SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE 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.

For the complete listing of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection for intramuscular administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Posology and method of administration

Posology

(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. 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 injection 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 as 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 at 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 via this administration route.

4.3 CONTRA-INDICATIONS

Hypersensitivity to any of the components.

Hypersensitivity to human immunoglobulins.

4.4 SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

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, and 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 have 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.

Thromboembolism
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 and 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 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.

4.5 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 to 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).

4.6 Pregnancy and lactation

The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

4.7 Effects on ability to drive and use machines

There are no indications that immunoglobulins may impair the ability to drive or use machines.

4.8 Undesirable effects

There are no robust data on the frequency of undesirable effects from clinical trials. The following undesirable effects have been reported:

MedDRA Standard System Organ Class	**Undesirable effects**	**Frequency**
Immune system disorders	Hypersensitivity, anaphylactic shock*	Rare
Nervous system disorders	Headache	Rare
Cardiac disorders	Tachycardia	Rare
Vascular disorders	Hypotension	Rare
Gastrointestinal disorders	Nausea, vomiting	Rare
Skin and subcutaneous tissue disorders	Skin reaction, erythema, pruritus	Rare
Musculoskeletal and connective tissue disorders	Arthralgia	Rare
General disorders and administration site conditions	Fever, malaise, chill At injection site: pain and sensitivity**, swelling, erythema, induration, warmth, pruritus, rash	Rare Unknown***

* For a clarification, see section 4.4 "Special warnings and special precautions for use"
** This can be reduced by dividing the larger doses over several injection sites
*** Unknown: cannot be identified from the available data

See section 4.4 for safety with regard to transmissible agents.

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. Healthcare professionals are asked to report any suspected adverse reactions via: Netherlands Pharmacovigilance Centre Lareb, website: www.lareb.nl.

4.9 Overdose

Consequences of an overdose are not known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins

- Hepatitis B immunoglobulin ATC code: J06BB04

Human hepatitis B immunoglobulin contains mainly immunoglobulin G (IgG) with a specifically high content of antibodies against hepatitis B virus surface antigen (HBs).

5.2 Pharmacokinetic properties

After intramuscular administration the immunoglobulin administered to the patient is gradually released from the intramuscular depot into the circulation. The maximum level is achieved after two to three days.

Human hepatitis B immunoglobulin has a half-life of about 3-4 weeks. This half-life may vary from patient to patient.

IgG and IgG-complexes are broken down in the reticuloendothelial system.

5.3 Preclinical safety data

Immunoglobulins are normal constituents of the human body. Animal experiments about the toxicity of a single administration are not relevant, since overdosage occurs at higher doses. Research about toxicity following repeated administration, and about toxicity for the embryo or foetus is not feasible due to induction of, and disturbance by, antibodies. No research has been carried out regarding the effects of the product on the immune system of neonates.
Given that clinical trials have not shown any evidence of a carcinogenic or mutagenic effect of immunoglobulins, experimental research, especially in heterological species, is considered unnecessary.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine, water for injections.

6.2 Incompatibilities

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

6.3 Shelf life

2 years.
The product should be used immediately after piercing the vial.

6.4 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.

6.5 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.

6.6 Instructions for disposal and other instructions

It is recommended that the product is brought 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.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

RVG 16926.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 February 1997

10. DATE OF REVISION OF THE TEXT

Last partial change concerns section: 4.4: 02 September 2016