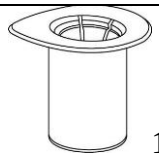
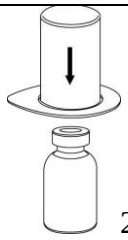
6.6 Special precautions for disposal and other handling

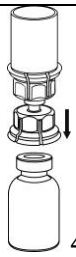
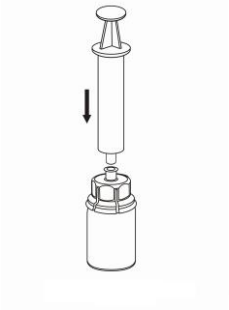
General instructions

– Reconstitution and withdrawal must be carried out under aseptic conditions.
– Usually the solution is clear or slightly opalescent. Reconstituted product should be inspected visually for particulate matter and discoloration after filtering/withdrawal (see below) and prior to administration. Do not use solutions which are cloudy or contain residues (deposits/ particles).

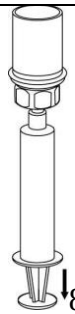
Reconstitution

Bring the solvent to room temperature. Ensure product and solvent vial flip caps are removed and the stoppers are treated with an antiseptic solution and allowed to dry prior to opening the Mix2Vial package.

 1	1. Open the Mix2Vial package by peeling off the lid. Do **not** remove the Mix2Vial from the blister package!
 2	2. Place the solvent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the blue adapter end **straight down** through the solvent vial stopper.
 3	3. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set.

 4	4. Place the product vial on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the transparent adapter end **straight down** through the product vial stopper. The solvent will automatically flow into the product vial.
 5	5. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew the set carefully counter-clockwise into two pieces. Discard the solvent vial with the blue Mix2Vial adapter attached.
 6	6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.
 7	7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial´s Luer Lock fitting by screwing clockwise. Inject air into the product vial.

Withdrawal and application

 8	8. While keeping the syringe plunger pressed, invert the system upside down and draw the solution into the syringe by pulling the plunger back slowly.

 9	9. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe by unscrewing counter-clockwise.

Administer immediately by slow intravenous injection or infusion (see section 4.2)

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

7. MANUFACTURER

CSL Behring GmbH
Emil-Von Behring St. 76,
35041 Marburg, Germany

8. LICENSE NUMBER

Mononine 1000: 139 54 31723 00

9. REGISTRATION HOLDER

Genmedix, 12 Beit Harishonim St. Emek-Hefer 38777.

The format of this leaflet has been set by the Ministry of Health and its content has been checked and approved – March 2017.