PACKAGE LEAFLET: INFORMATION FOR THE USER

Haemonine® 500 / Haemonine® 1000

Powder and solvent for solution for injection
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 your 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 Haemonine is and what it is used for

Haemonine is presented as a powder and a solvent for solution for injection, available in two packaging sizes. Each vial of Haemonine 500 contains **500 IU** (international units) of human coagulation factor IX. In a separate vial, 5 ml water for injections are provided. Each vial of Haemonine 1000 contains **1000 IU** (international units) of human coagulation factor IX. In a separate vial, 10 ml water for injections are provided.

The specific activity of Haemonine is ≥ 70 IU/mg protein.

Haemonine is being prescribed **to stop** or **prevent bleeding** because of a lack of factor IX (Haemophilia B) in the blood in adults, adolescents and children aged 6 years and older. Thus, Haemonine as a coagulation factor IX preparation belongs to the pharmacotherapeutic group of antihaemorrhagics. Factor IX is a protein that is part of the body's natural way of forming clots to stop bleeding. If it is absent or low in your blood, you will suffer from blood coagulation problems which may lead to bleeding in joints, muscles or internal organs. You may have this condition from birth or acquire it later in life. The administration of Haemonine can compensate for this deficiency.

2. What you need to know before you use Haemonine

Do not use Haemonine:
- if you are **allergic** to coagulation factor IX, to any of the other ingredients of this medicine (listed in section 6) or to heparin.
  Usually, if you are **allergic to Haemonine** it will show up within the first applications. The early signs of hypersensitivity reactions include reddening of the skin, nettle rash, itching over the entire body, swelling of lips and tongue, breathing difficulties, tightness of the chest, wheezing, drop in blood pressure, loss of consciousness, which can progress to severe allergic reactions (see also section "Possible side effects"). If you detect one or more of the symptoms listed above in yourself, call your doctor instantly.

Warnings and precautions

Talk to your doctor or pharmacist before using Haemonine

- Before you use Haemonine you should tell your doctor if you know that you have a **risk of thrombosis** or you have had **thromboembolic complications in the past**, if you suffer from **liver disease** or if a **surgery is planned.** These are conditions that increase your risk of developing internal blood clots, even if you have not been injured. If you are unsure, you should discuss this with your doctor. If you are taking medicines which have an impact on the clotting of the blood please talk to your doctor. The risk for developing internal blood clots might be increased.
- If you have existing cardiovascular risk factors, therapy with Haemonine may increase the cardiovascular risk. If you are unsure, you should discuss this with your doctor.
- **Allergic-type hypersensitivity reactions** are possible with Haemonine. Please contact immediately your doctor or Haemophilia center if you experience early signs of hypersensitivity/allergic reactions like (generalised) hives, tightness of the chest, wheezing, low blood pressure or anaphylaxis (severe allergic reaction such as difficulty in swallowing and/or breathing, low blood pressure, red or swollen face and/or hands) (see also section "Possible side effects").
- Please contact immediately your doctor or Haemophilia center **if your bleeding does not stop** as expected or if you experience a significant increase in your usage of Haemonine in order to control a bleed. Your doctor will do a blood test to check if you have developed neutralising antibodies (inhibitors) against your medicine. The risk for developing inhibitors is highest in patients who have not been treated with a factor IX replacement medicine before or in the early phases of treatment, i.e. for small children (see also section "Possible side effects").
- Inhibitors may develop together with allergies. Patients with factor IX inhibitors may be at an increased risk of anaphylaxis during future treatment with factor IX.
- 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/infections. 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 totally be 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), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A virus. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals whose immune system is depressed or who have some types of anaemia (e.g. sickle cell disease or haemolytic anaemia).
  Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived factor IX products.
- It is strongly recommended that every time you receive a dose of Haemonine the name and batch number of the product are recorded in order to maintain a record of the batches used.

Children
There are insufficient data to recommend the use of Haemonine in children less than 6 years of age.

Other medicines and Haemonine
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. No interactions of Haemonine with other medicinal products are known.

Pregnancy and breast-feeding
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. If you have already told your doctor then follow any instructions that may have been given to you.

Haemophilia B in women is rare. Therefore there is no experience regarding the use of Haemonine during pregnancy and breast-feeding.

Driving and using machines
Haemonine has no or negligible influence on the ability to drive and use machines.

Haemonine contains sodium
This medicinal product contains a maximum of 4.9 mmol (113 mg) sodium per standard dose of 2,000 IU. To be taken into consideration by patients on a controlled sodium diet.

3. How to use Haemonine

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

Haemonine treatment should always be on supervision of a doctor who has experience in the treatment of haemophilia.

Dosage and Frequency of Administration
The amount of Haemonine you need to use depends on your weight, the severity of your haemophilia, the site and severity of your bleed, and the need to prevent bleeding, for example before dentistry or an operation.
Your doctor will calculate the dose of Haemonine and how often you need to inject it to obtain the correct levels in your blood. Do not use higher doses than your doctor has told you.

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).

On demand treatment
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 IU factor IX per kg body weight raises the plasma factor IX activity by 1-2 % of normal activity. The required dose is determined using the following formula:

Required units = body weight (kg) x desired factor IX rise (%) (IU/dl) x 0.8

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 in IU/dl) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

Degree of haemorrhage/ Type of surgical procedure	Factor IX level required (%) (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	60 - 100	Repeat infusion every 8 to 24 hours

haemorrhages		until threat is resolved.
Surgery		
Minor surgery including tooth extraction	30 - 60	Every 24 hours, at least 1 day, until healing is achieved.
Major surgery	80 - 100 (pre- and post-operative)	Repeat infusion every 8 to 24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor IX activity of 30 to 60% (IU/dl).

Prophylaxis
For long term prophylaxis against bleeding in patients with severe haemophilia B, the usual doses are 20 to 40 IU of factor IX per kilogram of body weight at intervals of 3 to 4 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

It is recommended to not exceed a maximal infusion rate of 5 ml/min.

If you have the impression that the effect of Haemonine is too weak, talk to your doctor. You may have developed **antibodies to factor IX** (see section "Warnings and precautions" and "Possible side effects").

Paediatric population
Your doctor will calculate the dose of Haemonine and how often you need to inject it to obtain the correct levels in your blood.

If you use more Haemonine than you should
No case of overdose with human coagulation factor IX has been reported.

If you forget to use Haemonine
Do not take a double dose to make up for a forgotten dose.

If you stop using Haemonine
Do not stop using Haemonine without discussing this with your doctor. Always use Haemonine exactly as your doctor has told you.

Instructions for use
Haemonine is given by injection into a vein (intravenous use). If you have been prescribed Haemonine to use at home, your doctor or haemophilia centre nurse will have to make sure that you know how to use it.

If you are in any doubt about injecting Haemonine, go back to your doctor or Haemophilia Centre for more advice and training before attempting to give yourself any treatment. Follow the directions given to you by your doctor or haemophilia nurse.

During the preparation and injection of Haemonine, it is important to use sterile conditions.

Haemonine must not be mixed with other medicinal products.

Use only the provided injection set, otherwise treatment may not be efficient due to factor IX adsorption to the internal surfaces of some other injection equipment.

Fig. 1a

Fig. 1b

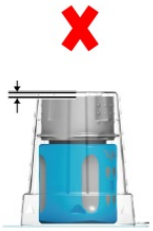

Fig. 1c

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig. 6

Fig. 7

Fig. 8

Dissolution of the concentrate:

- Bring the unopened vials of the solvent (water for injections) and product to room temperature. If a water bath is used for warming, it must be scrupulously ensured that the water does not come into contact with the caps or stoppers of the vials. Otherwise contamination of the medicine may occur.
- **Very important** for proper use of the transfer system: prior to opening, make sure that the white lower part of the transfer system sits directly on the ground of the blister (Fig. 1a: right/ Fig. 1b: wrong). If not right: push the transfer system down in the blister until the white lower part of the transfer system sits directly on the ground of the blister (Fig. 1c).
- Remove the caps from the solvent and the product vial in order to expose the central portions of the rubber stoppers (Fig. 2). Ensure that the rubber stoppers of the product and solvent vials are treated with a disinfectant.
- Remove the top of the transfer system packaging (Fig. 3).
- Place the solvent vial on even surface. Place the blue part of the transfer system within the blister straight onto the upright standing vial containing the solvent (Fig. 4). Do not twist the transfer system!
- Remove the remaining part of the blister from the transfer system. Do not squeeze the blister! Now the white part of the transfer system is visible (Fig. 5).
- Place the product vial on an even surface.
- Turn the combination of transfer system and solvent vial upside down. Push the spike of the white part of the adapter straight down through the product vial stopper (Fig. 6). The vacuum present in the product vial causes the solvent to flow into the product vial.
- Gently swirling the product vial helps in dissolving the powder. Do not shake vigorously, all foaming is to be avoided! The solution is clear or slightly opalescent.
- Afterwards unscrew the blue part of the transfer system together with the solvent vial counterclockwise (Fig. 7). Discard the solvent vial with the blue part of the transfer system attached. The Luer-Lock connector is now visible.

The solution ready for use should be used immediately after dissolving. Do not use solutions that are cloudy or contain visible particles.

Injection:

- Once you have dissolved the powder as described above, screw the enclosed syringe onto the Luer-Lock connector of the product vial with the white part of the transfer system (Fig. 8). This allows you to easily draw the dissolved drug into the syringe. A separate filter is not necessary because the transfer system has its own integral filter.
- Carefully disconnect the vial with the white part of the transfer system from the syringe. Use the enclosed butterfly needle and administer immediately by slow intravenous injection. The injection rate must not exceed 2-3 ml/minute.
- After the butterfly needle has been used, it can be made safe with the protective cap.

If you have any further questions on the use of the 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 you experience one of the following conditions please contact immediately your doctor or Haemophilia center (see also section "Warnings and precautions")

- Hypersensitivity or anaphylactic reactions (which may include swelling of the face, tongue or throat, difficulty in swallowing and breathing, back pain, chest discomfort, chills, dyspnoea, flushing, hives, headache, low blood pressure, injection site reactions (e.g. rash and pain), lethargy, nausea, itching, rash, restlessness, rapid heartbeat, abnormal sensation, vomiting, wheezing)
- Severe anaphylactic reactions (including anaphylactic shock)
- Bleeding; this might be associated with the development of neutralising antibodies (inhibitors) to factor IX.

The following side effects have been reported with human coagulation factor IX products:

- Nephrotic syndrome (a disorder where the kidneys are damaged) has been reported in haemophilia B patients with a history of allergic reaction.
- There is a small risk of thromboembolic episodes (blood clots).
- Haemonine may contain traces of heparin which may cause allergic reactions and reduced blood cell counts which may affect the blood clotting system. Patients with a history of heparin-induced allergic reactions should avoid the use of heparin-containing medicines.

The following side effects have been reported with Haemonine:
Very common (may affect more than 1 in 10 patiens):

- Hypersensitivity reactions, see above

Common (may affect up to 1 in 10 patients):

- Anxiety
- Abnormal increase in sensitivity (hyperaesthesia)
- Nausea
- Skin reactions (dermatitis allergic), hives (urticaria)
- Back pain
- Hot flush
- Shortness of breath (dyspnoea)
- Feeling cold, Injection site reaction (including e.g. pain and rash)

Not known (frequency cannot be estimated from the available data):

- Development of neutralising antibodies (inhibitors) to factor IX (factor IX inhibition)

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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard.

By reporting side effects you can help provide more information on the safety of this medicine

5. How to store Haemonine

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and the outer carton.
Once opened or dissolved, use the product immediately.

Do not store above 25°C.
Do not freeze.
Keep the vials in the outer carton in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Haemonine contains:

Powder:
The active substance is human coagulation factor IX. Each vial of Haemonine 500 contains **500 IU** of human coagulation factor IX. Each vial of Haemonine 1000 contains **1000 IU** of human coagulation factor IX.
The other ingredients are arginine, lysine, sodium chloride, and sodium citrate.

Solvent:
Water for injections

What Haemonine looks like and contents of the pack
Powder and solvent for solution for injection. White powder and clear, colourless solvent for solution for injection. After dissolving the powder in the provided water for injections, the Haemonine solution must be clear or slightly opalescent without any visible particles.

1 package Haemonine 500 contains:
- 1 glass vial with powder
- 1 glass vial with 5 ml water for injections
- 1 disposable syringe (5 ml)
- 1 double filter transfer system
- 1 butterfly cannula

1 package Haemonine 1000 contains:
- 1 glass vial with powder
- 1 glass vial with 10 ml water for injections
- 1 disposable syringe (10 ml)
- 1 double filter transfer system
- 1 butterfly cannula

Marketing Authorisation Holder and Manufacturer:
Biotest Pharma GmbH
Landsteinerstrasse 5
63303 Dreieich
Germany
Phone: +49 6103 801-0
Fax: +49 6103 801-150
Email: mail@biotest.com

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