ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zutectra 500 IU solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe of 1 ml contains Human hepatitis B immunoglobulin 500 IU.

Human protein 150 mg/ml of which at least 96 % is IgG, with a content of antibodies to hepatitis B virus surface antigen (HBs) of 500 IU/ml.

Distribution of IgG subclasses:
IgG1: 59 %
IgG2: 35 %
IgG3: 3 %
IgG4: 3 %

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

The solution is clear and pale yellow or light brown.

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.

Zutectra must not be administered intravascularly.

4.4 Special warnings and precautions for use

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. 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.

It is strongly recommended that every time that Zutectra is administered to a patient, the name and batch number of the medicinal product are recorded in order to maintain a link between the patient and the batch of the medicinal product. This recommendation applies also for documentation in the treatment diary during self-administration of the medicinal product in a home treatment.

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 criteria: 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).

The effects were grouped by system organ classes under relevant medical headings.

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*
Musculosceletal and connective tissue disorders	Muscle spams	Rare*
General disorders and administration site conditions	Injection site reactions like pain, urticaria at injection site, haematoma and 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.

Local reactions at injection sites
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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 1000 IU was allowed, if medically required to maintain a safety level of > 100 IU) and 1000 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, 1000 IU, 1500 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

2 years.

The solution should be administered immediately after opening the syringe.

6.4 Special precautions for storage

Store and transport refrigerated (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

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

Pack size of five 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 colourless to pale yellow up to light brown.

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. MARKETING AUTHORISATION HOLDER

Biotest Pharma GmbH
Landsteinerstrasse 5
D-63303 Dreieich
Germany
Tel.: +49 6103 801-0
Fax: +49 6103 801-150
Email: mail@biotest.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/600/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/11/2009 / 16/09/2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Biotest AG
Landsteinerstr. 5
D-63303 Dreieich
Germany

Name and address of the manufacturer responsible for batch release

Biotest Pharma GmbH
Landsteinerstrasse 5
D-63303 Dreieich
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

Official batch release
In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX

1. NAME OF THE MEDICINAL PRODUCT

Zutectra 500 IU solution for injection in pre-filled syringe
Human hepatitis B immunoglobulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains:
Human protein 150 mg of which at least 96 % is IgG, with a content of antibodies to hepatitis B virus surface antigen (HBs) of 500 IU.

IgG subclass distribution:
59 % IgG1, 35 % IgG2, 3 % IgG3, 3 % IgG4
IgA content ≤ 6,000 micrograms/ml

3. LIST OF EXCIPIENTS

Excipients: Glycine, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
5 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For subcutaneous use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
The solution should be administered immediately after opening the syringe.

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated (2°C-8°C).
Do not freeze.
Keep the container in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Biotest Pharma GmbH
Landsteinerstr. 5
D-63303 Dreieich
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/600/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zutectra 500 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number} [product code]
SN: {number} [serial number]
NN: {number} [national reimbursement number or other national number identifying the medicinal product]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Zutectra 500 IU injection
Human hepatitis B immunoglobulin
Subcutaneous use

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Biotest Pharma GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zutectra 500 IU injection
Human hepatitis B immunoglobulin

2. METHOD OF ADMINISTRATION

Subcutaneous use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 IU

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Zutectra 500 IU solution for injection in pre-filled syringe
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 or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Zutectra is and what it is used for

What Zutectra is

Zutectra contains antibodies against the hepatitis B virus which are the body's own defensive substances to protect you from hepatitis B. Hepatitis B is an inflammation of the liver caused by the hepatitis B virus.

What Zutectra is used for

Zutectra is used to prevent re-infection of hepatitis B in adults who have had a liver transplant at least 1 week ago because they had liver failure caused by hepatitis B.

2. What you need to know before you use Zutectra

Do not use Zutectra
- if you are allergic to human immunoglobulin or any of the other ingredients of this medicine (listed in section 6).

An allergic reaction may include sudden wheeziness, difficulty in breathing, fast pulse, swelling of the eyelids, face, lips, throat or tongue, rash or itching.

Zutectra is for subcutaneous (under the skin) injection only. Injection into a vein or a blood vessel may result in allergic shock.

Warnings and precautions

Please tell your doctor or healthcare professional prior to treatment
- if you have been told that you have antibodies against immunoglobulins of the type IgA in your blood. This is very rare and may result in allergic reactions.

You may be allergic to immunoglobulins (antibodies) without knowing it, even if you have tolerated previous treatments with human immunoglobulins. Particularly if you do not have enough immunoglobulins of the type IgA in your blood, allergic reactions such as a sudden fall in blood pressure or shock may occur.

You will be carefully observed during and shortly after the 1st injection with Zutectra to make sure that you do not suffer from a reaction. If you have an allergic reaction to Zutectra, the injection will be stopped immediately. Please tell your doctor or healthcare professional immediately if you notice any reactions during your injection with Zutectra.

If you are HBs antigen positive you will not receive Zutectra since there is no benefit in administering this medicine to you. Your doctor will be able to explain this to you.

For your own safety you will be monitored for antibody levels regularly.

Possible interference with blood tests
Zutectra might affect the results of certain blood tests (serological tests). Please tell your doctor about your treatment with Zutectra prior to any blood test.

Information on the starting material of Zutectra and the possibility of transmission of infectious agents:

The starting material or what Zutectra is made from is human blood plasma (this is the liquid part of the blood).
When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include

- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, *and*
- the testing of each donation and pools of plasma for signs of virus/infections.

Manufacturers of these medicines also include 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 virus (causative agent of Ringel rubella).

Immunoglobulins like Zutectra 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 Zutectra is used (both at hospital or in a home treatment), **the name and batch number of the medicine** are recorded in order to maintain a record of the batches used.

Other medicines and Zutectra
Tell your doctor or healthcare professional if you are taking, have recently taken or might take any other medicines.

Vaccinations

Zutectra can reduce the effectiveness of some vaccines (measles, rubella, mumps, chicken pox) for a period of up to 3 months.

You may have to wait at least 3 months after the last injection of Zutectra before you can have live attenuated vaccines.

Please tell your doctor about your treatment with Zutectra prior to any vaccination.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or healthcare professional for advice before taking this medicine.

Driving and using machines
Zutectra has no or negligible effects on your ability to drive or use machines.

3. How to use Zutectra

Zutectra is intended for **subcutaneous (under the skin) injection**. The contents of one syringe are intended for use once only. Do not inject into a blood vessel.

In most cases you will be given the injection by your doctor or nurse. However, if your antibody levels are sufficient and you have a fixed dose regimen, you or your caregiver may be trained to carry out the injection at home (see below).

For the documentation of your injections of Zutectra it is strongly recommended to use the treatment diary. Your doctor will explain you how to use it.

The dose can be individually established and adapted from 500 IU up to 1,000 IU (in exceptional cases up to 1,500 IU) weekly or fortnightly. The dose will depend on your condition. Your doctor will regularly check your condition and tell you how much and how often you need to use Zutectra.

Injecting by yourself or by caregiver
You can inject Zutectra yourself without the help of your doctor, if they have trained you to do this. **If you are administering Zutectra yourself, please read instructions in the section "How to inject Zutectra by yourself or by caregiver" carefully.**

Zutectra must be brought to room temperature (approx. 23°C-27°C) before use.

If you use more Zutectra than you should
Consequences of an overdose are not known. However, if you have used more than the prescribed dose of Zutectra, contact your doctor, healthcare professional or pharmacist straight away for advice.

If you forget to use Zutectra
Do not take a double dose to make up for a forgotten injection. Talk to your doctor about managing the dose. Your doctor will tell you how much and how often you need to use Zutectra.

Make sure you use Zutectra as prescribed and as instructed by your doctor to avoid the risk of a hepatitis B re-infection.

4. Possible side effects

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

Most side effects observed with Zutectra were mild to moderate in nature. In very rare cases human normal immunoglobulins may cause a serious allergic reaction.

If you notice any of the following effects stop the injection and tell your doctor immediately:
- rash,
- itching,
- wheezing,
- difficulty in breathing,
- swelling of the eyelids, face, lips, throat or tongue,
- low blood pressure, fast pulse

This can be an allergic reaction or a serious allergic reaction (anaphylactic shock).

In case of any adverse event after the injection speak to your doctor immediately.

The following side effects have been reported with Zutectra:

Common (may affect up to 1 in 10 people):
- injection site reactions: pain, hives (urticaria) at injection site, haematoma (a collection of blood in tissue under the skin), reddening of the skin (erythema).

Uncommon (may affect up to 1 in 100 people):
- headache
- upper abdominal pain (from your chest to the belly button)

Furthermore the following reactions have been reported once only:
- tiredness (fatigue)
- high blood pressure (hypertension)
- inflammation of the nose and throat (nasopharyngitis)
- muscle spasm
- allergic reactions (hypersensitivity)
- abnormal heartbeat (palpitations), cardiac discomfort
- itching (pruritus), rash
- pain in the mouth and throat

With other human immunoglobulin preparations the following additional symptoms have been reported:
- chills
- headache
- dizziness
- fever
- vomiting
- mild allergic reactions
- nausea (urge to vomit)
- joint pain
- low blood pressure
- moderate low back pain
- injection site reactions: swelling, soreness, redness, hardening of the skin, local heat, itching, bruising and rash.

Reporting of side effects
If you get any side effects, talk to your doctor, healthcare professional or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zutectra

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

Do not use this medicine after the expiry date which is stated on the outer carton and the syringe label after EXP.

Store and transport refrigerated (2°C-8°C). Do not freeze. Keep the container in the outer carton in order to protect from light.

The solution should be administered immediately after opening the syringe.

Do not use Zutectra if you notice that the solution is cloudy or has particles.

Any unused medicine or waste material should be disposed of in accordance with local requirements. Once the injection has been completed, dispose of all needles, syringes and empty glass containers without delay in a container intended for sharp objects you were provided with.

6. Contents of the pack and other information

What Zutectra contains

- The **active substance** is human hepatitis B immunoglobulin 500 IU/ml.
- Zutectra contains 150 mg/ml of human plasma protein of which at least 96 % is immunoglobulin G (IgG). The maximum immunoglobulin A (IgA) content is 6,000 micrograms/ml.
- The **other ingredients** are glycine and water for injections.

What Zutectra looks like and the contents of the pack

Zutectra is presented as a solution for injection provided in pre-filled syringes (500 IU/ml - pack size of 5 in a blister). The colour of the solution can vary from clear to pale yellow or light brown.

One pre-filled syringe of 1 ml Zutectra contains 500 IU. Zutectra is supplied in a pack size containing 5 pre-filled syringes each in a blister pack.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

7. How to inject Zutectra by yourself or by caregiver

The following instructions are intended to explain how to inject Zutectra. Please read the instructions carefully and follow them step by step. The doctor or his/her assistant will teach you the process of administration.

Do not attempt to inject Zutectra until you are sure that you understand how to prepare the injection solution and give the injection.

General information:

- Keep the syringes and syringe disposal unit out of the reach of children; lock the supplies if possible.
- Try to take the injection at the same time of day. This makes it easier to remember it.
- Always double-check the dose.
- The solution must be brought to room temperature before use.
- Open each syringe only when you are ready for an injection. You should administer the injection immediately after opening the syringe.
- The colour of the solution can vary from clear to pale yellow up to light brown. Do not use solutions that are cloudy or have particles.
- This medicine must not be mixed with other medicines.

Before the injection:

1. Wash your hands. It is important to have your hands and the items you use as clean as possible.

2. Lay out everything you need in advance. Find a clean place where you can spread out all the items you are going to use:

- two alcohol swabs,
- one syringe of Zutectra,
- one needle suitable for subcutaneous injection.

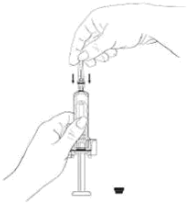
Please note that alcohol swabs and needles are not contained in the pack and you need to supply them yourself.

3. Before preparing the injection, decide where you are going to inject. You should inject Zutectra into the fatty layer between the skin and muscle (about 8 to 12 mm under the skin). The best places for injections are where the skin is loose and soft for example in the abdomen, arm, thigh or buttocks, and away from joints, nerves, bones.

Important: Do not use on any area where you can feel lumps, bumps, firm knots, pain or on an area that is discoloured, indented, scabbed, or where the skin is broken. Talk to the doctor or healthcare professional about these or any other unusual conditions you may find. You should rotate the injection site at every injection. If some areas are too difficult for you to reach, you may need a caregiver to help you with these injections.

4. Prepare the Zutectra syringe:

- Take the syringe out of the pack.
- Examine the solution carefully. It should be clear and contain no particles. If the solution is discoloured, cloudy or contains particles, discard it and start again with a new syringe.
- Remove the protective cap from the syringe.



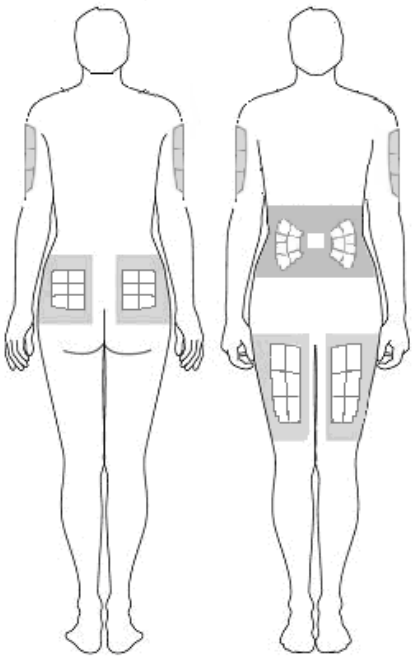
- Take the needle out of its sterile pack and fit the needle onto the syringe.

5. Get rid of any air bubbles that may be in the syringe.

- Hold the syringe with the needle pointing upwards, and tap the syringe gently with your fingers until the air has collected at the tip. Carefully push the plunger in until the air bubbles have disappeared.

Injection

1. Choose the area where you will make the injection and make a note of it in the diary.



Abdomen (stomach): Do not use the area within one inch around the navel. Avoid using the belt line area, as rubbing may irritate the injection site. Avoid surgical scars. This is likely to be the easiest place to inject if you are doing it yourself.

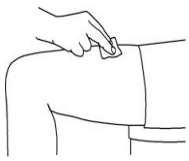
Thighs: Use middle and outer areas where you can pinch up tissue. You are likely to have more fatty tissue the closer you are to the hip and the further you are from the knee.

Arms: The back of the upper arm should be used. It is hard to pinch up the tissue and inject Zutectra yourself using this site. If you do choose to inject your arm yourself, try to pinch up the tissue by placing your upper arm over the back of a chair or brace it against a wall. It is much easier for someone else to use this site if you do need help.

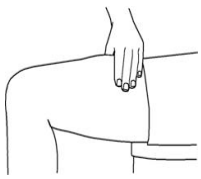
Buttocks: Use any area where you can pinch up tissue. It's harder to give yourself an injection here. Try standing in front of a mirror to locate the site or you may want to ask your caregiver to give you the injection.

It's important to change (rotate) the injection sites. This will help the skin stay supple and help the medicine be absorbed evenly. Rotating sites means starting at one site and using all other sites before going back to the first site you used. Then start the rotation again. It may be helpful to keep a record of where you had the last injection to avoid problems.

The administration in thighs is shown as an example in the following pictures:

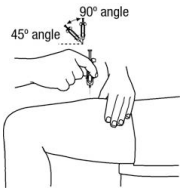


2. Wipe the intended area with an alcohol swab. Let the skin air-dry.

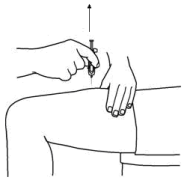


3. Gently pinch the skin together around the disinfected injection site (to raise it up a little) and push the needle into the skin with a rapid, confident movement at an angle of 45 to 90 degrees. Inject

beneath the skin as you have been shown by the doctor or nurse.



4. Inject the liquid by pressing gently on the plunger. Allow yourself enough time to inject the whole of the solution until the syringe is empty.



5. Then pull the needle out immediately and let go of the pinched skin.

6. Clean the injection site by wiping it in a circular motion with the alcohol swab.

Dispose of all used items

Once the injection has been completed, dispose of all needles and empty glass containers without delay in a container intended for sharp objects.