GRIFOLS

Niuliva® 250 I.U./ml

Solution for infusion

HUMAN ANTIHEPATITIS B IMMUNOGLOBULIN

QUALITATIVE AND QUANTITATIVE COMPOSITION

Human antihepatitis B immunoglobulin.

The percentage of IgG subclasses, which is determined by immunonephelometry, is approximately 74.3% IgG_1, 22.1% IgG_2, 1.99% IgG_3 and 1.61% IgG_4.

Human protein content is 50 g/l of which at least 97% is IgG.

The content of human antihepatitis B immunoglobulin is 250 I.U./ml (600 I.U./2.4 ml, 1,000 I.U./4 ml, 5,000 I.U./20 ml and 10,000 I.U./40 ml).

Contains trace amounts of IgA (lower than 0.05 mg/ml).

Excipient:

D-sorbitol content is 50 g/l.

For full list of excipients, see section "List of excipients".

PHARMACEUTICAL FORM

Solution for infusion.

The solution is clear or slightly opalescent and colourless or pale yellow.

CLINICAL PARTICULARS

Therapeutic indications

Niuliva® is indicated for:

Prevention of hepatitis B virus re-infection after liver transplantation for hepatitis B induced liver failure during the maintenance phase in non replicator patients.

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.
- In the newborn of a hepatitis B virus carrier-mother.
- In subjects who did not show an immune response (no measurable antihepatitis B antibodies) after vaccination and for whom a continuous prevention is necessary due to the continuous risk of being infected with hepatitis B.

Posology and method of administration

Posology

Prevention of hepatitis B virus re-infection after liver transplantation for hepatitis B induced liver failure during the maintenance phase in non replicator patients:

In adults:

2,000 - 10,000 I.U./month to maintain antibody levels above 100 - 150 I.U./l in HBV-DNA negative patients.

Immunoprophylaxis of hepatitis B:

- Prevention of hepatitis B in case of accidental exposure in non-immunised subjects:

  At least 500 I.U., depending on the intensity of exposure, as soon as possible after exposure, and preferably within 24 - 72 hours.
- Immunoprophylaxis of hepatitis B in haemodialysed patients:

  8 - 12 I.U./kg with a maximum of 500 I.U., every 2 months until seroconversion following vaccination.
- 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 I.U./kg. The antihepatitis B immunoglobulin administration may be repeated until seroconversion following vaccination.

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

In subjects who did not show an immune response (no measurable antihepatitis B antibodies) after vaccination, and for whom continuous prevention is necessary, administration of 500 I.U. to adults and 8 I.U./kg to children every 2 months can be considered; a minimum protective antibody titre is considered to be 10 mI.U./ml.

Method of administration

Niuliva® should be infused intravenously at a maximum initial rate of 0.02 ml/kg/min for the first 10 minutes. If well tolerated, the rate of administration may gradually be increased to a maximum of 0.04 ml/kg/min. Therefore, generally, the administration of 5,000 I.U. will be performed in less than 15 minutes.

In the case that there are no adverse reactions, the maximum initial rate of the following infusions will also be of 0.02 ml/kg/min and, if well tolerated, the rate of administration may gradually be increased to a maximum of 0.1 ml/kg/min. In general, the time for administration of 5,000 I.U. will be less than 10 minutes.

Contraindications

Hypersensitivity to any of the components.

(See special warnings about excipients, section "Special warnings and precautions for use").

Hypersensitivity to human immunoglobulins.

Special warnings and precautions for use

Thromboembolic complications have been associated with the use of normal IVIg. Therefore, caution is recommended especially for patients with thrombotic risk factors.

Patients should be monitored for serum anti-HBs antibody levels regularly.

Certain severe adverse drug reactions may be related to the rate of infusion. The recommended infusion rate given under "Posology and method of administration" must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Certain adverse reactions may occur more frequently

- in case of high rate of infusion,
- in patients with hypo- or agammaglobulinaemia with or without IgA deficiency.

There have been reports of non-cardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] in patients administered IVIg. TRALI is characterised by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function and fever, and typically occurs within 1 - 6 hours after transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

IVIg recipients should be monitored for pulmonary adverse reactions. If TRALI is suspected, appropriate tests should be performed for the presence of antineutrophil antibodies in both the product and patient serum.

True hypersensitivity reactions are rare. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. The treatment required depends on the nature and severity of the side effect.

Niuliva® 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 Niuliva® against the potential risk of hypersensitivity reactions.

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

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 HIV, HBV and HCV, and for the non-enveloped virus HAV. 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 and it is also assumed that the antibody content makes an important contribution to the viral safety.

It is strongly recommended that every time that Niuliva® 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.

Special warnings about excipients: This medicinal product contains 5 g of sorbitol per 100 ml as excipient. In case of fructose hereditary intolerance this product should not be used. Interferences with determination of blood glucose levels are not expected.

Interaction with other medicinal products and other forms of interaction

Live attenuated virus vaccines

Immunoglobulin administration may interfere with the development of an immune response to live attenuated virus vaccines such as rubella, mumps, measles and varicella for a period of up to 3 months. After administration of this product, an interval of at least 3 months should elapse before vaccination with live attenuated virus vaccines.

Human antihepatitis B immunoglobulin should be administrated three to four weeks after vaccination with such a live attenuated vaccine; in case administration of human antihepatitis B immunoglobulin is essential within three to four weeks after vaccination, then revaccination should be performed three months after the administration of human antihepatitis B immunoglobulin.

Interference with serological testing

After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patients 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).

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.

Effects on ability to drive and use machines

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

Undesirable effects

Adverse reactions such as chills, headache, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally.

Rarely human immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Cases of reversible aseptic meningitis, isolated cases of reversible haemolytic anaemia/haemolysis and rare cases of transient cutaneous reactions, have been observed with human immunoglobulin.

Increase in serum creatinine level and/or acute renal failure have been observed.

Very rarely: Thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses.

For safety with respect to transmissible agents, see “Special warnings and precautions for use”.

Overdose

Consequences of an overdose are not known.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins

- Hepatitis B immunoglobulin ATC code: J06BB04

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

Pharmacokinetic properties

The bioavailability of human antihepatitis B immunoglobulin for intravenous use is complete and immediate. IgG is quickly distributed between plasma and extravascular fluid, after approximately 3 - 5 days equilibrium is reached between the intra- and extravascular compartments.

Human antihepatitis 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.

Preclinical safety data

Immunoglobulins are normal constituents of the human body. Antihepatitis B immunoglobulin is a normal constituent of the human body after vaccination or recovery from previous infection. In animals, single dose toxicity testing is of no relevance since higher doses result in overloading.

Repeated dose toxicity testing and embryo-foetal toxicity studies with antihepatitis B immunoglobulin are impracticable due to induction of, and interference with antibodies. Effects of the product on the immune system of the newborn have not been studied.

PHARMACEUTICAL PARTICULARS

List of excipients

- D-sorbitol
- Water for injections

Incompatibilities

This medicinal product must not be mixed with other medicinal products or intravenous fluids. It should be administered by a separate intravenous line.

Shelf life

3 years.

Special precautions for storage

Store in a refrigerator (2 ºC - 8 ºC). Do not freeze.

Nature and contents of container

2.4 or 4 ml solution in a syringe (type I glass) with plunger stopper (bromo-butyl-rubber).

20 or 40 ml solution in a vial (type II glass) with stopper (chloro-butyl-rubber).

Pack size: 1 syringe or 1 vial.

Special precautions for disposal

The product should be brought to room or body temperature before use.

The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

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

NAME AND ADDRESS OF MANUFACTURER

Instituto Grifols, S.A.

Can Guasch, 2 - Parets del Vallès

08150 Barcelona - SPAIN

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