HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

16 November 2011

ZUTECTRA 500 IU, solution for injection in prefilled syringe
B/5 1 ml prefilled glass syringes (CIP code: 578 757 1)

Applicant: AELSLIFE SAS

Human hepatitis B immunoglobulin

ATC code: J06BB04

List I

For hospital prescription

Date of Marketing Authorisation: 30 November 2009 (centralised procedure)

Reason for request: Inclusion on the list of medicines approved for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Human hepatitis B immunoglobulin
Medicinal product derived from blood.

1.2. Indication

“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.”

1.3. Dosage

“In HBV-DNA negative adults ≥ 6 months after liver transplantation:
- patients with bodyweight < 75 kg: 500 IU (1 ml)/week
- patients with bodyweight ≥ 75 kg: 1000 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. The first ZUTECTRA dose should be administered approximately 14-21 days after the last intravenous dose at stabilised anti-HBs serum levels in order to ensure adequate anti-HBs coverage during the transition from intravenous to subcutaneous dosing. The dose of ZUTECTRA can be adapted up to 1,000 IU/week to maintain an anti-HBs serum level of > 100 IU/l in HBsAg-negative and HBV-DNA negative patients.
Patients must be monitored for serum anti-HBs antibody levels regularly.
There is no relevant indication for use of ZUTECTRA in children.

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.”

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

J : Antiinfectives for systemic use
J06 : Immune sera and immunoglobulins
J06B : immunoglobulins
J06BB : specific immunoglobulins
J06BB04 : hepatitis B immunoglobulins

2.2. Medicines in the same therapeutic category

2.2.1 Strictly comparator medicines
Not applicable

2.2.2 Not-strictly-comparator medicines
- IVHEBEX 5000 IU/100 ml, powder and solvent for solution for infusion:
human hepatitis B immunoglobulin indicated for “prevention of the recurrence of hepatitis B after hepatic transplantation in patients with hepatitis B surface antigen” and administered intravenously. (IAB I, 7 November 2001). For this proprietary medicinal product, treatment is initiated on the day of the procedure, perioperatively.
- two human hepatitis B immunoglobulin products administered by intramuscular injection are currently the subject of a cohort temporary usage authorisation (TUA), but they are not indicated for the prevention of reinfection after hepatic transplantation.

2.3. Medicines with a similar therapeutic aim

Antiviral agents active against the hepatitis B virus.

3. ANALYSIS OF AVAILABLE DATA

The company submitted five clinical studies: an efficacy study (study 958) and a pharmacokinetic study with a single dose of ZUTECTRA administered subcutaneously (study 956) which was taken into account only for the analysis of tolerance. The three other studies are pharmacokinetic studies concerning immunoglobulin preparations other than ZUTECTRA and administered intravenously; they were therefore not taken into account.

3.1. Efficacy

3.1.1 Study 958

Objective

To assess the efficacy of human hepatitis B immunoglobulin given by subcutaneous injection for the prevention of graft infection in patients who received a liver transplant after hepatitis B.

Method

Prospective, noncomparative study.

Inclusion criteria:

- Adult patients (18 to 75 years of age),
- Having received a liver transplant at least three months ago,
- HBsAg negative,
- Having received long-term prophylactic treatment with stable doses and intervals between injections of intravenous hepatitis B immunoglobulin,
- A stable liver profile,
- Baseline concentration of anti-HBs antibodies of ≥ 300 IU/l – 500 IU/l after the last intravenous administration of hepatitis B immunoglobulin and before initiation of subcutaneous treatment with immunoglobulin.

Exclusion criterion:

- HBV-DNA positive patients

Treatment:
Human anti-HBs immunoglobulin administered subcutaneously once a week at a dose of 500 IU (1 ml) for patients of < 75 kg and of 1000 IU (2 ml) for patients of > 75 kg.
The dose administered could be increased to 1000 IU/week if the serum concentration of anti-HBs antibodies was < 200 IU/l after the third dose.
The dose administered could be reduced or suspended if the serum concentration of HBs antibodies was > 500 IU/l.
One or more additional doses could be administered if the HBs antibody concentration was ≤ 120 IU/l, so as to maintain the minimum concentration of 100 IU/l which is recommended for the prophylaxis of infection of the transplanted liver.
Patients whose serum concentrations dropped below 100 IU/l even after adjustment of the dose to 1000 IU/week had to end their participation in the study.
The subcutaneous treatment was instigated 3 to 4 weeks after the last intravenous injection, according to the result of antibody determinations.
The treatment period was 18 to 24 weeks (optional extension of 6 weeks with self-administration at home for patients able to master the injection technique).

Endpoints:

- Primary efficacy endpoint
  Treatment failure rate assessed on the basis of the concentrations of anti-HBs antibodies before the first injection on D1 and before each of the following injections on D8, 15, 22, 29, 43, 57, 71, 85, 99, 113, 127 and for the optional extension on D148 and 169. The posologies were centralised.
  Treatment failure was defined as:
  1. either an anti-HBs antibody concentration of < 100 IU/l at the last visit
  2. or anti-HBs antibody concentrations dropping below 100 IU/l during the study and leading the patient to drop out of the study.
- Secondary endpoint
  Number of cases of hepatitis B diagnosed on the basis of clinical signs, the liver profile and the HBsAg test carried out at the start of the study, on D1, 29, 57, 85, 127 and on D169 in those participating in the optional extension.
- Feasibility: after training the patients, percentage of self-administration
- Time to the first self-administration.

Results
A total of 30 patients were included. Of those, seven were included before an amendment deleting the intramuscular administration of ZUTECTRA and allowing an adjustment of the daily dose as a function of weight and the serum concentration of anti-HBs antibodies. These patients received only five or fewer doses of ZUTECTRA and were not included in the efficacy analysis.

Twenty-three patients completed the period of 18 weeks of treatment and 16 completed the period of 24 weeks. They were 29 to 72 years of age, and their median age was 51 years.
The median time between the transplant and the first subcutaneous administration of immunoglobulins was 4.7 years (0.52 to 10.7 years).
The mean time between the last intravenous administration and the first subcutaneous administration was 20.3 ± 22.2 days.
An antiviral agent was being or had been taken by 18 patients/23: lamivudine (n = 15), tenofovir (n = 1), valaciclovir (n = 1) and valganciclovir (n = 1).

There were no failures at 18 and 24 weeks.

There was no reinfection with hepatitis B virus.

Feasibility of injections:
In the first 18 weeks of the study, 287 administrations were made by the patients themselves and 122 by the study personnel. One patient carried out self-administration for the first injection of the study and 22 patients for the last.

3.2. Adverse effects

3.2.1 Study 956
In this randomised open pharmacokinetic study in two parallel groups, 30 healthy volunteers aged 18 to 55 years received a single injection of 30 IU/kg of ZUTECTRA (1560 to 3000 IU), intramuscularly for one group and subcutaneously for the other.
Two adverse events were regarded as having a possible connection with the treatment: major fatigue (SC route) and nausea (IM route) and nine mild local reactions at the injection site were regarded as having a definite connection with the treatment: one urticaria and three haematomas for the SC route, one haematoma and four cases of pain for the IM route.

3.2.2 Study 958
A total of 24 patients/30 had an adverse event. Seven adverse events were regarded as having a possible connection with the treatment: headaches (n = 3), abdominal pain (n = 1), fatigue (n = 1), haematuria (n = 1), haematoma at the injection site (n = 1); one adverse event was regarded as having a probable connection with the treatment: haematoma at the injection site; two adverse events were regarded as having a definite connection with the treatment: haematomas at the injection site. They were all mild or moderate.
No serious adverse event was thought to be linked to the treatment.

It is mentioned in the SPC for ZUTECTRA that, because of the risk of anaphylactic reaction inherent in the injection of human hepatitis B immunoglobulin, patients must be kept under observation for 20 minutes after administration.

3.3. Conclusion

A total of 23 patients were treated with ZUTECTRA for 18 weeks for the prevention of reinfection with hepatitis B virus after a liver transplant; 16 of them continued the treatment for an additional 16 weeks, i.e. 24 weeks in all.
No patient had a treatment failure (concentration of anti-HBs antibodies < 100 IU/l at the last visit or anti-HBs antibody concentrations < 100 IU/l during the study and leading to withdrawal from the study) or reinfection with hepatitis B virus.

However, as stated in the EPAR for ZUTECTRA, the time to recurrence is often greater than the duration of the efficacy study, i.e. six months. Despite this, it was considered that the results observed were of the order of those obtained with the medical treatments available to patients who had received a liver transplant.

Although the high number of self-administrations shows their probable feasibility, the EMA asked the company to carry out a post-MA study so as to better assess compliance with treatment in the event of self-administration at home.

The most common adverse events during the two studies were mild local reactions. There were no serious adverse events regarded as linked to the treatment.
It is however mentioned in the SPC for ZUTECTRA that, because of the risk of anaphylactic reaction inherent in the injection of human hepatitis B immunoglobulin, patients must be kept under observation for 20 minutes after administration.

ZUTECTRA is a medicine derived from blood for which there is an obligation of traceability. It is stated in the SPC for ZUTECTRA that “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. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The recurrence of hepatitis B after liver transplantation may be life-threatening.

This proprietary medicinal product is intended to provide prophylactic treatment.

The efficacy/adverse effect ratio is high.

> Public health benefit
> The public health burden of hepatitis B in France is low (< 3000 DALYs lost per year according to WHO estimates). The burden constituted by the indication for ZUTECTRA (prevention of reinfection with HBV after liver transplantation) is at best low.
> The fight against infection with the hepatitis B and C virus is a public health priority and improving the quality of care and the quality of life of persons with chronic hepatitis B (or C) is one of the main aims of the National Plan for Combatting Hepatitis B and C (2009-2012).
> Given the existence of an injectable treatment alternative and in view of the available non-comparative and short-term clinical data, ZUTECTRA is not expected to have any impact on morbidity/mortality. A potential impact of ZUTECTRA is expected, because of its route of administration, on the quality of life of the patients treated and on the organisation of care (self-administration possible at home and reduction in the number of hospital admissions). However, in the absence of data, that impact cannot be quantified.
> ZUTECTRA does not meet the stated public health need.
> Consequently, there is not expected to be any public health interest in ZUTECTRA in the prevention of reinfection with HBV after liver transplantation.

This proprietary medicinal product is a first-line therapy. Because of the characteristics of the patients included in the efficacy study, ZUTECTRA cannot be administered until at least six months after the transplant, whereas IVheBex can be administered perioperatively on the day of the procedure.

There is a treatment alternative (IVheBex*).*

The actual benefit of this proprietary medicinal product is substantial.

4.2. Improvement in actual benefit (IAB)

Although the available efficacy and tolerance data are limited in quantity, the Transparency Committee took into account the changes in the organisation of healthcare which the proprietary medicinal product ZUTECTRA could produce.
Consequently, ZUTECTRA provides a minor improvement in actual benefit (IAB IV) in the management of the prevention of reinfection with the hepatitis B virus (HBV) in patients negative for HBV DNA ≥ six months after liver transplantation because of the liver failure induced by hepatitis B.

4.3. Therapeutic use

4.3.1 Therapeutic strategy

The prevention of the recurrence of post-transplant viral hepatitis B is based on a combination of human hepatitis B immunoglobulin and antivirals; the antivirals allow the doses of immunoglobulin to be reduced. Immunoprophylaxis with human hepatitis B immunoglobulin is initiated immediately.[1]

4.3.2 Therapeutic use of the proprietary medicinal product

ZUTECTRA is a human hepatitis B immunoglobulin which is administered subcutaneously. Unlike the other available human hepatitis B immunoglobulin, IVheBex 5000 IU/10 ml administered intravenously, subcutaneous ZUTECTRA, which can be self-administered, cannot be used until at least six months after transplantation (the efficacy of ZUTECTRA has not been studied in patients who underwent transplantation less than 6 months ago).

4.4. Target population

In France, according to data from the Biomedicine Agency, 20 to 40 liver transplants (2-4%) were carried out on account of viral cirrhosis B each year between 2005 and 2010.[2] Some of the transplants carried out on account of fulminant hepatitis and hepatocellular carcinoma are also linked to infection with virus B. In all about 100 transplants a year are said to result from infection with virus B (expert opinion).
The number of patients receiving transplants in France on account of infection with virus B is estimated to be 1000-1500 patients (expert opinion).
Consequently, the target population for ZUTECTRA is estimated to be about 1000 to 1500 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use in the indication and at the dosage in the Marketing Authorisation.

4.5.1 Packaging: Appropriate for the prescription conditions

4.5.2 Additional information requested from the company

The transparency Committee would like to have additional data, medium- and long-term, with a view to re-evaluating ZUTECTRA, on all patients newly treated with ZUTECTRA and on the following points:
- the characteristics of the patients treated,
- the methods of using ZUTECTRA, in particular the place of administration, the dosage and frequency of use, the treatments combined with it (particularly antiviral treatments), earlier treatments with immunoglobulins, the maintenance of medium- and long-term treatment,
- the efficacy of ZUTECTRA in preventing hepatitis B according to laboratory criteria,
- the adverse effects experienced by patients treated with ZUTECTRA, and particularly allergic phenomena, with the frequency of discontinuation of treatment and the reasons for it.

The duration of patient follow-up must be justified and sufficient to answer the questions raised by the transparency Committee.
Data must be available at the time ZUTECTRA is re-evaluated.
If scheduled or ongoing studies, in particular within the remit of the European Risk Management plan, do not answer all the questions raised by the transparency Committee, a specific study must be conducted.

1 Samuel D. Transplantation hépatique pour hépatite Chronique B [Liver transplantation on account of chronic hepatitis B]. Gastroentérologie clinique et biologique. 2008; 32: S25-S33
2 Rapport 2010 sur la greffe hépatique de l'agence de biomédicine [2010 report on liver transplantation by the Biomedicine Agency]. http://www.agence-biomedecine.fr/annexes/bilan2010/donnees/organes/05-foie/synthese.htm

ANNEX

Justification for the request for additional data

For the proprietary medicinal product ZUTECTRA, human hepatitis B immunoglobulin, indicated in the “prevention of hepatitis B virus (HBV) re-infection in HBV-DNA negative patients ≥ six months after liver transplantation for hepatitis B induced liver failure”, additional data were requested by the Transparency Committee during the meeting on 02/11/2011.

This request for additional information is justified by the lack of medium- to long-term data in the dossier submitted to the Transparency Committee on the following three main points:
- the methods of use of ZUTECTRA (place of administration, combined treatments, administered dosage, frequency of use, compliance);
- tolerance, in the medium and long term (in particular allergic phenomena);
- the maintenance of efficacy after six months.