European Medicines Agency
Evaluation of Medicines for Human Use

London, 24 September 2009
Doc.Ref.: EMA/CHMP/786410/2009

ASSESSMENT REPORT
FOR
Zutectra

International Nonproprietary Name:
Human Hepatitis B immunoglobulin

Procedure No. EMEA/H/C/001089

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Biotest Pharma GmbH submitted on 29 October 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Zutectra, through the centralised procedure under Article 3(2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 23-26th June 2008.

The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application for a known active substance.

The applicant initially applied for the following indication: Prevention of hepatitis B virus re-infection after liver transplantation for hepatitis B induced liver failure. Zutectra is indicated in adults only.

Licensing status:
Zutectra has not been given a previous Marketing Authorisation.
Zutectra contains the same active substance but different quantitative composition as Hepatect CP, which is also marketed by Biotest Pharma GmbH.

Hepatect CP has been given previous Marketing Authorisations in Austria, Belgium, Czech Republic, Germany, Hungary, Ireland, Italy, The Netherlands, Poland, Portugal, United Kingdom and other countries outside EEA. The first marketing authorisation of Hepatect CP in an EEA member state dates from 2000.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:
Rapporteur: **Christian K. Schneider** Co-Rapporteur: **Robert James Hemmings**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 29 October 2008.
- The procedure started on 19 November 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 6 February 2009. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 3 February 2009
- During the meeting on 16-19 March 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 March 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 May 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 July 2009.
- During the CHMP meeting on 20-23 July 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing and by the applicant.
- The applicant submitted the written responses to the CHMP LoOI on 18 August 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Oustanding Issues to all CHMP members on 7 September 2009.
- During the meeting on 24 September 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Zutectra on 24 September 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 21 September 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

The hepatitis B virus (HBV) is a double-stranded DNA virus in the hepadnaviridae family. Approximately 2 billion people in the world have been infected by HBV and 300-350 million of them are chronically infected with virus. Most of European countries fall into category of low or intermediate risk endemicity areas for HBV (<2% or 2-8% of chronic HBV, respectively). HBV is transmitted by perinatal, percutaneous, and sexual exposure, as well as by close person-to-person contact presumably by open cuts and sores, especially among children in hyperendemic areas. In low prevalence areas, injection drug abuse and unprotected sex are the primary transmission routes, although other factors may be important.

HBV infection may either be acute (self-limiting) or chronic (long-standing). Persons with self-limiting infection clear the infection spontaneously within weeks to months. Children are less likely than adults to clear the infection. More than 95% of people who become infected as adults or older children will stage a full recovery and develop protective immunity to the virus. However, only 5% of newborns that acquire the infection from their mother at birth will clear the infection. This population has a 40% lifetime risk of death from cirrhosis or hepatocellular carcinoma. Of those infected between the ages of one to six, 70% will clear the infection.

The prevention of recurrent HBV infection after liver transplantation for hepatitis B induced liver failure is a specific treatment objective. The mechanism of action of hepatitis B immunoglobulin (HBIG) is a passive immunisation against infection with the hepatitis B virus. The introduction of HBIG in the late 1980s and subsequently nucleotide analogues have significantly improved the outcome of liver transplantation with regard to re-infection and survival rates. The overall survival of patients transplanted for HBV-related cirrhosis now exceeds 85 % at one year and 75 % at five years. The current standard of care recommends using a combination of indefinite HBIG and antiviral and has led to <10% of HBV recurrence. The HBIG therapy without any viral prophylaxis is potentially an indefinite treatment aiming to maintain anti-HBs levels of 100-500 IU/l, depending on the viral replication status of the patient at the time of the transplantation.

Zutectra is a purified human hepatitis B immunoglobulin preparation obtained from plasma from selected and/or immunised donors having antibodies against hepatitis B surface (HBs) antigen. It is a sterile solution for subcutaneous (SC) injection containing 150 mg human plasma protein with at least 96 % IgG and 500 IU/ml anti-HBs antibody. The product is considered a further development of an already approved HBIG preparation for intravenous (IV) administration (Hepatect CP) with the difference being that the intravenous product is less concentrated. Zutectra is presented in 1 ml glass syringes.

A so-called full application has been submitted for the marketing authorisation; access to the centralised procedure was granted under the optional scope on the basis of the claim of therapeutic innovation. The application was exempted for the requirements of the paediatric legislation as the concept of the new product being part of the same global marketing authorisation as Hepatect CP was applied.

The initially claimed indication read as follows: “Prevention of hepatitis B virus re-infection after liver transplantation for hepatitis B induced liver failure. Zutectra is indicated in adults only.” The approved indication is: “Prevention of hepatitis B virus (HBV) re-infection in HBV-DNA negative patients ≥ 6 months after liver transplantation for hepatitis B induced liver failure. Zutectra is indicated in adults only. The concomitant use of adequate virostatic agents should be considered, if appropriate, as standard of hepatitis B re-infection prophylaxis.”

Patients with bodyweight < 75 kg should receive 500 IU (1 ml)/week; patients with bodyweight ≥ 75 kg should receive 1,000 IU (2 times 1 ml)/week. Prior to the initiation of subcutaneous treatment with Zutectra, anti-HBs serum levels should be stabilised with an adequate intravenous hepatitis B

immunoglobulin to levels at or above 300-500 IU/l. Anti-HBs serum level of > 100 IU/l should be maintained and levels of anti-HBs antibody should be regularly monitored.

No formal scientific advice from CHMP was obtained for the development of Zutectra.

Compliance with the current international GMP and EU-regulations has been demonstrated.

2.2 Quality aspects

Introduction

Zutectra is a medicinal product containing purified human hepatitis B immunoglobulin. Zutectra is obtained from plasma from selected and/or immunised donors having antibodies against hepatitis B surface (HBs) antigen. Human hepatitis B immunoglobulin complies with Ph. Eur. monograph no. 0722 on Human hepatitis B immunoglobulin and 0388 on Human normal immunoglobulin.

Zutectra is a sterile solution for subcutaneous (SC) injection containing 150 mg human plasma protein with at least 96 % IgG and 500 IU/ml anti-HBs antibody. It is presented in 1 ml glass syringes.

The excipients are human normal immunoglobulin, glycine and water for injections, the formulation does not contain preservatives. All excipients comply with the Ph. Eur.

Zutectra is a further development of Hepatect CP, a less concentrated hepatitis B immunoglobulin product manufactured by Biotest GmbH and intended for intravenous (IV) administration. It contains the same active substance as Zutectra and has been licensed in some member states in the EU since 2000. The essential difference between the two formulations is the concentration of the final product (Hepatect 50mg/ml human plasma protein; 50 IU/ml hepatitis B antibodies).

Active Substance

Zutectra contains human immunoglobulin G molecules as the active substance. The preparation is enriched for antibodies against hepatitis B virus. The activity of Zutectra is standardized based on the content of HBs antibodies. The active substance is prepared from pooled human plasma obtained from healthy donors, selected and/or immunized with hepatitis B surface antigen, having antibodies against hepatitis B surface antigen. It is manufactured from cryo-poor human plasma fractionated according to a modified cold ethanol plasma fractionation method. The quality of plasma and the donation centres are described in the Biotest Plasma Master File (PMF) dossier. The Biotest PMF has been certified by EMEA (EMEA/H/PMF/000009/05) in accordance with the specific requirements as laid down in Part III, section 1.1 of Annex I to the Directive 2001/83EC.

The production site of the intermediates and drug substance of Zutectra is Biotest AG and Biotest Pharma GmbH, Dreieich, Germany.

The drug substance of Zutectra is manufactured from human plasma under microbiological reduced conditions in a GMP controlled environment. The manufacturing process follows a modified cold ethanol fractionating process to isolate the intermediate, fraction II.

Human plasma for fractionation is used as starting material. Single plasma donations are pooled to obtain a representative plasma pool from which the cryoprecipitate is separated. An optional adsorption step to remove the coagulation factors of the prothrombin complex by filtration may be performed on the cryo-poor plasma. Results of validation studies confirm that this step can be optionally omitted without impairment of the drug substance quality. In subsequent steps, the following fractions are precipitated and separated from the cryo-poor plasma: Fraction I/II/III is precipitated with ethanol and separated. Fraction I/III is precipitated with ethanol and separated. Fraction II is precipitated and separated.

To remove impurities and inactivate viruses prior to a critical virus inactivation step, fractions II are pooled and treated with caprylic acid. The caprylic acid treated intermediate is filtered and subjected to the critical step of virus inactivation with polysorbate 80/tri-n-butyl phosphate.

Final purification using cation exchange chromatography, nanofiltration, concentration and purification by ultra- and diafiltration, adjustment of protein concentration and pH, and subsequent filtration result in the drug substance.

Final concentration by ultrafiltration, adjustment of protein concentration and pH, and subsequent filtration results in the drug substance of Zutectra. The drug substance may be stored at 5 ± 3°C.

The following steps in the manufacturing process of the drug substance of Zutectra were identified as critical steps: precipitation and separation of fraction I/III; treatment with caprylic acid solution and calcium acetate; virus inactivation with polysorbate 80 and tri-n-butyl phosphate; and nanofiltration. Critical process steps are adequately monitored by in-process controls. The consistency of the critical steps has been evaluated with production scale batches.

Reproducibility and consistency of the manufacturing process in pilot scale and production scale is adequately documented for all intermediates

General biological characteristics of pilot scale batches are presented. The characterisation of Zutectra is comprehensive. Extensive testing of biological characteristics and activities of batches of the drug product Zutectra is in accordance with the Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Subcutaneous and Intramuscular Use (CPMP/BPWG/283/00). These characterisation data can also be conferred to the drug substance, as the production process from the drug substance to the drug product, adjustment of the protein content and filling, does not change the functional characteristics of the immunoglobulin preparation.

The impurities arising from the starting material and the manufacturing process derived impurities were identified. All critical impurities are tested for the release of the drug substance. It is clearly demonstrated that these impurities can be removed in an acceptable manner.

The selected parameters and specifications are suitable to control the drug substance quality. Sixteen different analytical methods are used for the control of the drug substance. Description and validation data for methods used for the drug substance are sufficient. The applicant presented acceptable batch data from ten pilot and two production scale batches to demonstrate consistency of the full scale manufacturing process. The specifications proposed are sufficient.

In accordance with ICH guidelines Q5C and Q1E based on acceptable analytical (primary and supportive) real time data a shelf life of the drug substance of Zutectra for 12 months when stored at 5 ± 3°C is justified.

The applicant provided data for two production scale batches for 6 months at 2-8°C. An extension of the stability study for one additional batch is currently ongoing. The applicant commits to finalise the ongoing stability studies and submit to the EMEA the final report. Supportive real time/real temperature stability data were submitted. The data between the studies are comparable.

Medicinal Product

The medicinal product Zutectra is supplied as a solution for injection. The solution is clear to opalescent and colourless to pale yellow. The excipients are human normal immunoglobulin, glycine and water for injections, the formulation does not contain preservatives. All excipients comply with the Ph. Eur.

IgG subclass distribution is approx. 59 % IgG1, 35 % IgG2, 3 % IgG3, 3 % IgG4. The IgA content is limited to a maximum of 4 % of protein (IgA ≤ 6 mg/ml).

The drug product Zutectra is presented in glass-syringes containing 500 IU in 1 ml solution for injection.

The drug product is manufactured from the drug substance under controlled conditions in a GMP environment. Drug product manufacture consists of formulation and filling the product into 1 ml syringes. The drug substance is transported to the production building, where the production of the final filling pool is performed. For the production of a final filling pool, the necessary excipients are added. The final filling pool is subsequently sterile filtered into plastic bags where it remains until transporting to the contract manufacturer, where the aseptic filling into the final containers is performed. At the contract manufacturer the plastic bag with the final filling pool is transferred to the drug product filling site and connected to the filling line. The final filling pool is sterile in-line filtered and directly filled into the syringes pre-assembled with a closure. The filled syringes of drug product are automatically sealed with plungers, release tested, labelled, packaged, and finally released at Biotest.

The process and in-process controls performed during manufacture of the drug product including critical steps, acceptance criteria and points of sampling are sufficient.

The selected parameters and specifications are suitable to control the drug product quality. To demonstrate consistency of the full scale manufacturing process the applicant has presented batch data from ten pilot and two production scale batches and finally within the response document an update with two newly produced drug product batches of Zutectra.

The applicant presented an update of acceptable 12 month real time stability data for each drug product filling size (0.4 ml filling and 1.0 ml filling). The next two manufactured drug product batches will be included into the current stability study. In conjunction with extensive supportive stability data, the new requested shelf life of 18 months at 5 ± 3°C for Zutectra drug product (0.4 ml and 1.0 ml filling size) is justified with regard to ICH guideline Q5C (Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products; CPMP/ICH/138/95-ICH-Q5C) and ICH guideline Q1E (Evaluation for Stability Data; CPMP/ICH/ 420/02-ICH Q1E)). The applicant commits to submit the final report including at least 18 months stability data for Zutectra drug product.

TSE Safety

TSE reduction/removal studies have been performed for two steps of the manufacturing process for Zutectra i.e. the precipitation and separation of fraction I/III from fraction II and the nanofiltration step. Safety with regard to TSE has been adequately demonstrated.

Virus safety

Zutectra is produced from human plasma by cold ethanol fractionation up to fraction II followed by caprylic acid treatment, solvent/detergent (S/D) treatment with polysorbate 80 and tri-n-butyl phosphate, cation exchange chromatography and nanofiltration. The relevant production steps have been investigated for their capacity to remove or inactivate viruses. Two steps (caprylic acid treatment and S/D treatment) have been demonstrated to effectively inactivate enveloped viruses. Virus safety against enveloped viruses such as HIV, HCV, HBV has been adequately demonstrated. The precipitation and separation of Fraction I/III from Fraction II is important for removal of non-enveloped viruses from the product. Efficient removal of non-enveloped model viruses Reovirus and porcine parvovirus (a model for parvovirus B19 and a very stable, small non-enveloped virus for which antibodies are not present in the product) was demonstrated for this step. To improve the viral safety of Zutectra further, nanofiltration is also performed and effective reduction of both enveloped viruses and non-enveloped viruses has been demonstrated. Furthermore it is expected that neutralising antibodies make an important contribution of the safety of Zutectra against hepatitis A virus and parvovirus B19.
Virus and TSE safety has been adequately demonstrated.

Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted data, the marketing authorisation application for Zutectra is recommended for approval based on quality grounds. Overall, information on manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important quality characteristics.

At the time of the opinion, the applicant has committed to finalise the ongoing stability studies and report the outcome within an agreed timeframe.

2.3 Non-clinical aspects

Introduction

Zutectra is a sterile, purified solution of human hepatitis B immunoglobulin derived from plasma. It complies with the relevant Ph. Eur. monograph (see Quality aspects).

A limited nonclinical programme has been performed with Zutectra. Standard nonclinical models for the investigation were in general considered of limited relevance as the product is a human protein hence eliciting in animal species an immune response that is not predictive of the situation in humans. The scope of the programme was in compliance with the principles outlined in the Note for Guidance on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (CPMP/ICH/302/95, ICH S 6), which are applicable to plasma derived products. The applicant also made reference to nonclinical studies conducted with another immunoglobulin preparation, Intratect, and extrapolated these results to Zutectra. Intratect is a standard immunoglobulin preparation for intravenous administration. The manufacturing process of Intratect differed from the one for Zutectra in terms of the starting material (normal plasma instead of specific plasma), the nanometre filtration and the final ultra-/diafiltration step. The differences were considered marginal by the applicant with regard to product characteristics, production process and safety hence the nonclinical and clinical data were considered relevant for Zutectra.
Therefore, the nonclinical programme consisted of two local tolerance studies conducted with Zutectra as well as a study investigating single-dose toxicity and safety pharmacology of Intratect. These studies were GLP-compliant. References to published literature were provided where appropriate to address aspects which have not been covered by designated studies.

Pharmacology

- Primary pharmacodynamics

The mechanism of action of hepatitis B immunoglobulin is passive immunisation against infection with the hepatitis B virus. The immunoglobulins will neutralise viral particles, preventing them from binding to the target cells (hepatocytes). The viral particles will also be eliminated.

Specific pharmacodynamic studies have not been performed with Zutectra, except for the evaluation of a survey of antibody functional activity and binding function *in vitro* in a minimum of three batches of product. The study demonstrated the presence of anti-HBs antibodies required for anti-hepatitis B activity.

- Secondary pharmacodynamics

The above-mentioned *in vitro* studies further showed the presence of antibodies against a variety of bacteria, viruses and fungi. In addition, Fc functional activity was confirmed.

- Safety pharmacology programme

Reference was made from a safety pharmacology study using Intratect (study LPT 12422/99). In this study Intratect was compared with the previously marketed product (Intraglobin CP) by intravenous infusion of 0.6 ml/kg/min for 8 min in Beagle dogs. Measurements included respiratory rate, body temperature, blood pressure, electrocardiography recordings and urinalysis.

No significant effects on heart rate, blood pressure, respiratory rate or urinalysis. The ECG showed no substance-related alterations in PW, QT, QRS-interval or P-segment. Since Zutectra is given subcutaneously rather than intravenously, it is likely to reach Cmax more slowly than Intratect. It is accepted that the data from Intratect can be extrapolated to Zutectra.

- Pharmacodynamic drug interactions

No studies are required for this type of product.

Pharmacokinetics

No nonclinical pharmacokinetic studies have been conducted. The immunoglobulin molecules present in Zutectra are normal constituents of the human body. The plasma half-life in animals is usually considerably shorter than that in humans. Animals that are genetically similar to humans typically show a moderately reduced plasma half-life compared with humans (to two thirds in primates), whereas it is drastically reduced in rodents (few days). Therefore, pharmacokinetic studies in animals are in general of limited predictive value for the situation in humans and are not used for the justification of the dose and dosing scheme. With regard to excretion it can be assumed that Zutectra will be degraded into small peptides and component amino acids via catabolic pathways that are typically associated with endogenous IgG.

Therefore, in accordance with the principles applied for the nonclinical development of plasma-derived immunoglobulin preparations this approach is considered acceptable.

Toxicology

- Single dose toxicity

A single dose toxicity study was performed with Intratect (study LPT 12422/99) and the results were extrapolated to Zutectra. In this study, which was conducted together with the safety pharmacology analysis, beagle dogs (2/sex/group) were intravenously infused with 0.9 % NaCl solution, Intraglobin CP (reference product for Intratect) or Intratect (0.6 ml/kg bw/min for 8 minutes resulting in 240 mg/kg). Dogs were followed for 14 days after treatment. Samples for haematology and clinical biochemistry were taken during the first 24 hours after infusion and on test day 14.

No mortality occurred and no substance-related clinical signs were noted. With regard to haematology, a reduction in leukocytes and platelets was observed in the treated compared to control animals and the ratio of neutrophils to leukocytes had shifted toward leukocytes. These changes are considered typical for normal immune system responses to an antigenic material. At the end of the observation period leukocyte and platelet numbers had returned to normal. A slight to moderate increase in alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase activity was observed following treatment with Intratect. None of these changes is considered to raise any toxicological concerns. No test substance-related pathological macroscopic findings were observed at necropsy after the end of the 14-day follow up period.

Given that Intratect is produced by a comparable process, the data obtained with Intratect are considered indicative of the toxicity of Zutectra. In this study, Intratect was given intravenous which is considered as worst case because drug peak levels are reached faster than with the subcutaneous route of administration intended for Zutectra.

- Repeat dose toxicity (with toxicokinetics)

No repeat-dose toxicity studies were performed. This is considered acceptable given that human immunoglobulins administered to animals can be expected to elicit an immune response, which would interfere with the toxicity evaluation.

- Genotoxicity

No studies on genotoxicity were performed, which is in accordance with Note for Guidance on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (CPMP/ICH/302/95, ICH S 6). Human immunglobulins are not expected to directly interact with DNA or other chromosomal material.

- Carcinogenicity

No studies on carcinogenicity were performed, which is in accordance with Note for Guidance on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (CPMP/ICH/302/95, ICH S 6). Human immunglobulins are endogenous materials for which carcinogenicity studies are inappropriate.

- Reproduction Toxicity

No studies on the reproductive and developmental toxicity were performed. According to the Note for Guidance on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (CPMP/ICH/302/95, ICH S 6) the need for such studies depend on the product. In case of plasma-derived human immunoglobulin preparations such studies are not required.

- Toxicokinetic data

Toxicokinetic data has not been generated and are not considered necessary.

- Local tolerance

The local tolerance to Zutectra was investigated in two studies in New Zealand White rabbits. In addition, supportive data can be derived from the safety pharmacology/toxicology study with Intratect.

Study MDS AA74549

The acute local tolerance was investigated after a single subcutaneous, intramuscular, intra-arterial or intravenous injection of Zutectra (149 mg/ml) and the vehicle (0.9 % NaCl) as control article. Injection volume of both test article and vehicle was 1 ml per injection site. This study is considered the pivotal local tolerance study since the product used in that study was produced according to the latest process (with nanofiltration).

No local reactions attributable to the test item were observed. Haematoma observed at the injection sites after intra-arterial, intravenous and intramuscular injection occurred with similar incidence and similar severity in test and control animals hence these findings were considered to be associated with the administration procedure. At subcutaneous injection sites, no local reactions were recorded. Further macroscopic findings did not indicate a difference between the test article and the control-treated sites. Histopathology findings were few, of low severity, and with no difference between the test article-treated and the vehicle-treated sites for any route of application.

Based on this data it is concluded that administration of 150 mg Zutectra (1 ml) is well tolerated at the intended subcutaneous route and other accidental routes of administration (intra-arterial, intravenous or intramuscular).

Study10-3-0199-03:

The acute local tolerance was investigated in rabbits after single intramuscular and subcutaneous injection. Rabbits (6/sex) were treated with test article and vehicle by both routes of administration, intramuscular and subcutaneous. Injection volume was 2 ml (approximately 300 mg) per injection site and the observation period was 7 days. The product used in this study was produced without nanofiltration.

In all animals, there were no abnormal clinical signs and body weight changes were normal. At the injection sites, there were no findings during the 7 days observation period. The sites were visible due to the labelling, but no tissue reactions were observed macroscopically. Microscopically, a small number of morphologic findings was observed in skin and intramuscular injection sites, but the alterations in the test article-treated sites did not differ significantly from those observed in the vehicle-treated control sites. Posttraumatic changes were observed at almost all intramuscular injection sites (treated and control sites). These changes were considered to have been induced by the labelling suture material or to be due to the mechanical injury during the injection procedure rather than to a direct irritating effect of the test article.

In this study, the single intramuscular and subcutaneous injection of Zutectra to rabbits did not produce any evidence of a toxic effect. The fact that the product used in this study was manufactured slightly differently (without nanofiltration) was considered minor and not relevant for the conclusion that Zutectra is considered to be well tolerated after an intramuscular and subcutaneous administration.

Study LPT 12422/99

This combined safety pharmacology/single-dose toxicity study (see above) also addressed the local tolerance to Intratect administered intravenous. Beagle dogs (2/sex/group) were intravenously infused with 0.9 % NaCl solution, Intraglobin CP (reference product for Intratect) or Intratect (0.6 ml/kg bw/min for 8 minutes resulting in 240 mg/kg).

No substance related local intolerance reaction at or around the infusion sites was found during the daily observations of clinical symptoms. There were no substance-related findings at necropsy or during histopathology. The few microscopic findings were regarded spontaneous and related to the infusion procedure.

Overall, this study supports the results obtained in rabbits with Zutectra.

- Other toxicity studies

Process-related impurities in Zutectra are tri-n-butyl phosphate (TNBP) and polysorbate 80, both of which are used during manufacturing for virus inactivation. The applicant has provided a review of the toxicological properties of TNBP and polysorbate 80 after single and multiple doses in various animal species based on published references; the main findings are summarised in table 1:

Table 1 Toxicological data of tri-n-butyl phosphate (TNBP) and polysorbate 80 (summary based on published references)

TOXICOLOGICAL DATA		
Determinations	**TNBP**	**Polysorbate 80**
Mutagenicity:		
Salmonella	500 µg/plate	-
Mice	-	20 ppm
Human lymphocytes	-	20 ppm
Toxicity:		
Mice, oral	LD_{50} = 1189 mg/kg	LD_{50} = 25 g/kg
Mice, inhalation	LC_{50} = 1300 mg/m³	-
Mice, s.c	LD_{50} = 3 g/kg	-
Mice, i.p.	LD_{50} = 159 mg/kg	LD_{50} = 7600 mg/kg
Mice, i.v.	-	LD_{50} = 4500 mg/kg
Rat, oral	LD_{50} = 3000 mg/kg	-
Rat, inhalation	LC_{50} = 28 g/m³	-
Rat, i.p.	LD_{50} = 251 mg/kg	LD_{50} = 6804 mg/kg
Rat, i.v.	LDLo = 100 mg/kg	LD_{50} = 1790 mg/kg
Cat, inhalation	LDLo = 24.51 g/m³	-
Cat, i.v.	-	LDLo = 500 mg/kg
Dog, i.v.	-	LDLo = 500 mg/kg
Reproduction toxicity:		
Rat, oral	TDLo = 7500 mg/kg (6-15 D preg)	TDLo = 635 g/kg (multigenerations)

LC_{50} = Lethal Concentration Fifty (a calculated concentration of a substance in air, exposure to which for a specified length of time is expected to cause the death of 50% of an entire defined experimental animal population)

LDLo = Lethal Dose Low (the lowest dose, other than LD_{50}, of a substance introduced by any route, other than inhalation, over any given period of time in one or more divided portions and reported to have caused death in humans or animals)

LD_{50} = Lethal Dose Fifty (a calculated dose of a substance which is expected to cause the death of 50% of an entire defined experimental animal population)

TDLo = Toxic Dose Low (the lowest dose of a substance introduced by any route, other than inhalation, over any given period of time and reported to produce any toxic effect in humans or to produce carcinogenic, neoplastigenic, teratogenic, or mutagenic effects in humans or animals)

Taking into account the concentrations of TNBP and polysorbate 80 in the finished products, the exposure of patients to TNBP and polysorbate 80 is significantly lower than the toxic dose levels (LD50, LDLo, TDlo) referred to in the published nonclinical studies. Based on these data and also the long clinical experience with products that contain TNBP and polysorbate 80, it is considered acceptable to administer Zutectra to humans at the proposed doses. No further toxicity studies are warranted.

Ecotoxicity/environmental risk assessment

The applicant has justified the absence of an environmental risk assessment for this plasma-derived immunoglobulin preparation. In accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) proteins are exempted from the requirement to perform an environmental risk assessment because they are unlikely to result in a significant risk to the environment. Therefore, the lack of such assessment is acceptable.

2.4 Clinical aspects

Introduction

The main clinical programme to support the present marketing authorisation application comprised the following studies:

- Phase I study to establish the pharmacokinetics following subcutaneous administration compared to intramuscular administration (study 956);
- Phase III study investigating the efficacy and safety of subcutaneous use in liver transplanted patients (study 958).

An overview of the key elements of these studies is provided in Table 2. In addition, the data from supportive studies conducted with a different hepatitis B immunoglobulin preparation, Hepatect CP, has been provided. This product is authorised for intravenous use and therefore has a different composition; however the active substance is the same.

Table 2 Summary of the clinical studies with Zutectra

Study	Objective	Design	Dose Regimen	Duration of treatment	Number of subjects
956	Investigation of safety and pharmaco-kinetics of two application forms (SC/IM) of Zutectra in healthy volunteers	Phase I, open, randomized, parallel group	Single dose of IM or SC at a dose of 30 IU/kg (circa 2100 IU total dose).	Single dose. Follow-up period of 71 days.	30 (15 SC/15 IM)
958	Investigation of efficacy and safety of SC Zutectra in OLT** patients at risk of HBV re-infection	Phase III, open, prospective, single arm	Weekly SC injection of 500 IU (1 ml) for patients with bodyweight <75 kg and 1000 IU (2 ml) for patients ≥75 kg. Dose increase up to 1000 IU to maintain an anti-HBs >100 IU/l	18 weeks Optional further 6 weeks (total: 24 weeks) for patients compliant with Injection technique with stable anti- HBs serum levels.	23*

* ITT population
** orthotopic liver transplant

There is no specific European guideline for the clinical development of Hepatitis B immunoglobulin preparations for subcutaneous use currently available. The following guidance documents are to some extent applicable for this application:

- Core SPC for human plasma derived Hepatitis B Immunoglobulin for intravenous use (CPMP/BPWG/4027/02);
- Core SPC for human plasma derived Hepatitis B immunoglobulin for intramuscular use (CPMP/BPWG/4222/02);
- Guidance on the clinical investigation of human normal immunoglobulin for intramuscular and subcutaneous route of administration (CPMP/BPWG/283/00).

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

Pharmacokinetics

- Absorption / Distribution / Elimination

The pharmacokinetic profile of this specific plasma-derived Hepatitis B immunoglobulin preparation has been investigated in a single pharmacokinetic study comparing the subcutaneous administration against the intramuscular administration (study 956). Additional pharmacokinetic data was provided from studies using a different Hepatitis B immunoglobulin preparation for intravenous use (studies 886, 930, 944). For the general pharmacokinetic properties of subcutaneously administered human hepatitis B immunoglobulin it is established that with regard to distribution they are transported from subcutaneous compartments and are subsequently distributed between plasma and extravascular fluids. In terms of metabolism and elimination, immunoglobulins and immunoglobulin-complexes are broken down in the reticuloendothelial system and the vast majority of immunoglobulin is eliminated by catabolism. For all routes of administration, the half-life of natural human immunoglobulin is approximately 3-4 weeks.

Study 956

This was an open, mono-centre, randomized Phase I study investigating the pharmacokinetics and safety of Zutectra in 30 healthy volunteers following subcutaneous and intramuscular administration, each as 30 IU/kg (1560- 3000 IU) single dose. The follow-up was 71 days.

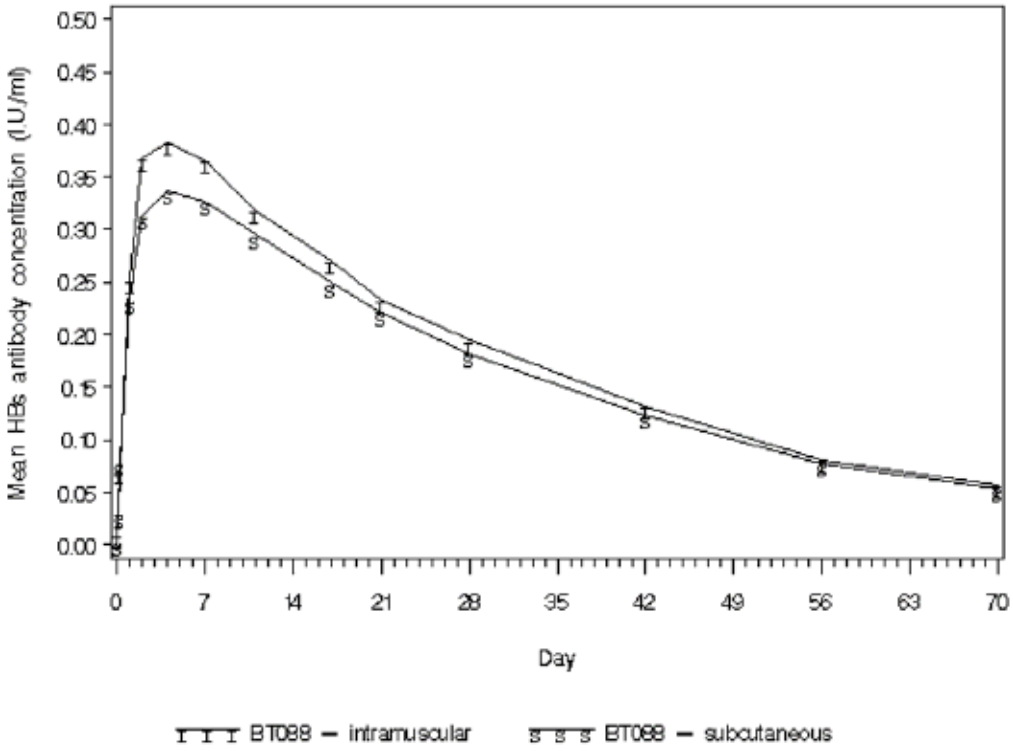
Male and female healthy volunteers (age 18-50 years) with negative hepatitis and HIV serology were eligible for enrolment. Fifteen subjects received Zutectra via the subcutaneous route, and 15 subjects via the intramuscular route. There were no withdrawals; all 30 subjects completed the study as intended in the study protocol. Demographic characteristics were well balanced between the subcutaneous and intramuscular groups. All 30 subjects were Caucasian. 7 (46.7%) subjects in the subcutaneous group and 8 (53.3%) subjects in the intramuscular group were male. The mean ± SD age was 34.3 ± 6.4 years for the subcutaneous group versus 36.3 ± 8.7 for the intramuscular group; the mean ± SD body weight was 69.7 ± 10.6 kg versus 75.1 ± 12.6 kg, respectively; and the mean ± SD body mass index was 23.1 ± 2.4 kg/m^2 versus 24.0 ± 3.1 kg/m^2, respectively.

The PK parameters were calculated using non-compartmental modelling. The parameters were described by statistical characteristics stratified for route of administration (subcutaneous and intramuscular). No formal statistical comparison between both routes of administration was performed.

Mean anti-HBs concentrations increased to maximum values of 0.34 ± 0.06 IU/ml (subcutaneous) and 0.38 ± 0.04 IU/ml (intramuscular), respectively, on Day 4 after application. On Day 42, mean ± SD anti-HBs concentrations were 0.12 ± 0.03 IU/ml for subcutaneous and 0.13 ± 0.03 IU/ml for intramuscular; at the end of the observation period on Day 71 anti-HBs concentrations were still above baseline levels at 0.05 ± 0.02 (subcutaneous) and 0.06 ± 0.02 (intramuscular) IU/ml, respectively. The mean ± SD terminal elimination half-life (t1/2el) was 23.7 ± 3.3 days for the subcutaneous group and 22.9 ± 3.6 days for the intramuscular group. A reliable elimination phase could be identified for all subjects.

The mean serum anti-HBs antibody concentrations measured during the course of the study are displayed in Figure 1 for the subcutaneous and intramuscular treatment groups.

Figure 1 Mean Time Courses of the Serum Anti-HBs Antibody Concentration with Subcutaneous and Intramuscular Administration of Zutectra (study 956)



It was noted by the CHMP that the product used in this study was a pre-nanofiltration product, i.e. not the actual product that will be marketed. For Zutectra the comparability between the nanofiltered and non-nanofiltered product was also shown from a quality perspective. Therefore, additional pharmacokinetic or efficacy studies are not deemed necessary.

The results of this study demonstrated that the half-life ($t_{½}$=23 days), tmax (~4 days) and clearance (Cl =0.11 ± 0.03) are in keeping with results expected from a typical immunoglobulin administered subcutaneously/intramuscularly. Given the lower dosing levels compared to the intravenous studies the Cmax (0.4 IU/ml) and AUC (11.7 IU*d/ml) values are accordingly lower. This is in part compensated by the fact that the subcutaneous treatment would be given four times per month and thus the Cmax values would be expected to provide stable levels throughout a given month of treatment. The larger fluctuations of serum anti HBs antibody levels of intravenous treatment would be mitigated.

The dosing in this pharmacokinetic study was considerably higher than in the efficacy study (mean 2280 IU in study 956 vs. 750 IU in the efficacy study 958), despite the fact that antibody consumption would be surmised to be higher in liver transplant patients. It was noted by the CHMP that a clear rationale for the dose "finding" was not provided, nor was a dose-proportionality study conducted. The dose chosen in the efficacy study was empiric due to a larger than expected decline in anti HBs trough levels (30%; expected rate 20%) which ultimately led to dosing by a body weight below and above 75 kg of 500 IU (1 ml) / week and 1,000 IU (2x 1 ml) / week respectively.

The core SPC for intravenous hepatitis B immunoglobulin products for the orthotopic liver transplant indication requires specific antibody levels to be maintained for the protection; this principle also applies to the subcutaneous administration. Given the pharmacokinetic characteristics of Zutectra after the subcutaneous administration, i.e. a long tmax (4d) and lower Cmax (0.4 IU/ml) obtained at doses larger than those used in the efficacy study, it appears appropriate that the product is not used in newly transplanted patients but in HBV-DNA negative, stable patients who had to have been transplanted > 6 months previously.

Studies 886, 930, 944

These three pharmacokinetic studies had been conducted with Hepatect formulations following intravenous administration. The results are summarised in table 3. The data shows the expected range of pharmacokinetic values for Cmax (1.8 – 3.3.IU/ml), Tmax (1.4 – 4.0 h), T1/2 (22 – 32 days), and AUC (29 – 55 IU*d/ml), depending on the population (healthy volunteers, immunodeficiency patients). All values were within the ranges reported in the literature for intravenous immunoglobulins.

Table 3 Pharmacokinetic data obtained with various Hepatitis B immunoglobulin preparations following intravenous and subcutaneous administration

Product		**Hepatect**	**Hepatect CP**	**Hepatect CP (FH)**	**Zutectra**	
Study		Study 886 IV	Study 930 IV	Study 944 IV	Study 956 SC	Study 956 IM
Dose [IU]		6100	8960	9600	1560 -3000	1560 - 3000
Subjects		Healthy volunteers (12)	CLL, MM (15)	CLL, MM (15)	Healthy volunteers (15)	Healthy volunteers (15)
C_{max} [IU/ml]		1.8 ± 2.04	2.9 (1.8 – 5.7)	3. 3 ± 0.74	0.4 ± 0.06	0.4 ± 0.03
T_{max}	Mean	1.4±1.2 h	3.6±1.1 h	4.0±1.6 h	4.6±1.9 d	3.9±1.8 d
	Median	-	4.0 h	4.0 h	4.0 d	4.0 d
	min-max	0*–3 h	1.0–6.0 h	3.0–9.0 h	2.0–7.0 d	2.0–7.0 d
T ½ [d]	Mean	22.1 ± 3.7	25.3 ± 8.3	31.9 ± 8.9	23.7 ± 3.3	22.9 ± 3.6
	Median	-	23.8	30.8	24.2	23.1
	min-max	17.6 – 30.2	12.9 – 37.7	18.2 – 50.1	19.6 – 30.4	16.8 – 29.5
AUC (0-t) [IU*d/ml]		28. 9 ± 5.6	42.2 (15.6 – 69.5)	55.0 ±16.1	11.7 ± 2.1	12.7 ± 1.7
Cl [ml/min]		0.13 ± 0.03	0.13 (0.08 – 0.4)	0.11 ± 0.05	0.11 ± 0.03	0.11 ± 0.03

CLL: chronic lymphatic leukaemia; MM: multiple myeloma; *directly after completion of infusion

Bioavailability with intravenous administration of Hepatitis B immunoglobulin was more or less immediate, with tmax reached at means of 1.4 to 4.0 hours post-infusion; whereas the maximum concentration with subcutaneous and intramuscular routes was reached at a mean of approximately 4 days post-administration. The calculated mean elimination half-life was between 3 and 4 weeks for all Hepatitis B immunoglobulin dosage forms and administration routes. It can be concluded that despite some shortcomings of the design of study 956 (larger doses than the efficacy study, pre-nanofiltration product) the expected pharmacokinetic characteristics of a subcutaneous immunoglobulin prevail.

- Dose proportionality and time dependencies

No dose-proportionality study was conducted. The Hepatitis B immunoglobulin core SPC for intravenous products does not state a specific dose, rather certain antibody levels are to be maintained as they are considered to be protective; this principle would apply to the subcutaneous administration as well.

- Special populations

Studies in special populations have not been performed, which is acceptable for this product containing a plasma-derived immunoglobulin.

- Pharmacokinetic interaction studies

No pharmacokinetic interaction studies have been conducted, which is acceptable for this product containing a plasma-derived immunoglobulin.

- Pharmacokinetics using human biomaterials

No pharmacokinetic studies using human biomaterials have been conducted, which is acceptable for this product containing a plasma-derived immunoglobulin.

Pharmacodynamics

There was no formal pharmacodynamic study conducted by the applicant. This is appropriate for this type of product.

- Mechanism of action

The mechanism of action of hepatitis B immunoglobulin is a selective binding of the immunoglobulin to viral particles (via HBsAg) and their elimination via complement-dependent and independent pathways thereby preventing further dissemination of the virus and its reuptake by neighbouring cells during post-exposure prophylaxis.

- Primary and Secondary pharmacology

The use in liver transplant patients is based on theoretical hypothesis that large quantities of hepatitis B immunoglobulin can prevent *de novo* infection of the graft with circulating virus which can reside in the extra-hepatic compartments of the recipient and may prevent interhepatocyte viral transfer as well. Hepatitis B immunoglobulin also undergoes endocytosis by hepatocytes and binds to HBsAg within cells already infected, thereby decreasing viral secretion. It is also hypothesized that the Fc-fragment-mediated complement activity can trigger the elimination of virally infected hepatocytes and other virus-harbouring cells.

Clinical efficacy

- Dose response study

As mentioned in the pharmacokinetic section a dose finding study was not conducted. The choice of weight guided dose for immunoprophylaxis in adults (500 IU/week for adults <75 kg and 1000 IU/week for adults ≥75 kg) was based on a trend for reduction of trough anti-HBs levels following use of 500 IU in the first 3 patients enrolled in the pivotal efficacy trial 958 (see below). The applicant claimed that the weight-based approach takes into account that the subcutaneous space may have a greater volume in patients with higher body weight. The greater volume in the subcutaneous space could lead to lower bioavailability, e.g. by influencing the kinetics of absorption of hepatitis B immunoglobulin from subcutaneous tissue into the vascular space.

Although this approach cannot be considered optimal from the point of view of clinical development, the outcome in terms of maintaining adequate trough levels in the HBV-DNA negative and stable population is recognised as it reflects the position of dosing by titre as stated in the core SPC for hepatitis B immunoglobulin preparations.

- Main study

Study 958: Prevention of Hepatitis B recurrence following liver transplantation

This was a Phase III, open, prospective, single-arm study investigating efficacy and safety and feasibility of home treatment after weekly subcutaneous applications of Zutectra in 23 liver

transplanted patients (HBsAg-cleared and DNA-negative liver transplant patients) for a duration of 18-24 weeks.

METHODS

Study Participants

The main inclusion criteria were as follows: male and female patients aged 18–75 years; ≥ 3 months after liver transplantation; HBsAg negative; regular long-term HBIg prophylaxis (combined re-infection prophylaxis) with stabilised HBIg dosage and administration intervals; stable liver function. In addition the patients included had to have a baseline serum HBs antibody concentration ≥ 300 IU/l – 500 IU/l from their intravenous treatment.

Treatments

Zutectra was given as a 500 IU (1 ml) dose for patients with bodyweight < 75 kg and a 1000 IU (2 ml) dose for patients with bodyweight ≥ 75 kg per week. This dosing was introduced after a Substantial Amendment following decline in trough levels in 2 of the first 7 patients of >30% over time which was larger than the anticipated 20% predicted from Study 956.

The study period comprised 18 weeks with a facultative extension for another 6 weeks (total study duration: 24 weeks). Patients were converted from standard intravenous to subcutaneous hepatitis B immunoglobulin according to their individual scheduled dosing interval, approximately 3 to 4 weeks after the last intravenous dosage. The planned treatment period was 18 weeks; therapy was to continue for a further 6 weeks (total duration 24 weeks) for patients who were compliant with the injection technique and had stable anti-HBs serum levels.

Objectives

The primary objective was to assess the efficacy of Zutectra in the prevention of HBV re-infection in liver transplant HBV DNA -negative patients by maintaining serum anti-HBs antibody trough levels of ≥ 100 IU/l.

The secondary objectives for efficacy encompassed the number of hepatitis B related infections and also included safety and tolerability, and feasibility of the subcutaneous home administration (percentage of self-administration, time to first self-administration, time to complete self-administration).

Outcomes/endpoints

The primary efficacy endpoint was the maintenance of serum trough levels of anti-HBs antibody ≥100 IU/l (level of effective prevention). Treatment failure was defined as C_{trough} of anti-HBs concentration < 100 IU/l at visit 18 or C_{trough} of HBs values < 100 IU/l leading to withdrawal prior to visit 18.

Secondary endpoints: Number of hepatitis B related infections (monitoring of clinical signs, liver function and measurement of HBsAg). Liver enzymes were measured regularly according to the schedule of assessment of safety laboratory parameters. Feasibility of the subcutaneous home administration was evaluated.

Sample size

Sample size calculation was based on a HBV re-infection rate of 20% for patients receiving no prophylactic treatment for HBV re-infection during an 18 week period. This estimate is a conservative one, because approximately 65% of transplanted patients with previous chronic HBV infection who do not receive HBIG are reinfected with HBV within 26 weeks of liver transplant. Patients requiring liver transplant because of HBV-related liver cirrhosis, who form the majority of patients in this setting,

have an even higher risk of re-infection. The upper 95% CI for a sample size of 20 patients with an assumed 20% proportion of re-infection is 37.5%, which was considered to be medically acceptable for the intended population. To allow a study population of 20 evaluable patients after adjusting for possible drop outs for non-medical reasons, 30 patients were planned for recruitment.

The study was small in size, but the estimation of sample size was considered acceptable in the light of very low expected recurrence rate in DNA-negative patients.

Randomisation / Blinding (masking)

The study was non-randomized and open label.

Statistical methods

C_{trough} measured concentration at the end of a dosing interval (taken directly before next administration) were used. The trough values were calculated for serum HBs antibody concentrations. Serum HBs antibody concentrations described as 'negative' were set to '0' for all calculations. The failure-rate after 18 weeks and the respective 95% confidence interval were calculated. A failure was defined by two possible outcomes as follows:

1) anti-HBs concentrations < 100 IU/l at last visit;
2) serum HBs antibody concentrations tending to decrease below a value of 100 IU/l during the weekly subcutaneous dosing schedule, resulting in premature withdrawal of the patient from the study by the investigator.

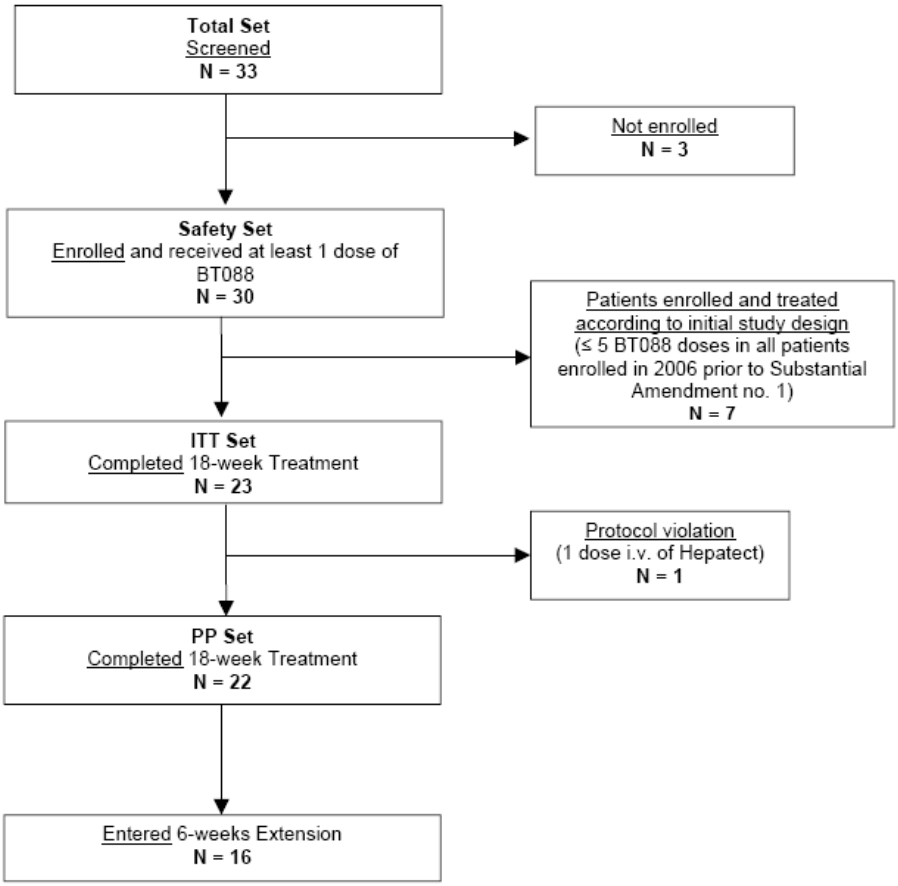
Time to failure was analysed using survival time methods. The failure rate over time was estimated using the Kaplan-Meier method, i.e. events were taken into account when they occurred. The failure rate at the end of the study and the according 95% CI were determined. The rate of patients with anti-HBs concentrations < 100 IU/l and the respective 95% CI were calculated. Patients whose serum HBs antibody concentration tended to decrease below a value of 100 IU/l during the weekly dosing schedule were prematurely withdrawn from the study by the investigator. The rate of patients prematurely withdrawn for reasons as defined above and the respective 95% confidence interval were calculated. The time to withdrawal was analysed using survival methods.

It was noted that the statistical analysis plan for this study was finalized at a time when the data of this open trial was known. In addition, there were several methodological flaws (definition of the ITT population, method for the calculation of confidence intervals, statistical model applied). However, it was considered that these issues do not *per se* impact on the actual clinical outcome.

RESULTS

Participant flow

Figure 2 Patient flow is study 958



Recruitment

Patients were recruited at two German centres. A centre in Italy, which was foreseen as study site, was closed following screening of three patients; this centre did not include any patient. The first patient was enrolled on 22 August 2006, the last patient completed treatment on 3 March 2008.

Conduct of the study

This study was initially planned as phase III comparative trial assessing the intramuscular versus the subcutaneous route. However, after enrolling 7 patients, the trial was suspended and amended to continue as a single arm, non-randomized, observational trial using only the subcutaneous route of administration. There were several reasons for amendments:

- The intramuscular arm was discarded due to localised pain and it was considered that this AE would impose a limitation to the quality of life in a population of patients for whom a lifetime of weekly administration was foreseen. Due to dispensing with the intramuscular arm the study was no longer a comparative trial but was converted into an observational non-randomized single-arm study
- The dose of 500 IU was thought to be low to maintain the required trough levels >100 IU/l (albeit trough levels showed only trend for reduction but were above >100 IU/l), so a change in dose regimen was required: for patients with ≥75 kg of weight 1000 IU/week dose was proposed.

Another amendment during the course of the study was related to a modified manufacturing process of the medicinal product. The production process of the second batch used in the study included an

additional nanofiltration step. The planned subgroup analysis to compare the two batches (nanofiltrated yes/no) was not performed for efficacy, due to small numbers.

Baseline data

23 Caucasian stable liver transplant patients aged 29 – 72, mean age was 50.8 years, were included, all of which were HIV and/or HCV negative. The median weight was 72 kg, ranging from 51 kg to 105 kg. The mean weight was 74.7 ± 15.3 kg.

The mean time from liver transplantation to the first administration of Zutectra in this study was 5.1 ± 3.1 years in patients of the ITT set. The median was 4.7 years ranging from 0.52 to 10.7 years. The reasons for liver transplantations were chronic Hepatitis B-cirrhosis, acute liver failure (ALF), co-infection with HCV, re-transplantation and others. Overall, 16.7% (5/30) of patients had ALF without evidence of previous HBV-related cirrhosis. Of these five patients, three were positive for HBV-DNA replication at the time of the initial diagnosis and all were receiving virostatic medication before the study, which continued during the study. Only 2/30 patients had ALF without cirrhosis and were HBV-DNA negative; these patients most likely have a better prognosis but given the size of this subgroup will not lead to a bias in the recurrence rate.

18 patients were taking concomitant antiviral drugs: 15 patients took lamivudine and 1 patient each took tenofovir, 'valaciclovir hydrochloride' or 'valganciclovir hydrochloride', respectively. All patients were on stable immunosuppressive therapy with no signs of concurrent rejection.

Numbers analysed

The study included 30 patients who had stable virological, immunological and biochemical characteristics of the liver disease (HBsAg-cleared and DNA-negative liver transplant patients). However according to the applicant, patients nos. 1, 2, 3, 4, 5, 6, and 7 who started the study in 2006 according to the initial study design (randomisation to subcutaneous or intramuscular administration) were not eligible due to missing data and, therefore, not included into the ITT set. Therefore the ITT set included 23 patients and 1 was excluded for PP analysis because of protocol violation (intravenous infusion of Hepatect CP was given).

Outcomes and estimation

All 23 patients achieved the primary endpoint of maintaining serum HBs antibody concentrations > 100 IU/l, which are required to offer effective protection against Hepatitis B virus re-infection of transplanted liver in non-replicators. 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 available data for at least 5 doses in the excluded 7 patients were also within the therapeutic range.

Overall, the population from Study 958 is considered to have a very low baseline risk of HBV recurrence since most of the patients were already well stabilised, with prior intravenous treatment with HBIG, and no signs of rejection or serological/molecular signs of infection (antigenaemia or DNA replication).

After the core and extension treatment periods with subcutaneous use in this study, patients were switched back to intravenous hepatitis B immunoglobulin. This was done safely, with no apparent adverse reactions related to the switch. Therefore, should the need arise patients can be switched back to intravenous administration. A further return to subcutaneous would require stable trough levels of 300-500 IU/l under prior intravenous administration, which is addressed in the SPC.

With regard to the secondary endpoint no hepatitis B related infection, as measured by HBsAg, occurred, however one must keep in mind that this is a comparatively short trial in 23 patients. Time to recurrence is often greater than six months. In a recent review of the literature in orthotopic liver transplant patients who were between 5 -100% HBV DNA positive at liver transplant and had a

follow-up of 18-88 months, HBV recurrence rates ranged between 2-22%. Although the 0% seen in Zutectra 6 month trial is most likely to be an underestimation the data provided lie within the range of what is attainable with the current medical regimens in liver transplant patients.

The high number of Zutectra self-administrations (287 versus 122 by study site staff) by patients demonstrates the general feasibility of self-administration. The number of patients with self-administration increased steadily during the study and showed good tolerability. The applicant will however be performing a further clinical study as a post-authorisation commitment to address the issue of compliance during home therapy in more detail.

Ancillary analyses

Ancillary analyses were not performed.

- Analysis performed across trials (pooled analyses and meta-analysis)

Analyses across trials were not performed.

- Clinical studies in special populations

Studies in special populations were not performed.

The low number of hepatic failure secondary to HBV and the accompanying number of liver transplants in children does not allow systematic collection of representative clinical data to assess the hepatitis B immunoglobulin prophylaxis in this population. However, the applicant is conducting a study in infants born to HBsAg positive mothers for the perinatal prophylaxis.

Elderly patients were included in Study 958, albeit the numbers were small: 4 patients were aged 60 – 72 years.

- Supportive study(ies)

In the pharmacokinetic study 956 the duration of serum HBs antibody concentrations above 0.1 IU/ml (level of effective prevention) as well as the time required to reach the target concentration were calculated as surrogate parameter for efficacy in 30 healthy volunteers. The mean ± SD time after administration, when serum concentrations above 0.1 IU/ml were achieved (onset of efficacy) was 20.4 ± 7.5 hours in the subcutaneous group and 19.9 ± 8.2 hours in the intramuscular group. The mean ± SD time with serum anti-HBs concentrations above 0.1 IU/ml (duration of effective prevention) was 42.0 ± 8.3 days (subcutaneous) and 43.0 ± 9.0 days (intramuscular), respectively.

This efficacy data is considered as additionally supportive to the results from study 958. Adequate anti-HBs antibody levels were reached with titres above 100 IU/l at ~ 1 day after application and lasted until 42 days thereafter.

Clinical safety

- Patient exposure

The safety database consists of 2 studies (956 and 958) performed with Zutectra encompassing 60 subjects (30 healthy volunteers and 30 liver transplant patients).

- Adverse events

Study 956

In this study each of the 30 volunteers received 30 IU/kg bodyweight of Zutectra (approximately 500 IU/ml) via subcutaneous or intramuscular administration. The total injection volume as calculated according to the individual body weight was 2.5 – 4.7 ml (total dose 1560 to 3000 IU).

A total of 57 adverse events (28/subcutaneous, 29/intramuscular) were reported in 24/30 (80%) healthy volunteers (13/ subcutaneous, 11/intramuscular) including 3 events which started before application of study medication. The investigator assessed 43/57 (75%) events (23/subcutaneous, 20/intramuscular) as not related to the study medication, 3 events as unlikely related (swelling and pain at the wrist (intramuscular) and pain at the thigh (intramuscular about 3 weeks after Zutectra application) and 2 events as possibly related (extraordinary tiredness/subcutaneous, nausea/intramuscular on the day of Zutectra application). For 9 adverse events (4/subcutaneous, 5/intramuscular) the relationship to study medication was assessed as certain according to the investigator. This concerned mild local reactions at the injection site in 4 subjects of the subcutaneous group and in 4 subjects of the intramuscular group starting on the day of Zutectra administration or on the day after the injections. In the subcutaneous group small hematoma and urticariae were observed, in the intramuscular group pain was reported as the main symptom. The latter concern contributed to the decision to remove intramuscular administration from the Study 958 protocol. All events resolved on the same day or within 1-4 days without any treatment. Two adverse events starting on the day of Zutectra application were assessed as possible related. This concerned transient extraordinary tiredness (subcutaneous) and a 6 day nausea (intramuscular). Both events were mild and resolved without any treatment.

Study 958
In Study 958, Zutectra (500 IU (1 ml) or 1000 IU (2 applications of 1 ml)) was injected subcutaneously weekly up to 24 weeks. The mean ± SD treatment duration was 124 ± 59.1 days; and the mean ± SD number of syringes used was 23.1 ± 13.7 (safety population).

10 patients received medication only from the first (not nanofiltrated) batch, 7 patients only from the second (nanofiltrated) batch and 13 patients from both batches.

A total of 139 adverse events occurred, 135 thereof were treatment-emergent adverse events (TEAEs) (4 were present at baseline) and were reported in 24/30 (80.0%) patients (5 in 2006, 19 in 2007). The investigator assessed 24 events as not related to the study medication, 101 events as unlikely to be related. Seven adverse events were possibly related and 1 probably related; these encompassed headache (3 patients), fatigue (1 patient), upper abdominal pain (1 patient), haematuria (1 patient), and injection site reaction (2 patients.). No clear conclusions could be drawn from the different batches administered as the numbers affected were too small. At the end of the study 117 events were resolved, 2 were in the process of resolving, 11 not resolved and 5 unknown

In general, in this 6 month study the rate of adverse events was low. All reported adverse events were either of mild or moderate severity.

- Serious adverse event/deaths/other significant events

In study 956 no serious adverse event related to Zutectra was reported.

In study 958 a total of 19 serious adverse event symptoms were reported in 9/30 (30%) patients, 16 of which were treatment-emergent. 10 treatment-emergent serious adverse event symptoms were assessed as unlikely related, 6 as not related, none were considered possibly, probably or certainly related. The SAEs mainly encompassed cholangitis and biliary draining procedures. At the end of the study 15 events were resolved, 1 was in the process of resolving.

In both studies there were no deaths. No allergic, anaphylactic or other immunologically relevant reactions were reported.

- Laboratory findings

In both studies (956 and 958) routine laboratory assessments (electrolytes, haematology, renal and hepatic function) and additionally IgG1, IgG2, IgG3, IgG4, IgA, IgM and Complement C3 and C4 were examined. No clinically relevant changes were observed during the studies for any subject.

- Safety in special populations

Studies in special populations have not been performed.

- Safety related to drug-drug interactions and other interactions

No formal interaction studies were performed. Most orthotopic liver transplant patients in study 958 were on concomitant virostatic medication. Other potential interactions e.g. with vaccines are described in the SPC.

- Discontinuation due to adverse events

In studies 956 and 958 there were no discontinuations due to adverse events. It is however noted that the applicant terminated the intramuscular arm of study 958 prematurely due to the apprehension that the intramuscular administration of 2 ml Zutectra into the deltoid muscle could impair the patient's well-being and consecutively the compliance.

- Post marketing experience

In addition to the safety data from clinical trials with Zutectra or the intravenous human hepatitis B immunoglobulin formulation Hepatect CP, post-marketing experience is available for the use of Hepatect CP in 28,932 patients.

The PSURs prepared for Hepatect CP so far (covering the period from April 2000 to October 2008) did not indicate findings changing the safety profile of the product. There was no new information on a change in characteristics of listed reactions with regard to severity, outcome or target population, on serious unlisted reactions, on non-serious unlisted reactions, or on an increased reporting frequency of listed reactions. No reports of drug interactions, overdose, and drug misuse were presented. The reported cases did not reveal any new safety issue on pregnancy/lactation, special patient groups, and long-term treatment. In general the reported recurrence of HBV in the post-marketing period is very low.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

Table 4 Summary of the risk management plan

<table>
<tr><th>Safety issue</th><th>Proposed pharmacovigilance activities</th><th>Proposed risk minimisation activities</th></tr>
<tr><td>Important identified risks

1. Injection site reactions
2. Unspecific hypersensitivity reactions
3. Allergic reactions</td><td>Routine pharmacovigilance activities:

Ongoing evaluation of these risks and all changes in severity, frequency or nature. Further included: signal detection process, policies for case evaluation, crisis management and annual PSUR compilation.

Additional pharmacovigilance activities:
1) Conduct of study 974.
2) Conduct of post authorisation safety study 978
3) Use of a treatment diary throughout post marketing use of BT088/Zutectra.</td><td>Routine risk minimisation:

Risks are regarded adequately identified, characterised and described in the SPC, section 4. (Especially undesirable effects, section 4.8).

1) Injection site reactions
SPC section 4.8 Undesirable effects
<table>
<tr><td>MedDRA SOC</td><td>Undesirable effects</td><td>Frequency</td></tr>
<tr><td>General disorders and administration site conditions</td><td>Pain, urticaria, haematoma</td><td>Common</td></tr>
</table>
2) Unspecific hypersensitivity reactions

SPC section 4.8 Undesirable effects
<table>
<tr><td>MedDRA SOC</td><td>Undesirable effects</td><td>Frequency</td></tr>
<tr><td>Nervous system disorders</td><td>Headache</td><td>Uncommon</td></tr>
<tr><td>Gastrointestinal disorders</td><td>Upper abdominal pain</td><td>Uncommon</td></tr>
</table>
3) Allergic reactions
SPC section 4.8 Undesirable effects
"Other:
Additionally (...), in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration."</td></tr>
<tr><td>Important potential risks

1. Transmission of infective agents

2. Lack of adequate monitoring of anti-HBs levels</td><td>Routine pharmacovigilance activities:

Ongoing evaluation of these risks and all changes in severity, frequency or nature. Further included: signal detection process, policies for case evaluation, crisis management and annual PSUR compilation. At Biotest, reports of</td><td>Routine risk minimisation:

Risks are regarded adequately identified, characterised and described in the SPC.

1) Transmission of infective agents
SPC section 4.4 Special warnings and precautions for use
"Standard measures to prevent infections resulting from the use of medicinal products</td></tr>
</table>

	interference with serological testing and suspected transmission of infective agents and other quality related effects are under control by the following measures added to routine pharmacovigilance: - Quality complaints are documented by the corporate drug safety department. - Policies are established describing a specific signal detection procedure involving batch record review and look back **Additional pharmacovigilance activities:** 1) Conduct of study 974. 2) Conduct of post authorisation safety study 978 3) Use of a treatment diary throughout post marketing use of BT088/Zutectra.	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." **2) Lack of adequate monitoring of anti-HBs levels** **SPC section 4.2 Posology and Method of Administration** **Posology:** "(...) Prior to the initiation of subcutaneous treatment with Zutectra, anti-HBs serum levels should be stabilised with an adequate intravenous hepatitis B immunoglobulin to levels at or above 300-500 IU/l. (...)" "Patients must be monitored for serum anti-HBs antibody levels regularly. (....)." **Method of Administration:** "Zutectra should be administered via the subcutaneous route." "Zutectra is accompanied by a package leaflet with detailed instruction for use to be followed. 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. 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."
Important identified interactions 1. Interference with live attenuated virus vaccines 2. Interference with serological testing	**Routine pharmacovigilance activities:** Ongoing evaluation of these risks and all changes in severity, frequency or nature. Further included: signal detection process, policies for case evaluation, crisis management and annual PSUR compilation. At Biotest, reports of interference with serological testing and suspected transmission of infective agents are under control by the following measures added to routine pharmacovigilance: - Quality complaints are documented by the corporate drug safety department. - Policies are established describing a specific signal detection procedure involving batch record review and look back	**Routine risk minimisation:** Risks are regarded adequately identified, characterised and described in the SPC. **1) Interference with live attenuated virus vaccines** **SPC section 4.5 Interaction with other medicinal products and other forms of interaction** "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." **2) Interference with serological testing** **SPC section 4.5 Interaction with other medicinal products and other forms of interaction** "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)."
Important missing information Use in relation to 1. Pregnancy and breast feeding 2. Prevention of hepatitis B in neonates of HBV positive mothers 3. Efficacy in HBV-DNA positive patients after liver transplant. 4. Post exposure* prophylaxis against hepatitis B in adults and children	**Routine pharmacovigilance activities:** Ongoing evaluation of these risks and all changes in severity, frequency or nature. Further included: signal detection process, policies for case evaluation, crisis management and annual PSUR compilation.	**Routine risk minimisation:** Risks are regarded adequately identified, characterised and described in the SPC. **1) Use in relation to Pregnancy and breast feeding** **SPC section 4.6Pregnancy and lactation** "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." **2) Use in relation to prevention of hepatitis B in neonates of HBV positive mothers** **SPC section 4.2: Posology and method of administration** "(...) In HBV-DNA negative **adults** ≥ 6 months after liver transplantation (...)." **3) Use in relation to efficacy in HBV-DNA positive patients after liver transplantation** **SPC section 4.4Special warnings and precautions for use** "(...)If the recipient is a carrier of HBsAg, there is no benefit in administering this medicinal product. (...)." **4) Post exposure* prophylaxis against hepatitis B in adults and children** **SPC section 4.4 Special warnings and precautions for use** "(...) There is no data about efficacy in post-exposure* prophylaxis."

*****In the current RMP version 3.0 the word "exposition" is used. This will be amended with the next revision of the RMP.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

Zutectra is a purified human hepatitis B immunoglobulin preparation which complies with the Ph. Eur. monograph no. 0722 on human hepatitis B immunoglobulin and is obtained from plasma from selected and/or immunised donors having antibodies against hepatitis B surface (HBs) antigen. It contains the same active substance as Hepatect CP (licensed in Germany since 2000) with an adapted formulation for the subcutaneous route.

Non-clinical pharmacology and toxicology

A limited nonclinical programme has been performed, which is acceptable for this type of product, i.e. a plasma derived human hepatitis B immunoglobulin preparation. The principles of the Note for Guidance on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (CPMP/ICH/302/95, ICH S 6) have been adequately considered. In addition, reference was made to nonclinical data from another immunoglobulin preparation, Intratect.

Pharmacology aspects were covered with quality data. The safety pharmacology data generated with Intratect are considered indicative for Zutectra; no effect was observed on the cardiovascular and the respiratory system. In terms of toxicology studies the local tolerance of Zutectra was investigated, which showed that the product is well tolerated when administered subcutaneously. The single dose toxicity study was performed with Intratect; no specific findings requiring further investigation.

Overall, the nonclinical programme is considered adequate.

Efficacy

The proposed indication in prevention of HBV re-infection in patients ≥6 months following liver transplantation was accompanied by the data from two trials: an open parallel group single-dose in Study 956 (study comparing PK parameters between intramuscular and subcutaneous administration in 30 healthy volunteers) and an open non-randomized single arm prospective in Study 958 (study monitoring trough levels of anti-HBs in 30 stable HBsAg-negative, HBV DNA-negative liver transplant patients).

Study 956 demonstrated the typical pattern of pharmacokinetics for immunoglobulin products with maximum plasma level reached within 2.0-7.0 days after either subcutaneous or intramuscular injection. The anti-HBs Ig is slowly cleared with an elimination half-life of around 3 to 4 weeks. The mean ± SD time with serum anti-HBs concentrations above 0.1 IU/ml (duration of effective prevention) was 42.0 ± 8.3 days (subcutaneous) and 43.0 ± 9.0 days (intramuscular), respectively. C_{max} seems to be somewhat lower by subcutaneous route of administration compared with intramuscular (median values of 0.35 IU/ml and 0.40 IU/ml, respectively). This is expected with subcutaneous route, which is accompanied by slower tissue resorption and higher tissue diffusion/local elimination. The limitations of the pharmacokinetic study include the fact that the study was conducted with hepatitis B immunoglobulin produced using the process prior to introducing a 20 nm filtration step. In addition the posology 30 IU/kg utilized in the study has not been taken into phase III efficacy trial, where it was reduced to 6.67-13.3 IU/kg. Extrapolation of pharmacokinetic parameters to lower doses is limited in terms of predicting half-life and Cmax changes and certainly inadequate in extrapolating time to reach optimal trough levels >100 IU/l. However the overall conclusion from the study was that the hepatitis B immunoglobulin pharmacokinetic parameters derived from Study 956 confirm the integrity of the hepatitis B immunoglobulin molecules. The nanofiltration step introduced into the manufacturing at a later stage did not change the immunoglobulin properties from the quality point of view. In addition, since both materials were included in the subsequent study 958 with consistent trough anti-HBs levels and satisfactory safety results, the pharmacokinetic characterisation of the product is considered to be sufficient for the licensure.

Study 958 in 30 liver transplant patients was initially planned as a randomized comparative trial assessing trough levels of patients administered with HBIG either via intramuscular or subcutaneous routes. However the study protocol was amended to terminate the intramuscular route due to potential issues with compliance and long-term impact on the quality of life. The study was converted into the non-randomized study and included a new hepatitis B immunoglobulin batch manufactured using the newly introduced nanofiltration step. All patients enrolled in Study 958 had well established immunological, virological and biochemical control of the graft (no HBsAg, DNA-negative, no signs of rejection, concomitant antiviral medications). The range of time elapsed since the liver transplantation varied between 0.52 to 10.7 years. Thus, Study 958 would support a prevention starting no sooner than ≥6 month after liver transplant in accordance with characteristics of the enrolled population.

Although HBV-related acute live failure represented a significant proportion of patients in study 958, at least 43.3% of patients at the stage of diagnosis were HBV-DNA positive. Only 2/30 patients had acute liver failure without cirrhosis and were HBV-DNA negative; these patients most likely have a better prognosis but given the size of this subgroup will not lead to a bias in the recurrence rate. Since trough levels of anti-HBs antibodies were successfully maintained in all patients enrolled in study 958, there is no reason to believe that findings from this study cannot be extrapolated to both patients with acute and chronic liver failure.

The required baseline concentration of serum HBs antibody concentration ≥ 300 IU/l – 500 IU/l in this study was higher than the "maintenance concentration" of >100 IU/l to ensure that serum anti-HBs levels remained in the safety margin during the transition from intravenous to subcutaneous administration. As there was a delay in reaching peak concentrations with subcutaneous administration (T_{max} of 4 days) and the subcutaneous dosing was divided into 4 weekly doses/month, the serum baseline concentration had to supplement a period of 1-2 weeks. The carry-over from the last intravenous administration is estimated to have lasted during the first 3-5 weeks of subcutaneous dosing. This baseline concentration is recommended in the SPC prior to starting on subcutaneous administration.

The survival analysis showed that all 30 patients in the study had the trough serum anti-HBs antibody concentration above 100 IU/l at each time point. (7 of the 30 patients were excluded from the study since data were missing.) The failure rate was 0% after 18 and 24 weeks (95% CI: [0, 14.8%] and [0, 20.6%] respectively). A HBV re-infection could not be detected for any patient. The study also indicated that all patients were able to learn self-administration and gradually were able to inject Zutectra on weekly basis at home themselves with good degree of compliance.

After treatment with subcutaneous Zutectra, patients were switched back to intravenous hepatitis B immunoglobulin without any untoward reactions indicating that this can be done safely if the need arises.

Study 958 had a number of methodical issues concerning the change from a controlled two arm study to an open one-arm study, additionally it was a small (n=30) trial in low risk liver transplant patients (HBV DNA-negative patients, long periods since liver transplantation, good immunological control of the graft survival) conducted over a fairly short period (24 weeks) so that the overall probability to identify a recurrence was very low, thereby enhancing the success rate of the study. However, not only has the population now been adequately addressed in the SPC, but the product has to be seen in the light of its own historical development and the development of hepatitis B immunoglobulins in general in the liver transplant setting.

Safety

Zutectra appears as a reasonably safe product in respect of local and systemic adverse events and immunological events. There were no product related deaths, serious adverse events and immunologically related events such as allergies and anaphylactic reactions. There were no other adverse events previously reported with other immunoglobulin products such as haemolytic anaemia, renal complications, aseptic meningitis and complement abnormalities.

Theoretically, the safety of product with subcutaneous administration is expected to be better than one of the same product for intravenous use. Lesser systemic exposure and lower propensity to induce a hypersensitivity response of immediate type or complement-mediated adverse events during the subcutaneous administration of Zutectra is anticipated to translate into the safety benefit.

The safety profile of Zutectra for subcutaneous maintenance therapy in stable liver transplant patients is considered acceptable. No untoward risks were identified.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

- User consultation

A user consultation on the package leaflet has been performed. The main objectives of the readability testing have been achieved by this readability test, well-finding, understanding and adequate using by the participants. The key messages for safe use of Zutectra have been identified and the questions reflect the key messages. Adaptations of the package leaflet have been made after the first round of user testing. Both rounds of user testing showed that, for each question, at least 90% of the volunteers were able to find the information as requested, and at least 90 % of the participants were able to answer the questions correctly. Therefore, the results of the user testing showed that the readability testing is acceptable.

Risk-benefit assessment

The risk/benefit can be considered favourable based on the clinical data generated for Zutectra. The efficacy of Zutectra in prevention of Hepatitis B recurrence in HBV-DNA negative patients ≥ 6 months after liver transplant by maintaining anti-HBs serum levels in line with those required by the core SPC for hepatitis B immunoglobulin preparations (> 100 IU/l) was demonstrated. In addition, the available data and experience with the intravenous preparation Hepatect can be regarded as supportive.

From the clinician/hepatologist's and patient's point of view, the weekly self-administration of the product is both convenient and less burdensome for public health services in terms of minimal involvement of medical personnel and requirements for home visits. The treatment is feasible provided appropriate training is given, initial supervision is in place and monitoring anti HBsAg levels is carried out regularly. The compliance and convenience for patients are mutually dependent, bearing in mind that the treatment is potentially indefinite.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the risk-benefit balance of Zutectra in the:

Prevention of hepatitis B virus (HBV) re-infection in HBV-DNA negative patients ≥ 6 months after liver transplantation for hepatitis B induced liver failure.

Zutectra is indicated in adults only.

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

was favourable and therefore recommended the granting of the marketing authorisation.