EU PACKAGE LEAFLET– EU-PI (PI/EU/ENGLISH)

MONONINE® 1000

Rev.: **02-MAY-2017** / Switch to 1-Box Version

Supersedes previous versions
Rev.: 16-SEP-2015 / CCSI update
Rev.: 06-NOV-2014 / Adaptation to FIX Core-SPC, QRD, etc. / RSI

Package leaflet: Information for the user

Mononine 1000

1000 IU
Powder and solvent for solution for injection/infusion
Human coagulation factor IX

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Mononine is and what it is used for

What is Mononine?
Mononine is made from human plasma (this is the liquid part of the blood) and it contains human coagulation factor IX. It is used to prevent or to stop bleeding that is caused by the congenital lack of factor IX (haemophilia B) in the blood.

What Mononine is used for
Factor IX is very important for blood clotting (coagulation). Lack of factor IX means that blood does not clot as quickly as it should and so there is an increased tendency to bleed. The replacement of factor IX with Mononine will temporarily repair the blood clotting mechanisms.

The made up solution is to be given by injection or infusion into a vein.

2. What you need to know before you use Mononine

The following sections contain information that you and your doctor should consider before you use Mononine.

Do not use Mononine:

- If you are allergic to the human coagulation factor IX or any of the other ingredients of this medicine (listed in section 6) or to mouse protein. Please inform your doctor if you are allergic to any medicine or food.
- If you have a high risk of forming blood clots (thrombosis) or if you are more likely to form blood clots than normal (disseminated intravascular coagulation).

Warnings and precautions

- Allergic reactions are possible. The early signs include hives, generalised skin rash, tightness of the chest, wheezing, fall in blood pressure and anaphylaxis (a serious allergic reaction that causes severe difficulty in breathing, or dizziness). **If these symptoms occur, you should stop using the product immediately and contact your doctor.**
- Mononine contains, as remains of a special purification step, **traces of mouse protein**. While the levels of mouse protein are extremely low, infusion of these proteins can lead to allergic reactions.
- The formation of **inhibitors** (neutralising antibodies) to factor IX is a known complication of treatment and it means that the treatment stops working. If your bleeding is not being controlled with Mononine, tell your doctor immediately. You should be monitored carefully for the development of an inhibitor.
- There is a risk of an increased formation of **blood clots in a blood vessel** (thromboembolic complications), particularly:
  - if you suffer from a liver disease
  - if you have just had surgery
  - in new-born infants
  - if you have additional thrombotic risk factors, e.g. pregnancy, oral contraceptives, obesity, smoking.
- If you are a person with existing cardiovascular risk factors therapy with factor IX may increase the cardiovascular risk.
- If a central venous access device is required a risk of catheter-related complications including local infections, bacteraemia and catheter site thrombosis should be considered.
- There is no safety and efficacy data for continuous infusion application in children, particularly the potential for development of inhibitors is unknown.

Your doctor will consider carefully the benefit of treatment with Mononine compared with the risk of these complications.

Virus safety

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,
- the testing of each donation and pools of plasma for signs of virus/infections.
- the inclusion of 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 infections.

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

Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived products (e.g. factor IX).

It is strongly recommended that every time Mononine is given, you should record the date of administration, the batch number and the injected volume in your treatment diary.

Other medicines and Mononine
- Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
- Factor IX and ε-aminocaproic acid (a chemical drug that stops the breakdown of blood clots) can be used to treat bleeding from the mouth, either if this happens after injury or after dental surgery, such as having teeth removed. However, there is not very much information about what happens when ε-aminocaproic acid and Mononine are given at the same time.
- Mononine must not be mixed with other medicinal products, diluents and solvents except for those that are recommended by the manufacturer (see section 6)

Pregnancy, breast-feeding, and fertility
- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- During pregnancy and breast-feeding, Mononine should be given only if it is clearly needed.
- No fertility data are available.

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

Important information about some of the ingredients in Mononine
A standard dose of 2000 IU Mononine contains up to 30.36 mg sodium. Please take this into account if you are on a controlled sodium diet.

3. How to use Mononine

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Treatment of Haemophilia B should be started and supervised by a physician who is experienced in this type of disorder.

Dosage

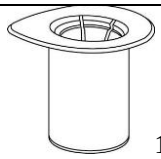
The amount of factor IX you need and the duration of treatment will depend on several factors, such as your body weight, the severity of your disease, the site and intensity of the bleeding or the need to prevent bleeding during an operation or investigation.
If you have been prescribed Mononine to use at home, your doctor will make sure that you are shown how to inject or infuse it and how much to use.
Follow the directions given to you by your doctor or haemophilia centre nurse.

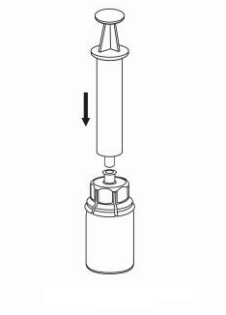
If you take more Mononine than you should
No symptoms of overdose with factor IX have been reported.

Reconstitution and application
General instructions:
- The product must be dissolved and withdrawn from the vial under aseptic conditions.
- The made up solution should be clear or slightly opalescent, i.e. it might be sparkling when held up to the light but must not contain any obvious particles. After filtering or withdrawal (see below) the solution should be checked by eye for small particles and discoloration, before it is administered. Do not use the solution if it is visibly cloudy or if it contains flakes or particles.
- Any unused product or waste material should be disposed of in accordance with local requirements and as instructed by your doctor.

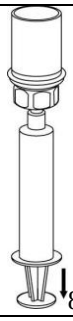
Reconstitution:
Without opening either vial, warm the Mononine product and the solvent to room or body temperature. This can be done either by leaving the vials at room temperature for about an hour, or by holding them in your hands for a few minutes.
DO NOT expose the vials to direct heat. The vials must not be heated above body temperature (37 ºC).

Carefully remove the protective caps from the vials containing the product and the solvent, and clean the exposed rubber stoppers with an alcohol swab. Allow the vials to dry before opening the Mix2Vial package, then follow the instructions given below.

 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 counterclockwise 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, turn 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 counterclockwise.

Single intravenous injection
Use the venipuncture kit that is supplied with the product, insert the needle into a vein. Let blood flow back to the end of the tube. Attach the syringe to the threaded, locking end of the venipuncture kit. **Inject the made up solution slowly into the vein** following the instructions given to you by your doctor. Take care not to get any blood in the syringe containing the made up solution. The maximum rate of administration is 2 millilitres per minute.

Continuous infusion
Mononine can also be given by a long-term (continuous) infusion over several hours or days. This must be done and controlled by your doctor.

Check yourself for any side effects that might happen straight away. If you have any side effects that might be related to the administration of Mononine, the injection or infusion should be stopped (see also section "Warnings and precautions").

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible Side Effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If any of the following happen, contact your doctor immediately or go to the Emergency Department or Haemophilia Centre at your nearest hospital:
- A sudden allergic reaction (such as skin rash or hives, itchiness, swelling of the face, lips, tongue or other parts of the body),
- Shortness of breath, wheezing or trouble breathing,
- Fits,
- Loss of effect (continuous bleeding).

Other side effects are:
- Allergic reactions, which may include:
  - burning and stinging, redness and swelling of the vein where the injection or infusion was given
  - Swelling of the face, throat or other parts of the body, chills, flushing, skin rash over the whole body, wheals
  - headache

  - fall in blood pressure, restlessness, faster heart beat, tightness of the chest, wheezing
  - tiredness (lethargy)
  - feeling/being sick
  - tingling

  These side effects have been observed rarely, and may in some cases progress to severe allergic reactions (anaphylaxis) including shock (this has been closely associated with development of factor IX inhibitors).
- Rarely, fever has been reported.
- Very rarely, a special form of inflammation of the kidneys (nephrotic syndrome) has been reported after treatment of patients who suffer from factor IX inhibitors. These patients were also known to have a history of allergic reaction.
- There is a potential risk of increased formation of blood clots that can lead to heart attack (myocardial infarction), blood clots in the leg (venous thrombosis) and blood clots in the lungs (pulmonary embolism), after administration of factor IX products. The use of Mononine is rarely linked with these side effects.
- Very rarely, you may develop an inhibitor (neutralising antibody) to factor IX, in which case factor IX will not work properly any more. If this happens, it is recommended that a specialised haemophilia centre be contacted.

Side effects in children and adolescents
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V [to be completed nationally]. By reporting side effects you can help provide more information of the safety of this medicine.

5. How to store Mononine

Do not use Mononine after the expiry date, which is stated on the label and carton.

- **Keep this medicine out of the sight and reach of children.**
- Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- Store in a refrigerator (2 °C – 8 °C).
- 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 the period, the product has to be used or discarded.
- The made up solution should be used immediately.
- If the made up solution is diluted (up to one part in 10), the solution must be used immediately, however the physico-chemical stability has been demonstrated for 24 hours.
- Your doctor will inform you how to dispose of unused product or waste material.

6. Contents of the pack and other information

What Mononine contains
Mononine contains 1000 IU human coagulation factor IX per vial.

Once dissolved with 10 ml of the solvent, the made up solution contains approximately 100 IU human coagulation factor IX per ml.

Other ingredients are:
Histidine, mannitol, sodium chloride, hydrochloric acid or sodium hydroxide (in small amounts for pH adjustment). *Solvent:* Water for injections.

What Mononine looks like and contents of the pack
Mononine is presented as a white powder and is supplied with water for injections as solvent.

The made up solution should be clear to slightly opalescent, i.e. it might sparkle when held up to the light but must not contain any obvious particles.

Presentation
Box with 1000 IU containing:
- 1 vial with powder
- 1 vial with 10 ml water for injections
- 1 filter transfer device 20/20

Administration set (inner box):
- 1 disposable 10 ml syringe
- 1 venipuncture set
- 2 alcohol swabs
- 1 non-sterile plaster

Marketing Authorisation Holder and Manufacturer
CSL Behring GmbH
Emil-von-Behring-Straße 76
35041 Marburg
Germany

This medicinal product is authorised in the Member States of the EEA under the following names:

Mononine:	**Italy, Sweden, Poland**
Mononine, Poeder en oplosmiddel voor oplossing voor injectie of infusie 1000 IE	**Netherlands**
Mononine 1000:	**France, Germany, Luxembourg, Portugal**
Mononine 1000 i.e. prašek in vehikel za raztopino za injiciranje/infundiranje:	**Slovenia**
Mononine 1000 I.E. Pulver und	

Lösungsmittel zur Herstellung einer Injektions- oder Infusionslösung: _____Austria
Mononine 1000 IU: _____Slovakia
Mononine 1000 IU, powder and solvent for solution for injection or infusion: _____UK
Mononine 1000 UI polvo y disolvente para solución inyectable o perfusión: _____Spain
Mononine 1000 NE por és oldószer oldatos injekcióhoz vagy infúzióhoz: _____Hungary

This leaflet was last revised in May 2017

The following information is intended for healthcare professionals only

Posology
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	20-40	Repeat every 24 hours. At

bleeding or oral bleeding		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.

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.

Application
Mononine could be administered either by single intravenous injection (see instructions in section 3.), or by continuous infusion (see instructions below).

Continuous infusion
Mononine should be reconstituted with water for injections as described in section "Reconstitution and application". After reconstitution, Mononine can be given for continuous infusion **either undiluted or diluted** using a syringe pump or an approved infusion set.
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 1000 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	90.0 ml	40.0 ml

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

The safety and efficacy in children have not been studied under continuous infusion. 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.