HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

7 November 2012

HUMAN HEPATITIS B IMMUNOGLOBULIN LFB 100 IU/ml, injectable solution in pre-filled syringe (IM)

injectable solution in pre-filled 1 ml syringe – B/1 (CIP code: 34009 581 576 4 6)
injectable solution in pre-filled 5 ml syringe – B/1 (CIP code: 34009 581 577 0 7)

Applicant: LFB-BIOMÉDICAMENTS

INN	Human hepatitis B immunoglobulin
ATC code (2012)	J06BB04 (hepatitis B immunoglobulins)
Reason for the review	**Inclusion**
List concerned	**For hospital use (French Public Health Code L.5123-2)**
Indications concerned	**"Hepatitis B immunoprophylaxis** **- in accidental exposure in non-immunised people (including when vaccination is incomplete or unknown)** **- in haemodialysis patients pending vaccination being effective** **- in newborn babies of mothers carrying the hepatitis B virus** **- in patients who have not developed an immune response after vaccination against the hepatitis B virus (undetectable antibodies against hepatitis B) and who require continued protection against this disease."**

AB	**The actual benefit of HUMAN HEPATITIS B IMMUNOGLOBULIN LFB in the Marketing Authorisation indications is substantial**
IAB	**HUMAN HEPATITIS B IMMUNOGLOBULIN LFB provides a high level of improvement in actual benefit (level II) in hepatitis B immunoprophylaxis:** **- in accidental exposure in non-immunised people (including when vaccination is incomplete or unknown)** **- in haemodialysis patients pending vaccination being effective** **- in newborn babies of mothers carrying the hepatitis B virus** **- in patients who have not developed an immune response after vaccination against the hepatitis B virus (undetectable antibodies against hepatitis B) and who require continued protection against this disease.**
Therapeutic use	**Hepatitis B immunoprophylaxis, in combination with vaccination**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation	Cohort temporary usage authorisation from January 1995 to October 2012 Marketing Authorisation: 20 June 2012 (national procedure) As part of its Marketing Authorisation, the company has in particular undertaken to: - Discuss the feasibility of carrying out a retrospective or prospective post-Marketing Authorisation study in a sufficient number of newborn babies, assessing the efficacy of preventing seroconversion with testing for Ag, anti-HBs Ab and HBV DNA between one and four months after the last dose of vaccine. - Through a retrospective analysis, to consider the best management regimen for newborn babies of mothers with high level viral replication with respect to co-administration of the vaccine and specific hepatitis antiviral agents.
Prescribing and dispensing conditions	List I Medicine for hospital prescription only

ATC Classification	2012	
	J	Antiinfectives for systemic use
	J06	Immune sera and immunoglobulins
	J06B	immunoglobulins
	J06BB	specific immunoglobulins
	J06BB04	hepatitis B immunoglobulins

02 BACKGROUND

Hepatitis B is a potentially serious hepatotropic viral disease. Its acute form is mostly asymptomatic and patients recover in 90% of cases. Its chronic form is defined by persistence of the HBs antigen (HBsAg) six months after the acute hepatitis. Two outcomes are then possible: chronic inactive HBsAg carrier status and chronic active hepatitis which may cause serious complications (cirrhosis, liver cancer).

The hepatitis B virus (HBV) has several means of transmission: blood or blood product transfusion (a method of transmission which has become very rare since routine screening for the infection in donations and excluding chronic HBV carriers from donating blood), accidental inoculation, particularly through acupuncture, tattooing, unsterilised injection materials (particularly in drug addicts), accidental wounds with contaminated material (particularly in health staff) or during hospitalisation (nosocomial infection), infection from sexual contact and "vertical" transmission of the B virus from an infected mother to her newborn baby at or after birth.
The virus appears in the blood between 10 and 20 days after injection. The viraemia disappears after 2 or 3 months in 90% of people. The viraemia becomes chronic in less than 10% of people. Progression to the chronic stage depends on age: from 5 to 10% in immunocompetent adults, 30 to 40% in children under 4 years old, rising to 90% in newborn babies born to mothers with positive HBsAg and HBeAg in the absence of serovaccination within 24 hours after birth.

Prevention is based on vaccination, which is recommended in all infants and adolescents up to the age of their 16th birthday and exposed groups. Hepatitis B is an occupational disease and vaccination is mandatory in health professionals. Vaccination generally involves two injections, one month apart and a 3rd injection in the 6th month. Protection is obtained from the 2nd month in responders. There are non-responders, particularly men over 40 years old (10 to 20%) and to a lesser extent, women over 40 years old (5%).
In the specific situation of someone who has just been infected, or who must be immediately protected, passive immunisation must be combined with specific anti-HBs immunoglobulins and active immunisation with the vaccine. Passive immunisation provides immediate but temporary protection, lasting approximately six weeks. Passive immunisation must never be used in isolation and must always be combined with active immunisation, except in patients who do not respond to the vaccine.

HUMAN HEPATITIS B IMMUNOGLOBULIN LFB 100 IU/ml injectable solution in pre-filled syringe (IM) has been marked in France since 1995 as a cohort TUA and is currently the only immunoglobulin with Marketing Authorisation for passive immunisation in the indications shown below.

03 THERAPEUTIC INDICATIONS

"hepatitis B immunoprophylaxis:
- in accidental exposure in non-immunised people (including when vaccination is incomplete or unknown)
- in haemodialysis patients pending vaccination being effective
- in newborn babies of mothers carrying the hepatitis B virus
- in patients who have not developed an immune response after hepatitis B virus vaccination (undetectable antibodies against hepatitis B) and who require continued protection against this disease."

04 DOSAGE

"- Prevention of hepatitis B in accidental exposure in an non-immunised person: minimum of 500 IU depending on the extent of exposure as soon as possible after the exposure and preferably within 24-72 hours.
- immunoprophylaxis against hepatitis B in haemodialysis patients. 8-12 IU/kg with a maximum of 500 IU, repeatable every two months until seroconversion after vaccination.
- Prevention of hepatitis B in newborn babies of mothers carrying the hepatitis B virus, at birth or as soon as possible after birth: 30-100 IU/kg. Administration of hepatitis B immunoglobulin should be repeated until seroconversion after vaccination. […].
- 500 IU may be administered to adults and 8 IU/kg to children every two months in patients who have not developed an immune response after hepatitis B virus vaccination (undetectable anti-hepatitis B antibodies) and who require continuous protection against this disease. […]".

05 THERAPEUTIC NEED

05.1 Accidental exposure in non-immunised people

Following an exposure accident to HBV in an non-immunised person (unvaccinated or who has not responded to the vaccine), early serovaccination[1] with an injection of 500 IU of specific anti-HBs immunoglobulins and a dose of vaccine must be given within 48 hours after exposure[2]. Serovaccination is supplemented by a second injection of anti-HBs immunoglobulins at one month and a booster vaccination at one month and six months. Passive immunoprophylaxis with immunoglobulins alone can be given to people who have been shown[3] not to respond to vaccination.[4]

05.2 In haemodialysis patients pending vaccination being effective

The immunogenicity of vaccination is lower in patients who are being dialysed than in the general population and passive immunisation is required pending the vaccination taking effect.[5,6]

05.3 In newborn babies of mothers carrying the hepatitis B virus

Screening for the HBs antigen has been mandatory in France in the 4th antenatal examination (at 6 months of pregnancy) since 1992.[7]
If the mother is seropositive, serovaccination is recommended for the newborn babies. The newborn baby must be given an injection of anti-HBs immunoglobulins at birth and the first vaccination of the regimen as three injections (one dose at 0, 1 and 6 months) with a vaccine other than HBVAXPRO 5 µg. A four dose regimen (one dose at 0, 1, 2 and 6 months) is recommended for premature infants under 32 weeks old or of bodyweight under 2.0 kg.[8]

05.4 In patients who have not developed an immune response after vaccination

A further protocol of three vaccination injections must be given followed by measurement of antibodies 1 to 4 months later in people who have not responded to vaccination (anti-HBs antibody titre < 10 mIU/ml). If a person fails to produce an immune response after the further vaccination, the only alternative is anti-HBs immunoglobulin injection in patients in whom continued protection against hepatitis B is required.[2,9]

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[1] Serovaccination is an immunisation technique combining the complementary action of immunoglobulins and the vaccine.
[2] DGS/VS2/DH/DRT Circular n°99-680 of 8 December 1999 on recommendations for action following a risk of transmission of HBV and HCV by blood and biological fluids.
[3] A non-responder to anti-HBV vaccination is a person with an anti-HBs antibody titre of < 10 IU/ml after having received the recommended vaccine regimen twice.
[4] SFHH. Ministry of Health. HCSP. Monitoring and preventing care-related injections. September 2010.
[5] SFHH. Good haemodialysis hygiene practice. 2005.
[6] Joint Committee on Vaccination and Immunisation. "Chapter 18 Hepatitis B". *Immunisation Against Infectious Disease 2006 ("The Green Book")*, Edinburgh, Stationery Office, 2006 (Chapter 18 revised 10 October 2007).
[7] Decree 92-143 of 14 February 1992.
[8] BEH/ Invs. The vaccination calendar and 2012 vaccination recommendations according to the opinion of the French National Public Health Council. 10 April 2012 / n°14-15.
[9] Directorate-General for Health. "National Hepatitis B and C Plan 2009-2012.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

There is no strictly comparable medicinal product to human hepatitis B immunoglobulin LFB.

For information, the other hepatitis B immunoglobulins used for passive immunisation have different indications.

Name (Company)	Indication (Route of administration)	Date of opinion	AB	IAB
IVHEBEX (LFB Biomédicament)	Prevention of recurrence of hepatitis B after liver transplantation in patients carrying the HBs antigen. (Intravenous)	07/11/2001	Substantial	I (major)
ZUTECTRA (AELSLIFE SAS)	Prevention of hepatitis B virus (HBV) re-infection in HBV-DNA negative patients ≥ 6 months after liver transplantation for hepatitis B-induced liver failure. (Subcutaneous)	16/11/2011	Substantial	IV (minor) in prevention of HBV reinfection.

Conclusion

There is no relevant comparator for the proprietary medicinal product HUMAN HEPATITIS B IMMUNOGLOBULIN LFB, as the other hepatitis B Ig have different indications.

07 ANALYSIS OF AVAILABLE DATA

No controlled clinical study has been carried out with HUMAN HEPATITIS B IMMUNOGLOBULIN LFB in its indications at the administration regimen in the Marketing Authorisation.

The Marketing Authorisation was granted based on a literature file including:

- three clinical studies carried out in the 1970s assessing the efficacy of different preparations of hepatitis B immunoglobulins (HBIg) in people who have been accidentally exposed[10,11] or in haemodialysis patients,[12]
- a meta-analysis[13] assessing the results of 29 studies on the management of newborn babies of mothers infected with the hepatitis B virus (HBV),
- two non-comparative studies [14,15] assessing the practice and efficacy of serovaccination with HUMAN HEPATITIS B IMMUNOGLOBULIN LFB in newborn babies of mothers infected with HBV, carried out in France between 1993 and 2007.

07.1 Efficacy

7.1.1 In non-immunised people following accidental exposure and in haemodialysis patients

The studies carried out in people exposed accidentally or in haemodialysis patients are old studies conducted in a situation in which routine vaccination (active immunisation) did not exist, and in which the patients were given IM injections of different preparations of immunoglobulins: high titre (between 1/500,000 and 1/100,000 titre), intermediary titre (1/5,000) or normal titre (1/50 or <1/8) anti-HBs antibodies. These studies were intended to demonstrate that high titre preparations of immunoglobulins were superior to conventional preparations (normal HBIg) used as empirical treatments when these studies were performed.
The methods of use were not consistent with current practice and the results of these studies are only presented for information purposes.

[10] Seeff L.B, Wright E.C, Zimmerman H.J et al. Type B Hepatitis after Needle-Stick Exposure: Prevention with Hepatitis B Immune Globulin. Final Report of the Veterans Administration Cooperative Study. Ann Intern Med 1978; 88 (3): 285-283
[11] Grady GF, Lee VA, Prince AM et al. Hepatitis B Immune Globulin for Accidental Exposures among Medical Personnel: Final Report of a Multicenter Controlled Trial. J Infect Dis 1978; 138 (5): 625-638.
[12] Prince AM, Szmuness M, Mann MK et al. Hepatitis B Immune Globulin: Final Report of a Controlled, Multicenter Trial of Efficacy in Prevention of Dialysis-Associated Hepatitis. J Infect Dis 1978; 137 (2): 131-144.
[13] Lee C, Gong Y, Brok J et al. Hepatitis B immunization for newborn infants of hepatitis B surface antigen-positive mothers. Cochrane Database of Systematic Reviews 2006, Issue 2. Art.No.:CD004790.DOI: 10.1002/14651858.CD004790.pub2.

<table>
<tr><th>Study</th><th>Type of study</th><th>Protocol</th><th>Incidence of hepatitis B</th></tr>
<tr>
<td>Seeff L.B

1978</td>
<td>Controlled HBIg titre ≈ 1/100,000 against serum Ig titre (titre <1/8), randomised, double blind, in patients with accidental exposure</td>
<td>
<table>
<tr><td rowspan="2">Injection regimen:</td><td colspan="2">Treatment groups</td></tr>
<tr><td>A (n=203)</td><td>B (n=216)</td></tr>
<tr><td>D0 to D7</td><td>Serum Ig titre < 1/8, 5 ml IM</td><td>HBIg titre ≈ 1/100,000, 5 ml IM</td></tr>
<tr><td>D28</td><td>Serum Ig titre < 1/8, 5 ml IM</td><td>HBIg titre ≈ 1/100,000, 5 ml IM</td></tr>
</table>
</td>
<td>
<table>
<tr><td rowspan="2">Result:</td><td colspan="2">Treatment groups</td></tr>
<tr><td>A</td><td>B</td></tr>
<tr><td>After 6 months</td><td>5.9%</td><td>1.4%</td></tr>
<tr><td>RR</td><td colspan="2">0.23 [0.07-0.82]</td></tr>
</table>
</td>
</tr>
<tr>
<td>Grady G.F

1978</td>
<td>Controlled HBIg titre ≈ 1/5,000 or between 1/500,000 and 1/100,000 against normal HBIg titre (1/50), randomised, in patients with accidental exposure</td>
<td>
<table>
<tr><td rowspan="2">Injection regimen:</td><td colspan="3">Treatment groups</td></tr>
<tr><td>A (n=265)</td><td>B (n=223)</td><td>C (n=269)</td></tr>
<tr><td>D0 to D7</td><td>HBIg titre ≈ 1/50, 3 ml IM</td><td>HBIg titre ≈ 1/5,000, 3 ml IM</td><td>HBIg titre between 1/500,000 and1/100, 000, 3 ml IM</td></tr>
<tr><td>D25 to D35</td><td>HBIg titre ≈ 1/50, 3 ml, IM</td><td>HBIg titre ≈ 1/5,000, 3 ml, IM</td><td>HBIg ≈1/500 000, 3 ml, IM</td></tr>
</table>
</td>
<td>
<table>
<tr><td rowspan="2">Result*</td><td colspan="3">Treatment groups</td></tr>
<tr><td>A</td><td>B</td><td>C</td></tr>
<tr><td>at 4 months</td><td>6.8%</td><td>6.2%</td><td>0%</td></tr>
<tr><td>at 9 months</td><td>8.7%</td><td>7.3%</td><td>7.2%</td></tr>
</table>
*difference significant between B and C compared to A at 4 months and not significant between the groups at 9 months.
</td>
</tr>
<tr>
<td>Prince A.M

1978</td>
<td>Controlled HBIg titre ≈ 1/5,000 or 1/500,000 vs HBIg titre ≈ 1/50, randomised, double blind, in haemodialysis patients</td>
<td>
<table>
<tr><td rowspan="2">Injection regimen:</td><td colspan="3">Treatment groups</td></tr>
<tr><td>A (n=92)</td><td>B (n=101)</td><td>C (n=91)</td></tr>
<tr><td>2 IM injections of 3 ml, 4 months apart</td><td>HBIg titre ≈ 1/50</td><td>HBIg titre ≈ 1/5,000</td><td>HBIg ≈ 1/500,000</td></tr>
</table>
</td>
<td>
<table>
<tr><td rowspan="2">Result*</td><td colspan="3">Treatment groups</td></tr>
<tr><td>A</td><td>B</td><td>C</td></tr>
<tr><td>at 8 months</td><td>22.9%</td><td>22.6%</td><td>6.6%</td></tr>
<tr><td>at 12 months</td><td>27.4%</td><td>25.7%</td><td>21.7</td></tr>
</table>
*difference significant between B and C compared to A at 8 months and not significant between the groups at 12 months.
</td>
</tr>
</table>

D0: exposure to HBV
Ig: immunoglobulin
HBIg: hepatitis B immunoglobulins

Note: These studies were conducted in the 1970s before the introduction of international units (IU). Anti-HBs antibody measurements were expressed as passive haemagglutination. There is no conversion factor to compare the different ways of expressing anti-Hbs antibody titres between haemagglutination, ELISA or radio-immunological methods.

7.1.2 In newborn babies of mothers carrying the hepatitis B virus

- Data from clinical studies

In 2006 the Cochrane group conducted a meta-analysis (Lee C; 2006)[13] evaluating the results of 29 studies on the management of children born to mothers with HBV infection.
This meta-analysis included clinical studies comparing three types of intervention:

- vaccine versus placebo or no treatment.
- hepatitis B immunoglobulin (HBIg) versus placebo or no intervention
- **HBIg combined with vaccination** versus placebo or no treatment or vaccination alone.

This showed that the combination of hepatitis B immunoglobulin and vaccination was more effective than vaccination alone in preventing hepatitis B developing in the newborn babies of HBs antigen positive mothers (RR = 0.54; 95% CI [0.41; 0.73]; 10 studies). The mother's HBe antigen status was not incorporated in this analysis. In addition, no conclusion can be drawn about the optimal administration regimen or on the reduction in the risk of chronic hepatitis B (the studies were short term).

The results of the two main, double-blind, randomised, controlled studies evaluating the combination of hepatitis B immunoglobulin and vaccination against vaccination alone and placebo included in this meta-analysis are summarised below. The methods of use, however, were not consistent with current practice (HBIg + first vaccine injection of the three injection regimen at birth, at 1 month and at 6 months), and these data are therefore shown for indicative purposes.

<table>
<tr><th>Study</th><th>Protocol</th><th>Results</th></tr>
<tr><td>Ip H.M ; (Lancet 1989)</td><td>
<table>
<tr><td>Injection regimen:</td><td colspan="4">Treatment groups</td></tr>
<tr><td></td><td>A (n=60)</td><td>B (n=64)</td><td>C (n=64)</td><td>D (n=47)</td></tr>
<tr><td>birth</td><td>PDV + 200 IU HBIg</td><td>PDV + 200 IU HBIg</td><td>PDV</td><td>P</td></tr>
<tr><td>1 month</td><td>PDV + 100 IU HBIg</td><td>PDV</td><td>PDV</td><td>P</td></tr>
<tr><td>2 months</td><td>PDV + 100 IU HBIg</td><td>PDV</td><td>PDV</td><td>P</td></tr>
<tr><td>3 months</td><td>100 IU HBIg</td><td>P</td><td>P</td><td>P</td></tr>
<tr><td>4 months</td><td>100 IU HBIg</td><td>P</td><td>P</td><td>P</td></tr>
<tr><td>5 months</td><td>100 IU HBIg</td><td>P</td><td>P</td><td>P</td></tr>
<tr><td>6 months</td><td>PDV + 100 IU HBIg</td><td>PDV</td><td>PDV</td><td>P</td></tr>
</table>
</td><td>After 3 years

Efficacy of protection
A: 87%
B: 80%
C: 65%</td></tr>
<tr><td>Halliday ML; 1992 (Int J Epidemiol, 1992)</td><td>
<table>
<tr><td>Injection regimen:</td><td colspan="4">Treatment groups</td></tr>
<tr><td></td><td>A (n=55)</td><td>B (n=55)</td><td>C (n=55)</td><td>D (n=60)</td></tr>
<tr><td>birth</td><td>PDV</td><td>RV 20 µg</td><td>RV 20 µg + 260 IU HBIg</td><td>RV 10 µg + 260 IU HBIg</td></tr>
<tr><td>1 months</td><td>PDV</td><td>RV 20 µg</td><td>RV 20 µg</td><td>RV 10 µg</td></tr>
<tr><td>2 months</td><td>PDV</td><td>RV 20 µg</td><td>-</td><td>-</td></tr>
<tr><td>6 months</td><td>PDV</td><td>RV 20 µg</td><td>RV 20 µg</td><td>RV 10 µg</td></tr>
</table>
</td><td>After 9 months

The efficacy of the RV was greater when it was administered with HBIg (92% in group C and 87.8% in group D compared to 82.6% in group B).</td></tr>
</table>

PDV: plasma-derived vaccine (3 µg)
RV: recombinant vaccine
P: placebo

- Real life usage data

Two non-comparative studies evaluating the practice and efficacy of serovaccination with HUMAN HEPATITIS B IMMUNOGLOBULIN LFB were carried out in France between 1993 and 2007.

Study by Selton et al. (2009):[14] this was a prospective study conducted at Nancy between 1993 and 2001, evaluating the following serovaccination protocol:

- birth: First injection of anti-HBV vaccine and an intramuscular injection of HBIg, dosage 0.3 ml/kg (1 ml = 100 IU)
- 1 month: second injection of anti-HBV vaccine combined, if the mother was HBeAg+, with a second injection of IM HBIg, dose 0.3 ml/kg
- 2 months: third injection of anti-HBV vaccine
- 1 year: booster of anti-HBV vaccine

The children were followed up for 260±211.4 days. Effective serovaccination was obtained from the regimen used in this study in 57 of the 60 children included (95%). Chronic HBsAg carrier status was found in one child (1.7%).

[14] Selton D, André M, Gosselin J, Hascoët J-M. "Efficacité de la sérovaccination chez des nouveau-nés de mères antigènes HBs positif: à propos de 60 observations". *Journal de Gynécologie Obstétrique et Biologie de la reproduction.* 2009; 38: 500-509.

Study by Chakvetadze C et al. (2011):[15] this was a retrospective study conducted at Mayotte in the period between 1994 and 2007, evaluating the following serovaccination protocol:

- in the first 12 hours after birth: first injection of recombinant vaccine (ENGERIX B 10 µg or GENHEVAC B 20 µg) and 100 IU of HBIg
- 1 month +/- second injection of 100 IU of HBIg
- 1 and 6 months (or 2 and 12 months): second and third injection of the vaccine (or third and fourth injection of the vaccine).

Median follow up was 5 years. Serovaccination was given using the intended protocol to 83 of the 100 newborn babies included. An anti-HBs Ab titre of > 10 IU/l combined with negative HBsAg and anti-HBc Ab with undetectable HBV viral DNA was found in 76 children (76%). Of the 24% serological serovaccination failures (negative anti-HBs Ab independently of other markers), a 3% rate of hepatitis B was found.

The results of these studies carried out with HUMAN HEPATITIS B IMMUNOGLOBULIN LFB according to the administration regimen is similar to that recommended in the Marketing Authorisation to support the efficacy of serovaccination with hepatitis B immunoglobulin in preventing the risk of hepatitis B developing in newborn babies.

- Studies in progress

An observation cohort study (ELFE cohort)[16] began in 2011. This study is following 18,000 children born in France between April and December 2011 for 20 years. One of the objectives of the study is "to estimate the HBs antigen detection coverage during pregnancy and clinical and serological follow-up of children born to mothers carrying HBsAg who are serovaccinated at birth". This validity study is ongoing.

7.1.3 People who have not developed an immune response after vaccination who require protection against HBV

No clinical study has been performed specifically in patients who have not developed an immune response after active vaccination.

07.2 Adverse effects

7.2.1 SPC data

"There are insufficient data on the incidence of adverse effects seen in the clinical studies".

The following adverse effects have been found with the hepatitis B immunoglobulin class:

- immune system disorders: hypersensitivity, anaphylactic shock
- nervous system disorders: headaches
- cardiac disorders: tachycardia
- vascular disorders: hypotension
- gastrointestinal disorders: nausea, vomiting
- skin and subcutaneous tissue disorders: skin rash, pruritus, erythema
- musculoskeletal and systemic disorders: arthralgia
- general disorders and administration site problems: fever, malaise, chills; at the injection site: oedema, pain, erythema, swelling, warmth, pruritus, skin rash".

[15] Chakvetadze C, Roussin C, Roux J, Mallet V, Petinelli M.E, Pol S. Efficacy of hepatitis B sero-vaccination in newborns of African HBsAg positive mothers. *Vaccine.* 2011; *29*: 2846-2849.
[16] ELFE study. Available at: http://www.elfe-france.fr/index.php/fr/ (accessed on 14 September 2012)

7.2.2 PSUR Data

According to the sales data from 1st July to 31 December 2011, exposure in France is estimated to be 9306 patient-years.

The periodic safety update reports (PSUR) for HUMAN HEPATITIS B IMMUNOGLOBULIN LFB cover the period from 1st January 1995 to 31 December 2011. During this period, six serious cases including one case of arthralgia and one seroconversion were reported. Forty-two cases of incorrect use were also reported, mostly due to administration of an expired product. No adverse effects associated with incorrect use have been reported. This data analysis does not change the safety profile and no specific measures have been taken.

07.3 Usage data

HUMAN HEPATITIS B IMMUNOGLOBULIN LFB has been used in a cohort TUA since 1995 in the Marketing Authorisation indications.
Approximately 10,000 patients have been treated annually in the TUA. The indications in which these immunoglobulins have been prescribed have not been listed and no safety or efficacy data have been collected.
The Committee regrets that it does not have efficacy or usage data in the different circumstances of exposure to the virus based on the experience obtained from this TUA.

07.4 Summary & discussion

No controlled clinical study has been carried out with HUMAN HEPATITIS B IMMUNOGLOBULIN LFB according to the vaccination regimen in the Marketing Authorisation.

The Marketing Authorisation was granted based on a literature file including studies carried out with different specific immunoglobulin preparations (HB-Ig) of hepatitis B and different immunisation protocols in haemodialysis patients or in people exposed accidentally and in the newborn babies of mothers infected with HBV, together with real life usage studies of HUMAN HEPATITIS B IMMUNOGLOBULIN LFB in the newborn babies of mothers infected with HBV. No clinical study has been carried out specifically in people who have not developed an immune response after vaccination who require protection against HBV.

The clinical data, although limited, in haemodialysis patients or those exposed accidentally to HBV support the recognised therapeutic utility of the HB-Ig. Although very old and obtained at a time when vaccination was not used, these data show good although transient action.
Studies in the newborn babies of mothers carrying the hepatitis B virus have shown HBIg combined with hepatitis B vaccination to be 75 to 95% effective in terms of HBV infection.
No conclusion can be drawn from this set of studies on the optimal administration regimen, particularly based on the level of contagiousness of the source person.
No clinical study has been performed in patients requiring protection against hepatitis B but who have not developed an immune response after vaccination against the hepatitis B virus.
There are limited clinical data allowing the evaluation of the safety profile of HUMAN HEPATITIS B IMMUNOGLOBULIN LFB (small numbers in the studies), although the reported clinical experience on the use of this immunoglobulin (TUA since 1995) has not revealed any major safety concerns.

08 THERAPEUTIC USE

Specific hepatitis B immunoglobulins are recommended in passive HBV immunisation by the current recommendations in the various populations targeted by the Marketing Authorisation for HUMAN HEPATITIS B IMMUNOGLOBULIN LFB.

It is therefore recommended as first-line therapy in combination with an active vaccination in hepatitis B immunoprophylaxis:

- in accidental exposure in non-immunised people
- in haemodialysis patients pending vaccination being effective
- in the newborn babies of mothers carrying the hepatitis B virus,

and alone:

- in patients who have not developed an immune response after vaccination against the hepatitis B virus and who require protection against this disease.

09 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all of the above data and information and following the debate and vote, the Committee has reached the following conclusions:

09.1 Actual benefit

- Hepatitis B is a serious, potentially life-threatening disease.
- HUMAN HEPATITIS B IMMUNOGLOBULIN LFB is a preventative treatment.
- The efficacy/adverse effect ratio is high
- There is no treatment alternative.
- This is a first-line treatment alone or in combination usually with active immunoprophylaxis.

- Public health benefit:

The public health benefit of HUMAN HEPATITIS B IMMUNOGLOBULIN LFB can only be established as part of the overall preventative strategy for hepatitis B in France due to a risk of transmission of the hepatitis B virus (HBs Ag serology particularly and serovaccination).

Hepatitis B is a moderate public health burden in France (approximately 30,000 DALYs according to the WHO estimate).
The burden of the only indications for HUMAN HEPATITIS B IMMUNOGLOBULIN LFB due to exposure carrying a risk of transmission of the hepatitis B virus is low.

Reduction in the morbidity and mortality of chronic hepatitis and improving the quality of care and quality of life of people suffering from chronic hepatitis B (or C) is a public health need which is one of the established public health priorities.[17] This need is generally covered in the curative situation by antiviral agents and the overall preventive strategy adopted, including prophylactic vaccination in particular. Following a risk of transmission of the hepatitis B virus and if this need is not optimally covered by vaccination (non-immunised people, or those awaiting an immune response post vaccination), immunoprophylaxis combined with vaccination offers an additional response compared to the other preventative measures (DGS/VS2/DH/DRT 1999, DGS/SD5C/DHOS/E2/2004/532 2004 circulars).

[17] 9 August 2004 Law on public health policy - objective 35, strategic directions of the National Hepatitis B and C Plan 2009-2012.

In the absence of:
- a clinical study available on HUMAN HEPATITIS B IMMUNOGLOBULIN LFB,
- efficacy and usage data in the different exposure situations to the virus based on experience gained since 1995 in the cohort TUA,
and based on the only studies carried out in the newborn babies of infected mothers, the public health benefit of HUMAN HEPATITIS B IMMUNOGLOBULIN LFB in its indications cannot be established.

Its benefit is only as part of the overall hepatitis B prevention strategy which itself has a recognised public health benefit and which has been recommended for many years in France for a risk of transmission of the hepatitis B virus.

In view of the above, the Committee deems that the actual benefit of HUMAN HEPATITIS B IMMUNOGLOBULIN LFB is high in the Marketing Authorisation indications.

09.2 Improvement in actual benefit (IAB)

In view of the available clinical data and the clinical experience obtained on the use of hepatitis B immunoglobulins in combination with vaccination in preventing hepatitis B following exposure to HBV, HUMAN HEPATITIS B IMMUNOGLOBULIN LFB provides an important (level II) improvement in actual benefit in hepatitis B immunoprophylaxis following accidental exposure in non-immunised people, in haemodialysis patients pending vaccination taking effect, in the newborn babies of mothers carrying the hepatitis B virus and in patients requiring protection against hepatitis B but who have not developed an immune response after vaccination against the hepatitis B virus.

09.3 Target population

- Hepatitis B immunoprophylaxis following accidental exposure in non-immunised people

Occupational exposure in health care staff has become extremely rare as a result of mandatory vaccination.

The target population for HUMAN HEPATITIS B IMMUNOGLOBULIN LFB (IM) cannot be quantified because of a lack of data about the number of non-immunised people at risk of accidental contamination from the hepatitis B (IM) virus in this indication. Accidental exposure to hepatitis B in non-immunised people involves sporadic cases.

- Immunoprophylaxis in haemodialysis patients pending vaccination taking effect

34,735 patients were undergoing haemodialysis in 2010 in metropolitan France and Réunion (REIN register[18]).
Vaccination is given routinely to haemodialysis patients. HUMAN HEPATITIS B IMMUNOGLOBULIN LFB (IM) immunoprophylaxis for haemodialysis patients will only involve sporadic cases.

- Hepatitis B immunoprophylaxis in the newborn babies of mothers carrying HBV

The prevalence of HBs antigen in pregnant women ranges from 0.54 to 1.56% (depending on the origin of the mother).[19] There were 802,224 births in 2010;[20] the number of children liable to be contaminated as a result of materno-fetal transmission is understood to be between 4,332 and 12,515 births.

[18] Nephrology Information Epidemiology Network Register. Annual Report 2010. Biomedicines Agency.
[19] Bacq Y. "Hépatite virale B et grossesse". Gastroentérologie clinique et biologique 32 (2008) S12-S-19.
[20] http://www.ined.fr/fr/france/naissances_fecondite/naissances_par_sexe/ Website accessed on 14/09/2012.

- Immunoprophylaxis in patients who have not developed an immune response after HBV vaccination, who require continued protection against this disease.

The target population for HUMAN HEPATITIS B IMMUNOGLOBULIN LFB (IM) cannot be quantified in this indication because of a lack of data on the number of patients who do not develop an immune response after vaccination against the hepatitis B virus and who require continuous protection. These patients are sporadic cases in view of the high response rate to hepatitis B vaccination.

Quantitative evaluation:

In the absence of reliable epidemiological data to quantify the target population in the different Marketing Authorisation indications, the sales data from the cohort TUA are a good indicator to assess the target population.

Based on the data provided by ANSM, approximately 10,000 patients have been treated annually for the cohort TUA indications.

The target population for HUMAN HEPATITIS B IMMUNOGLOBULIN LFB can be estimated as approximately 10,000 patients per year.

010 TRANSPARENCY COMMITTEE RECOMMENDATIONS

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

Request for data

ANSM has requested further studies to evaluate the preventative efficacy of serovaccination and the best management regimen for the newborn babies of mothers carrying HBV with this immunoglobulin. The Transparency Committee supports this request and requests that the company provide them with the conclusions of these studies. It will decide on the relevance of reviewing its opinion based on these data.