SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

UMAN BIG 180 IU/ml Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human hepatitis B immunoglobulin.

	UMAN BIG 180 IU/1 ml	**UMAN BIG 540 IU/3 ml**
Human proteins	100-180 g/l	100-180 g/l
of which human immunoglobulin at least to	90%	90%
antibodies to HBs antigen (HBsAb) not less than	180 IU/ml 180 IU/vial	180 IU/ml 540 IU/vial

Distribution of IgG subclasses:

IgG_1 63.7 %
IgG_2 31.8 %
IgG_3 3.3 %
IgG_4 1.2 %

Maximum content of IgA: 300 micrograms/ml.

Sodium content: 3.9 mg/ml (0.170 mmoles/ml)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
The liquid preparation is clear and colourless or pale-yellow or light brown; during storage it may show formation of slight turbidity or a small amount of particulate matter.

4 CLINICAL PARTICULARS

This is a translation of the Italian Summary of Product Characteristics (SPC). As not all the information given applies to your country, please refer to your local SPC.

4.1 Therapeutic indications

- Prevention of hepatitis B virus recurrence after liver transplantation for hepatitis B induced liver failure.

  The concomitant use of adequate virostatic agents should be considered, if appropriate, as a standard in hepatitis B re-infection prophylaxis.

- 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 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

- Prevention of hepatitis B virus recurrence after liver transplantation for hepatitis B induced liver failure.

In adults
The suggested posology is 2160 IU IM every 15 days in the period after the transplantation, excluding the first week. This posology should be modified in the long term treatment to ensure the maintenance of the serous level of HBsAg antibodies above 100 IU/l in HBV-DNA negative patients and above 500 IU/l in HBV-DNA positive patients.

Paediatric population
There is no documented use of UMAN BIG in the paediatric population for the indication prevention of hepatitis B virus recurrence after liver transplantation for hepatitis B induced liver failure.

Immunoprophylaxis of hepatitis B

- Prevention of hepatitis B in case of accidental exposure in non-immunised subjects:
  at least 500 IU, 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 IU/kg with a maximum of 500 IU, 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 IU/kg. The hepatitis B immunoglobulin administration may need to 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 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 to adults and 8 IU/kg to children every 2 months can be considered; a minimum protective antibody titre is considered to be 10 mIU/mL.

Method of administration

UMAN BIG should be administered via the intramuscular route.
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.

When simultaneous vaccination is necessary, the immunoglobulin and the vaccine should be administered at two different sites.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Ensure that UMAN BIG 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.
True hypersensitivity reactions are rare.
UMAN BIG 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 UMAN BIG 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 product contains 3.9 mg sodium per ml. Depending on the total dose required, this must be taken into consideration in patients on a controlled sodium diet.

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 viruses such as 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 UMAN BIG 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.

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).

Paediatric population
No specific measures or monitoring are required for the paediatric population.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breast-feeding mothers. 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.

Breastfeeding
Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate.

Fertility
Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

4.7 Effects on the ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).
Frequencies have been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

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	Not known
	Anaphylactic shock	Not known
Nervous system disorders	Headache	Not known
Cardiac disorders	Tachycardia	Not known
Vascular disorders	Hypotension	Not known
Gastrointestinal disorders	Nausea	Not known
	Vomiting	Very rare
Skin and subcutaneous tissue disorders	Skin reaction	Not known
	Erythema	Not known
	Itching	Not known
	Pruritus	Not known
Musculoskeletal and connective tissue disorders	Arthralgia	Not known
General disorders and administration site conditions	Fever,	Not known
	Malaise,	Not known
	Chill	Not known
	At injection site:pain	Uncommon
	At injection site: swelling, erythema, induration, warmth, pruritus, rash, itching	Not known

For safety with respect to transmissible agents, see 4.4.

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Reporting of suspected adverse reactions
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 the national reporting system.

4.9 Overdose

Consequences of 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).

A study carried out in HBsAg negative subjects, liver transplanted after infection of HBV, proved the efficacy of UMAN BIG in maintaining the levels of HBsAb above 100 IU/l. In this study UMAN BIG was administered with doses of 2000/2160 IU (according to the pack size), every 15 days for a period of six months.
The average of the levels of HBsAb, measured before each of the 12 administrations, were above the considered threshold (390 IU/l for concentration 334 IU/ml, with a minimum level of 109 IU/l and 403 IU/l for concentration 180 IU/ml with a minimum level of 106 IU/l).

Paediatric population
Published data related to efficacy and safety studies have not revealed major differences between adults and children suffering from the same disorder

5.2 Pharmacokinetic properties

Human hepatitis B immunoglobulin for intramuscular use is bioavailable in the recipient's circulation after a delay of 2-3 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. Moreover, as administration of immunoglobulins in animal studies may lead to the formation of antibodies, preclinical safety data are limited. However, the limited animal studies did not show special risks for humans, based on acute and sub-acute toxicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Glycine
Sodium chloride
Water for injections

6.2 Incompatibilities

UMAN BIG must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

Once the container has been opened the contents should be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C/ 8°C).
Keep in the outer carton in order to protect from light.

6.5 Nature and contents of container

One Type I glass vial with Type I stopper made of an elastomer of halobutyl rubber, suitable for perforation.

- Vial with 1 ml of solution containing 180 IU
- Vial with 3 ml of solution containing 540 IU

6.6 Instructions for use and handling and disposal

The product should be brought to room or body temperature before use.
Remove the central protection from the rubber stopper and draw the solution with an injection syringe. Change the needle and inject. Once the solution is withdrawn from the container into the syringe, the medicinal product must be administered immediately.

The colour can vary from colourless to pale-yellow up to light brown. Do not use solutions which are cloudy or have deposits.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Kedrion S.p.A. - Loc. Ai Conti, 55051 Castelvecchio Pascoli, Barga (Lucca) Italy.

8 MARKETING AUTHORISATION NUMBERS

UMAN BIG 180 IU/ml Solution for injection, vial with 180 IU/1 ml n° 023782028
UMAN BIG 180 IU/ml Solution for injection, vial with 540 IU/3 ml n° 023782016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Renewal : June 2010

10 DATE OF REVISION OF THE TEXT

18/02/2014

UMAN BIG-SPC-StEng
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