(English translation of official Dutch version)

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

HepBQuin 100 IU solution for injection
HepBQuin 150 IU solution for injection
HepBQuin 500 IU solution for injection

Human hepatitis B immunoglobulin

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, pharmacist or nurse.
- Do you get any side effects that are mentioned in section 4? Or, do you get a side effect that is not mentioned in this package leaflet? Talk to your doctor, pharmacist or nurse.

What is in this leaflet:

1. WHAT IS THIS PRODUCT USED FOR?

HepBQuin is a solution for injection which contains the protein “human hepatitis B immunoglobulin” (human hepatitis B antibody). Immunoglobulins are antibodies and normal constituents of human blood and they protect you against infections. This involves immunoglobulin G (= IgG), an antibody that works against the hepatitis B virus, which causes jaundice. The maximum IgA content is 6 g/l.

Hepatitis B immunoglobulin is an antibody effective against the hepatitis B virus. The hepatitis B virus can induce hepatitis in humans. The antibodies that are present in this product and directed against the hepatitis B virus nullify the harmful effects of the virus. In this way, infection with hepatitis B is prevented (so-called passive immunisation).

2. WHAT YOU NEED TO KNOW BEFORE YOU USE THIS PRODUCT

Do not use this product:

If you are allergic (hypersensitive) to immunoglobulins or any of the other ingredients of HepBQuin. You can find these ingredients in section 6.

In case of an allergic reaction the administration of HepBQuin should be discontinued immediately.

The product is not suitable for intravenous administration (administration into a vein).

Warnings and precautions

There is no benefit for individuals who have already been infected with the hepatitis B virus but it also induces no harm.

Thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of immunoglobulins.
Contact you doctor immediately if you experience symptoms like shortness of breath, chest pain, pain and swelling of a limb, weakness or numbness on one side of your body after administration of HepBQuin.

HepBQuin contains a small amount of IgA. HepBQuin may induce a severe hypersensitivity attack (anaphylactic reaction) in patients that have no immunoglobulin A (IgA deficiency) and have antibodies against immunoglobulin A. An anaphylactic reaction may also occur in patients who have not demonstrated hypersensitivity to previous use of blood or blood products.

If you have an IgA deficiency and antibodies against immunoglobulin A or have demonstrated hypersensitivity to previous use of blood or a blood product, then this product must only be administered if strictly necessary. In these cases HepBQuin must be administered under the careful supervision of a physician. After the administration of HepBQuin you will be monitored by a physician or nurse for at least 20 minutes. For side effects you can consult section 4 of this package leaflet.

Other medicines and HepBQuin

Do not mix HepBQuin with other medicinal products.

Tell your doctor or pharmacist if you are using, have recently used, or might use any other medicines.

Vaccination
Tell your doctor if you have been vaccinated in the past 3 to 4 weeks, or will shortly be vaccinated (within 3 months after administration of HepBQuin). HepBQuin might impair the efficay of vaccines, such as measles, rubella (German measles), mumps and varicella (chicken pox). After using HepBQuin an interval of at least three months should elapse before vaccination with any of these vaccines.

Effects on blood tests

The use of HepBQuin may influence the results of certain blood tests.

HepBQuin with food, drink and alcohol?

No effects of food, drink and alcohol on the use of HepBQuin are known.

Pregnancy and breast-feeding

The use of HepBQuin during pregnancy or breast-feeding has not been investigated. To date the use of immunoglobulins, such as HepBQuin, during pregnancy or while breastfeeding has never led to harmful effects. Immunoglobulins are transferred to new-born infants through breast milk and contribute to the new-born infants' defences.
Ask your doctor or pharmacist for advice before taking this medicine if you are pregnant, think you may be pregnant, are planning to have a baby, or are breast-feeding.

Driving and using machines

No effects on the ability to drive or operate machinery have been observed.

Special warnings and precautions for use

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These measures include:
- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded,
- 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), 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.

Immunoglobulins have not been associated with hepatitis A or parvovirus B19 infections possibly because the antibodies against these infections, which are contained in the product, are protective.

It is strongly recommended that every time you receive a dose of HepBQuin the name and batch number of the medicine are recorded in order to maintain a record of the batches used.

Excipients

The product contains the following excipients: glycine and water for injections.

3. HOW TO USE THIS PRODUCT?

Administration

Administration of HepBQuin should be performed by a doctor. HepBQuin must be injected into the muscle (intramuscular). The injection will generally be given in the upper arm or buttock. For new-born infants the injection will be given at the front side of the upper leg. The product may not be too cold when it is administered. It is recommended to bring the product to body temperature before administration.

It is recommended to divide the dose over multiple injection sites when administering a large dose (for children more than 2 ml and for adults more than 5 ml).

The product must be administered as soon as possible after the infection. For new-born infants the product should be administered within 2 hours after birth. In all other cases this must occur within 24 hours, because it is not certain whether the product is effective after this period.
When the hepatitis B vaccine is simultaneously administered with HepBQuin, then the vaccine must be given at another site (other upper arm or buttock).

If you have any questions about the use of this medicine, ask your doctor.

The product may be administered underneath the skin (subcutaneous) in patients with an exceptional tendency towards spontaneous, sometimes long-lasting, haemorrhages. The effectiveness of the product can not be guaranteed in this case.

Dosage

(500 IU = 5 ml, 150 IU = 1.5 ml, 100 IU = 1 ml, 8 IU = 0.08 ml HepBQuin)

- Prevention of hepatitis B in case of accidental exposure in non-immunised subjects: At least 500 IU (5 ml), depending on the intensity of exposure, as soon as possible after exposure, and preferably within 24 - 72 hours.
- Immunoprophylaxis in haemodialysed patients: 8-12 IU (0.08 – 0.12 ml) per kg body weight with a maximum of 500 IU (5 ml), every 2 months until the start of anti-HBs seroconversion following vaccination is identified.
- Prevention of hepatitis B in the newborn, of a hepatitis B virus carrier-mother, at birth or as soon as possible after birth: 30-100 IU (0.3 – 1 ml) per kg body weight. Administration may need to be repeated until active formation of antibodies following vaccination is identified.

In all these situations, vaccination against hepatitis B virus is highly recommended. The first vaccine dose can be injected the same day as human hepatitis B immunoglobulin, however in different sites.

In subjects who did not show an immune response (no measurable hepatitis B antibodies) after vaccination, and for whom continuous prevention is necessary, administration of 500 IU (5 ml) to adults and 8 IU (0,08 ml) per kg body weight to children every 2 months can be considered; a minimum protective antibody titer is considered to be 10 mIU/mL.

Consideration should also be given to dose and dose schedules for human hepatitis B immunoglobulin for intramuscular use recommended in other official guidance.

4. POSSIBLE SIDE EFFECTS

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

Allergic reactions are rare. In case of a very severe hypersensitivity reaction (anaphylactic shock), administration must be discontinued immediately and standard medical treatment for the reaction must be given.

The following side effects are possible: pain/sensitivity, swelling, redness, induration, local heat, itching and rash at the site of injection.
Rare side effects are: fever, nausea, vomiting, fall in blood pressure, increased heart rate (tachycardia), malaise, chills, hypersensitivity reactions, headache, arthralgia, skin reaction and itching and redness of the skin.

The risk of transfer of pathogens through the use of a blood product is exceptionally small.

Reporting side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Netherlands Pharmacovigilance Centre Lareb, website: www.lareb.nl. By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE THIS PRODUCT?

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

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

Do not use HepBQuin after the expiry date which is stated on the carton.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist what to do with medicines you no longer use. It will then be destroyed in a responsible way and will not end up in the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What HepBQuin contains

- The active substance in this medicine is human hepatitis B immunoglobulin
- The other ingredients in this medicine are glycine and water for injections

What HepBQuin looks like and contents of the pack

HepBQuin is a clear solution. The colour of the solution can vary from colourless or light yellow to light brown.

The commercial package of HepBQuin consists of a box containing:
- A vial HepBQuin of 100 IU, 150 IU or 500 IU.

The product is supplied as solution for injection for intramuscular use (for injection into the muscles).

Marketing authorisation holder and manufacturer

Sanquin Plasma Products B.V., Plesmanlaan 125, 1066 CX Amsterdam, The Netherlands, tel.: 020 – 512 3355.

RVG 16926

This leaflet was last approved in September 2016.

The following information is intended for healthcare professionals only:

Composition

Human hepatitis B immunoglobulin prepared from plasma of human donors.
The product contains 100 - 180 grams of protein per litre. The protein fraction consists of at least 90% immunoglobulin G (IgG). The content of hepatitis B antibodies is at least 100 IU/ml. The maximal IgA content is 6 g/l.
HepBQuin is supplied in the filling sizes 100 IU, 150 IU and 500 IU.

Therapeutical indications

Immunoprophylaxis of hepatitis B

- In case of accidental exposure in non-immunised subjects (including persons whose vaccination is incomplete or status unknown).
- In haemodialysed patients, until vaccination has become effective, determined by the presence of antibodies.
- In the newborn of a hepatitis B virus carrier-mother.
- In subjects who did not show an immune response (no measurable hepatitis B antibodies) after vaccination and for whom a continuous prevention is necessary due to the continuous risk of being infected with hepatitis B.

Posology

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- Prevention of hepatitis B in case of accidental exposure in non-immunised subjects: at least 500 IU (5 ml), depending on the intensity of exposure, as soon as possible after exposure, and preferably within 24 - 72 hours.
- Immunoprophylaxis in haemodialysed patients: 8-12 IU (0.08 – 0.12 ml) per kg body weight with a maximum of 500 IU (5 ml), every 2 months until the start of anti-HBs seroconversion following vaccination is identified.
- Prevention of hepatitis B in the newborn, of a hepatitis B virus carrier-mother, at birth or as soon as possible after birth: 30-100 IU (0.3 – 1 ml) per kg body weight. The hepatitis B immunoglobulin

administration may need to be repeated until active formation of antibodies following vaccination is identified.

In all these situations, vaccination against hepatitis B virus is highly recommended. The first vaccine dose can be injected the same day as human hepatitis B immunoglobulin, however in different sites.

In subjects who did not show an immune response (no measurable hepatitis B antibodies) after vaccination, and for whom continuous prevention is necessary, administration of 500 IU (5 ml) to adults and 8 IU (0,08) per kg body weight to children every 2 months can be considered; a minimum protective antibody titer is considered to be 10 mIU/mL.

Consideration should also be given to dose and dose schedules for human hepatitis B immunoglobulin for intramuscular use recommended in other official guidance.

Method of administration
HepBQuin should be administered slowly and deep via the intramuscular route (in neonates into the anterolateral side of the thigh). It is recommended that the product is warmed to body temperature before administration.

If a large volume (>2 ml for children or >5 ml for adults) is required, it is recommended to administer this in divided doses at different sites.

If hepatitis B vaccine is being administered simultaneously, the vaccination should be carried out to the opposite side of the body.

If intramuscular administration is contraindicated (hemorrhagic diathesis), the injection can be administered subcutaneously. However, it should be noted that there are no clinical efficacy data to support the effectiveness of the product for prevention of hepatitis B by this administration route.

Contra indications

Hypersensitivity to any of the components.
Hypersensitivity to human immunoglobulins.

Special warnings and precautions

Ensure that HepBQuin is not administered into a blood vessel, because of the risk of shock.

If the recipient is a carrier of HBsAg, there is no benefit in administering this product, but there are also no harmful consequences.

True hypersensitivity reactions are rare.

HepBQuin contains a small quantity of IgA. Individuals who are deficient in IgA have the potential for developing IgA antibodies and may have anaphylactic reactions after administration of blood components containing IgA. The physician must therefore weigh the benefit of treatment with HepBQuin against the potential risk of hypersensitivity reactions.

Rarely, human hepatitis B immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human immunoglobulin.

Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the injection. In case of shock, standard medical treatment for shock should be implemented.

The patient must be kept under observation for at least 20 minutes after administration.

<u>Thromboembolism</u>

Arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of immunoglobulins. Patients should be sufficiently hydrated before use of immunoglobulins. Caution should be exercised in patients with preexisting risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilization, severely hypovolemic patients, patients with diseases which increase blood viscosity). Patients should be informed about first symptoms of thromboembolic events including shortness of breath, pain and swelling of a limb, focal neurological deficits and chest pain. Patients should be advised to contact their physician immediately upon onset of symptoms.

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 virus hepatitis A virus. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.

There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins. It is also assumed that the antibody content makes an important contribution to the viral safety.

It is strongly recommended that every time that HepBQuin 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.

Interaction with other medicinal products and other forms of interaction

Live attenuated vaccines
Immunoglobulin administration may interfere with the efficiency of live attenuated virus vaccines for measles, rubella, mumps, and varicella for a period of 3 months. After administration of this product, an interval of at least 3 months should elapse before vaccination with live attenuated virus vaccines.
Human hepatitis B immunoglobulin should be administrated 3 t o 4 weeks after vaccination with such a live attenuated vaccine. In case administration of human hepatitis B immunoglobulin is essential within 3 to 4 weeks after vaccination, then revaccination should be performed three months after the administration of human hepatitis B immunoglobulin.
Interference with serological testing
After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.
Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell antibodies, for example the antiglobulin test (Coombs' test).

List of excipients

Glycine, water for injections.

Incompatibilities

Given the lack of investigation on incompatibilities, this medicinal product must not be mixed with other medicinal products.

Shelf life

2 years.

The product should be used immediately after piercing the vial.

Special precautions for storage

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

Nature and contents of container

100 IU, 150 IU and 500 IU in glass, colourless vials (glass type I), fitted with a bromobutyl rubber stopper and sealed with an aluminium cap. Filling sizes are 1, 1.5 and 5 ml.

It might occur that not all package sizes are marketed.

Instructions for disposal and other instructions

It is recommended that the product be warmed to body temperature before administration.

During the storage period a slight cloudiness or formation of a small amount of deposits might occur. This is no impediment for clinical use.

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