ZUTECTRA

1. NAME OF THE MEDICINAL PRODUCT

Zutectra

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human hepatitis B immunoglobulin

One mL contains:
Human hepatitis B immunoglobulin 500 IU (purity of at least 96% IgG)

Each pre-filled syringe of 1 mL solution contains: 150 mg of human protein, with a content of antibodies to hepatitis B virus surface antigen (HBs) of 500 IU.

Distribution of IgG subclasses (approx. values):
IgG1: 59 %
IgG2: 35 %
IgG3: 3 %
IgG4: 3 %

The maximum IgA content is 6,000 micrograms /mL.

Produced from the plasma of human donors.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear to opalescent and colourless to pale yellow with a pH of 5.0-5.6 and an osmolality of 300-400 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of hepatitis B virus (HBV) re-infection in HBsAg and HBV-DNA negative adult patients at least one week after liver transplantation for hepatitis B induced liver failure. HBV-DNA negative status should be confirmed within the last 3 months prior to OLT. Patients should be HBsAg negative before treatment start.

The concomitant use of adequate virostatic agents should be considered as standard of hepatitis B re-infection prophylaxis.

4.2 Posology and method of administration

Posology

In HBV-DNA negative adults at least one week after liver transplantation:

- subcutaneous injections of Zutectra per week or fortnightly according to serum anti-HBs trough levels.

Prior to the initiation of subcutaneous treatment with Zutectra, adequate anti-HBs serum levels should be stabilised with an intravenous hepatitis B immunoglobulin to levels at or above 300-500 IU/L in order to ensure adequate anti-HBs coverage during the transition from intravenous to subcutaneous dosing. Antibody levels >100 IU/L should be maintained in HBsAg and HBV-DNA negative patients. The dose can be individually established and adapted from 500 IU up to 1,000 IU (in exceptional cases up to 1,500 IU) subcutaneous injections on a weekly or fortnightly basis, according to the serum anti-HBs concentrations and at the discretion of the physician in charge. Antibody levels >100 IU/L should be maintained.
Patients must be monitored for serum anti-HBs antibody levels regularly. Serum anti-HBs antibody levels should be measured at least every 2-4 weeks and at the discretion of the physician in charge for at least half a year.

Paediatric population
There is no relevant indication for use of Zutectra in children under the age of 18.

Method of administration

For subcutaneous use only.

Precautions to be taken before handling or administering the medicinal product
Injection of the medicinal product by the patient or by caregiver in a home treatment requires training by a physician experienced in the guidance of patients for home treatment. The patient or caregiver will be instructed in injection techniques, the keeping of a treatment diary and measures to be taken in case of severe adverse events. A sufficient surveillance period with stable anti-HBs trough serum levels of > 100 IU/L as well as a fixed dosage regimen is required: the monitoring schedule of patients anti-HBs antibody levels (see above) needs to be closely followed. In addition, patient or caregiver must comply with the injection technique as well as with the dosing regimen to ensure anti-HBs trough serum levels > 100 IU/L after extended periods between level controls.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to human immunoglobulins. In particular, in very rare cases of IgA deficiency when the patient to be treated has antibodies against IgA.

Zutectra must not be administered intravascularly.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. This recommendation applies also for documentation in the treatment diary during self-administration of the medicinal product in a home treatment.

Ensure that Zutectra 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 medicinal product.

There is no data about efficacy in post-exposure prophylaxis.

Hypersensitivity

True hypersensitivity reactions are rare.

Zutectra contains a small quantity of IgA (see section 2). 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 Zutectra 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.

Potential complications can often be avoided by ensuring that patients:
- are not sensitive to human normal immunoglobulin, by initially injecting the product slowly;
- are carefully monitored for any symptoms throughout the injection. In particular, patients naive to human normal immunoglobulin, patients switched from an alternative product or when there has been a long interval since the previous injection should be monitored during the first injection and for the first hour after the first injection, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration.

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.

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 direct antiglobulin test (DAT, direct Coombs' test).

Transmissible agents
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 (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.

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 medicinal 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. 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.

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

Fertility
No fertility studies have been performed (see section 5.3).

4.7 Effects on ability to drive and use machines

Hepatitis B immunoglobulin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Most adverse drug reactions (ADRs) were mild to moderate in nature. In isolated cases human normal immunoglobulins may cause an anaphylactic shock.

Tabulated list of adverse reactions
The following adverse reactions have been reported in the context of 4,810 subcutaneous applications of Zutectra during four completed clinical trials and 1,006 applications during a non-interventional post marketing safety study (PASS).
The ADRs reported in four trials are summarised and categorised according to the MedDRA system organ class and frequency below. Frequency per injection has been evaluated using 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). Within each frequency grouping the adverse reactions are presented in decreasing seriousness.

MedDRA System Organ Class	**Adverse reactions**	**Frequency**
Infections and infestations	Nasopharyngitis	Rare*
Immune system disorders	Hypersensitivity	Rare*
Nervous system disorders	Headache	Uncommon
Cardiac disorders	Palpitations, cardiac discomfort	Rare*
Vascular disorders	Hypertension	Rare*
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	Rare*
Gastrointestinal disorders	Upper abdominal pain	Uncommon
Skin and subcutaneous tissue disorders	Pruritus, rash	Rare*
Musculoskeletal and connective tissue disorders	Muscle spams	Rare*

General disorders and administration site conditions	Injection site pain, injection site urticaria, injection site haematoma, injection site erythema	Common
	Fatigue, tiredness	Rare*
* single case reports		

Adverse reactions observed with other human immunoglobulin preparations
With normal immunoglobulins adverse reactions such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally.
Rarely human normal 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.

Injection site reactions
Swelling, soreness, redness, induration, local heat, itching, bruising and rash.

For safety information with respect to transmissible agents, see section 4.4.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il
Additionally, you should also report to Kamada LTD to email address:
pharmacovigilance@kamada.com

4.9 Overdose

Consequences of an overdose are not known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immune sera and immunoglobulins, Specific immunoglobulins, Hepatitis B immunoglobulin.
ATC code: J06BB04

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

Clinical efficacy and safety

The open, prospective, single-arm clinical trial enrolled 23 liver transplant recipients, who had been receiving intravenous hepatitis B immunoglobulin prophylaxis and subsequently switched to subcutaneous Zutectra. The weekly subcutaneous dose was 500 IU for patients with bodyweight < 75 kg (a dose increase to 1,000 IU was allowed, if medically required to maintain a safety level of > 100 IU) and 1,000 IU for patients with bodyweight ≥ 75 kg . 2 patients received a higher and 2 patients received a lower dose than recommended by the weight based dosing regimen. Serum anti-HBs trough levels of 100 IU/L and higher (primary efficacy endpoint) were maintained for all patients

during the 18 to 24 week trial period. The > 100 IU/L safety margin is the generally accepted level of effective prevention against HBV re-infection in liver transplant patients at risk. No patient experienced HBV re-infection. Self-administration was feasible for most patients.

The mean anti-HBs serum level before switching was 393 ± 139 IU/L. All patients used antiviral medicine.

Using the Clopper Pearson method, the failure rate after 18 weeks was 0 % for patients of the ITT set (95 % CI: [0, 14.8 %]). A failure rate of 0 % was also found for the facultative extension phase (week 24) (95 % CI: [0, 20.6 %])

The objectives of the open, prospective, single-arm clinical trial were the investigation of feasibility of home self-administration (including patient compliance), efficacy and safety of subcutaneous application of Zutectra in a population of stable patients during long-term treatment for prophylaxis against re-infection of a transplanted liver in 66 patients. All patients included in this study had to run through a training period of at least 29 days and home self-administration could start on day 36 at the earliest. With the exception of 6 patients who withdrew prior to day 36, all patients achieved complete hospital and home self-administration. No patient prematurely discontinued the study due to lack of feasibility of home self-treatment. During the 48-weeks treatment phase constant serum HBs antibody concentrations ≥ 100 IU/L were measured in all patients at all assessments with mean values of 312.0 ± 103.5 IU/L at the end of the treatment period. In total, 53/66 patients (80.3 %) used antiviral medication and 13 patients received monotherapy with Zutectra during this study. No hepatitis B re-infection was reported and no patient was tested HBsAg positive during the treatment period of 48 weeks. No serious adverse events were reported to be related to study medication. No fatal case was observed during the study.

The objective of the open, prospective, single-arm clinical trial was the investigation of efficacy and safety of Zutectra for prevention of hepatitis B virus (HBV) re-infection ≥ one week after orthotopic liver transplantation in HBsAg and HBV-DNA negative patients. At the time of transplantation 21 patients (42.9%) were tested positive for HDV, patients with a positive HIV or HCV test were excluded from study participation. 49 patients received subcutaneous injections of Zutectra of 500 IU (1 mL) or 1,000 IU (2 mL) (dose adaptation in exceptional cases up to 1,500 IU) per week or fortnightly according to serum anti-HBs trough levels. The individual treatment duration per patient was planned to be up to 24 weeks after transplantation. No treatment failures occurred during the 6-month study period. Serum HBs antibody concentrations above the minimum safety trough level of >100 IU/L were measured in all patients at all timepoints independent of the type of administration (investigator, caregiver or self-injection), the dose regimen (500 IU, 1,000 IU, 1,500 IU) or the treatment intervals. No clinical signs of a hepatitis B re-infection were observed and no patient was tested HBsAg positive or HBV-DNA positive during the study which confirms that effective protection against Hepatitis B virus re-infection was provided by subcutaneous administration of Zutectra as part of the combination treatment with HBV virostatic therapy 8 – 18 days after orthotopic liver transplantation. One non-serious adverse event was reported to be related to Zutectra (injection site haematoma). No fatal case was observed during the study.

The non-interventional post authorization safety study (PASS 978) enrolled 61 adult patients ≥ 6 months after liver transplantation for hepatitis B induced liver failure. The objective of the study was to evaluate the level of compliance of patients using subcutaneous Zutectra as home self-treatment for preventing hepatitis B re-infection. Patients were to be treated with Zutectra in accordance with the information and dosage given in the SPC. Compliance according to anti-HBs serum levels could be shown for 57 (of 61) patients (93%), with no values below 100 IU/L and a mean anti-HBs serum level of 254.3 IU/L at the final visit. In total, 42/61 patients (68.9 %) used antiviral medication and 19 patients received monotherapy with Zutectra during this study. No treatment failure defined as positive HBV-DNA and HBsAg findings occurred during the entire observation period. No re-infection was observed. No serious adverse reaction was reported. No fatal case was observed during the study.

5.2 Pharmacokinetic properties

Distribution
Zutectra is slowly absorbed into the recipient's circulation and reaches a maximum after a delay of 2-7 days.

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

Elimination
Zutectra has a half-life of about 3-4 weeks. This half-life may vary from patient to patient.

5.3 Preclinical safety data

Immunoglobulins are normal constituents of the human body, therefore toxicity testing in heterologous species is of no relevance.

In a local tolerance trial in rabbits, there was no evidence of irritation attributable to Zutectra.

No other non-clinical trials have been carried out.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

No other preparations may be added to the Zutectra solution as any change in the electrolyte concentration or the pH may result in precipitation or denaturisation of the proteins.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Once the protective cap has been removed from the pre-filled syringe, the solution should be administered immediately.

6.4 Special precautions for storage

Store and transport refrigerated (2°C-8°C).

Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

6.5 Nature and contents of container

One mL solution for injection in a pre-filled syringe (Type I glass) with a stopper (bromobutyl) and a tip cap (bromobutyl rubber).

Pack size of five pre-filled syringes in a blistered pack.

6.6 Special precautions for disposal and other handling

This medicinal product should be brought to room temperature (approx. 23°C-27°C) before use.

The solution can vary from clear to opalescent and colourless to pale yellow.

Solutions that are cloudy or have deposits should not be used.

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

7. MANUFACTURER:

Biotest Pharma GmbH, Landsteinerstrasse 5, D-63303 Dreieich, Germany.

8. LICENSE HOLDER:

Kamada Ltd., Beit Kama, Israel.

LICENSE NUMBER: 1502633639

Revised in April 2022 according to MOHs guidelines