



European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMA/47765/2010

CHMP ASSESSMENT REPORT

FOR

ImmunoGam

International Nonproprietary Name: human hepatitis B immunoglobulin

Procedure No. EMEA/H/C/001055

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 Cangene Europe Limited submitted on 23 July 2008 an application for Marketing Authorisation to the European Medicines Agency for ImmunoGam, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004 based on demonstration of interest of patients at Community level.

The eligibility to the centralised procedure was agreed upon by the CHMP on 2 February 2008.

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

The applicant initially applied for the indication of Immunoprophylaxis of Hepatitis B (Intramuscular use) and for the indication of Prevention of hepatitis B virus recurrence after liver transplantation in HBsAg-positive patients (Intravenous use). During the procedure the applicant requested the withdrawal of the Prevention of hepatitis B virus recurrence after liver transplantation in HBsAg - positive patients indication.

Licensing status:

ImmunoGam has been given a Marketing Authorisation in USA for Immunoprophylaxis indication in January 2006 and for Liver transplant indication in April 2007, in Canada for Liver transplant indication in January 2007 and for the Immunoprophylaxis indication in April 2009 and in Israel in April 2009 for both indications.

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

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 23 July 2008.
- The procedure started on 20 August 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 3 November 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 7 November 2008. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 18 December 2008, 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 18 December 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 June 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 September 2009.
- During the CHMP meeting on 24 September 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 13 November 2009.
- During the meeting on 14-17 December 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 ImmunoGam on 17 December 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 15 December 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Hepatitis B (HBV) infection is caused by a small enveloped DNA hepadnavirus that infects the liver. Approximately 2 billion people in the world have been infected by HBV and 300-350 million of them chronically infected with virus. Most of Northern and Western Europe is considered a low endemicity area for HBV (<2% of chronic HBV). The incidence of reported HBV cases in the European Union (EU) and European Economic Area/European Free Trade Association (EEA/EFTA) countries has declined over the past ten years from 6.7 cases per 100,000 population in 1995 to 1.5 cases per 100,000 population in 2005. In 2005, a total of 6,977 new HBV cases were reported.

The most affected age group was 25-44 year-olds followed by 15-24 year-olds. Men were 1.8 times (range 1-3) more frequently affected than women. The prevalence of hepatitis B surface antigen (HBsAg) in the general population varies widely between European countries. The most common HBV genotypes in Europe are A and D of which the former is more prevalent in Northern Europe, and the latter in the Mediterranean region and Eastern Europe. Some groups are more frequently affected by HBV infection than the general population. The prevalence of HBsAg in injecting drug users (IDUs) ranges from 0 to 21% and the prevalence of antibodies to hepatitis B core antigen (anti-HBc), which indicates past infection, ranges from 20 to 85%. Concurrent infections with HBV and/or HCV and HIV are common, especially among IDUs. In Spain and in England, the HBsAg prevalence among sex workers varies between 6-7%. In many European countries immigrants from highly endemic regions are 5-90 times more frequently affected by HBV than the general population. Other populations at high risk of HBV infection are men having sex with men, and those having multiple sexual partners.

Immunoprophylaxis with human hepatitis B immunoglobulin (HBIG) products is a well-established use. Clinical studies conducted in the 1970's demonstrated that Human Hepatitis B Immunoglobulin products provide passive immunization for individuals exposed to the hepatitis B virus, reducing hepatitis B transmission. Subsequent studies demonstrated the advantage of simultaneous administration of hepatitis B vaccine and HBIG (see Cochrane meta-analysis by Lee et al., 2006). Current recommendations for immunoprophylaxis of hepatitis B are based on national guidelines which rely on published studies and clinical practice.

Population who could be at benefit of treatment includes:

- Infants born to HBsAg-positive mothers are at risk of being infected with HBV and becoming chronic carriers. Mother to child transmission occurs often, either in utero or through exposure to blood or blood contaminated fluids at or around birth. Such perinatal transmission is believed to account for 35% to 50% of hepatitis B carriers. The risk of perinatal transmission is associated with the HBeAg status of the mother. If a mother is positive for both HBsAg and HBeAg, 70% to 90% of her children become chronically infected. If a mother is HBsAg-positive but HBeAg-negative, the risk of transmission is significantly lower. For an infant with perinatal exposure to an HBsAg-positive and HBeAg-positive mother, a regimen combining one dose of HBIG at birth with the hepatitis B vaccine series started soon after birth has been shown to be 85-98% effective in preventing development of the HBV carrier state. Regimens involving either multiple doses of HBIG alone or the vaccine series alone have a 70-75% efficacy, while a single dose of HBIG alone has 50% efficacy.
- HBV infection is a well-recognized risk to health-care personnel (HCP). The risk of HBV infection is primarily related to the degree of contact with blood in the work place and also to the HBeAg status of the source person. In studies of HCP who sustained injuries from needles contaminated with blood containing HBV, the risk of developing clinical hepatitis if the blood was HBsAg and HBeAg-positive was 22%-31%; the risk of developing serologic evidence of HBV infection was 37%-62%. In comparison, the risk of developing clinical hepatitis from needles contaminated with HBsAg-positive, HBeAg-negative blood is 1%-6%, and the risk of developing serological evidence of HBV infection is 23%-37%. Immunoprophylaxis with HBIG

and hepatitis B vaccine series is recommended for any susceptible, unvaccinated person who sustains an occupational blood or body fluid exposure.

- Sexual partners of HBsAg-positive persons are at increased risk of acquiring HBV infection. A single dose of HBIG is 75% effective if administered within two weeks of the last sexual exposure to a person with acute hepatitis B. Likewise, certain populations, such as haemodialysis patients, or subjects who do not show an immune response to hepatitis B vaccination (anti-HBs levels <10 IU/L) may need HBIG immunoprophylaxis to prevent infection in the case of continuous risk of exposure.

Although hepatitis B vaccines can be efficacious in almost 90% of uninfected, healthy normal individuals, most of HBV vaccines are unable to achieve >10 mIU/ml protective levels in 5-10% of remaining healthy individuals. This category of patients includes immunosuppressed, drug users and liver transplanted patients when the donor or recipient is infected with HBV (Akbar & Onji, 2008).

The applicant initially applied for two indications associated with two different routes of administration, namely immunoprophylaxis of hepatitis B (intramuscular use) and prevention of hepatitis B virus recurrence after liver transplantation in HBsAg positive patients (intravenous use). During the assessment procedure, the applicant withdrew the intravenous use indication for prevention of hepatitis B virus recurrence from the application. The approved indication for ImmunoGam is:

“Immunoprophylaxis of Hepatitis B

- In case of accidental exposure in non-immunised subjects (including persons whose vaccination is incomplete or status unknown).
- In haemodialysed patients, until vaccination has become effective.
- In the newborn of a hepatitis B virus carrier-mother.
- In subjects who did not show an immune response (no measurable hepatitis B antibodies) after vaccination and for whom a continuous prevention is necessary due to the continuous risk of being infected with hepatitis B.

Consideration should also be given to other official guidance on the appropriate use of human hepatitis B immunoglobulin for intramuscular use.”

2.2 Quality aspects

Introduction

ImmunoGam, Hepatitis B Immunoglobulin (Human), is a sterile solution containing 5% (50 mg/mL) of purified gamma globulin (IgG) fraction containing anti-HBs, antibodies to Hepatitis B surface antigen (HBsAg).

ImmunoGam is manufactured from source plasma collected from selected and/or immunised healthy donors with high titres of anti-HBs that is purified by an anion-exchange chromatography method.

The ImmunoGam manufacturing process includes a solvent/detergent treatment step and a viral nanofiltration step for the inactivation of lipid enveloped viruses and the removal of lipid and non-lipid enveloped virus by size exclusion respectively.

ImmunoGam is stabilized with 0.03% polysorbate 80 and 10% maltose and contains no preservative.

The product potency is expressed in International Units (IU) by comparison to the World Health Organization (WHO) international reference Hepatitis B Immunoglobulin reference preparation. Each

millilitre of ImmunoGam contains 312 IU of anti-HBs. ImmunoGam may be administered only intramuscularly.

ImmunoGam, solution for injection, is supplied in the following pack sizes:

- 1 mL single dose (312 IU/mL) in a Type 1 glass vial, with a plastic flip off seal
- 5 mL single dose (312 IU/mL) in a Type 1 glass vial, with a plastic flip off seal

Each vial contains 312 IU/mL of anti-HBs.

Active Substance

ImmunoGam is a sterile solution containing 5% (50 mg/mL) of purified gamma globulin (IgG) fraction containing anti-HBs, antibodies to Hepatitis B surface antigen (HBsAg).

ImmunoGam is manufactured from source plasma collected from selected and/or immunised healthy screened donors with high titres of anti-HBs. The donor selection, testing for contaminating viruses and pooling of plasma have been certified and are covered in the Cangene Plasma Master file (PMF).

The drug substance, as defined by the applicant, contains information concerning manufacturing up to the final vial filling and labelling.

Manufacture

ImmunoGam is manufactured by the Cangene Corporation in Winnipeg, Manitoba, Canada.

Information related to establishments responsible for plasma collection, testing, storage, transportation and control of Human Plasma are described within the current Plasma Master File (PMF).

Human plasma for fractionation is used as starting material. The manufacture starts with the thawing of the plasma which is followed by a clarification step. Downstream manufacturing process include anion exchange chromatography, viral filtration, solvent detergent treatment, reverse phase chromatography and diafiltration steps.

The applicant confirmed that no reprocessing / reworking is allowed during the manufacturing process.

All materials used in the ImmunoGam manufacturing process are from non-animal sources and purchased from approved suppliers. Release test of substances not described in Ph. Eur. were provided. The MAH has confirmed that in all cases, a test for identity will be performed.

Critical steps in the manufacturing process of the drug substance of ImmunoGam were identified and are adequately monitored with the quality in-process controls and manufacturing specifications. Standard test methods for in-process controls are identical to finished product testing.

The applicant has used a number of process and validation reports that were generated to support their WinRho product (a hyperimmune anti-D). This is an acceptable approach as the proportion of the IgG targeted towards a named group of antigens e.g. anti-Hepatitis B forms a very small percentage of the total IgG contained within the product and so different hyperimmune products are in essence human normal immunoglobulin that contains a relatively high titre of IgGs that are directed towards a specific group of antigens. It has been confirmed that the WinRho and ImmunoGam processes are sufficiently similar so that validation data obtained from WinRho can be used to support ImmunoGam.

The reproducibility and effectiveness of process steps designed to remove and/or inactivate potential viral contamination have been demonstrated in studies of model viruses in compliance with ICH and CHMP guidance. Validation of the liquid-formulated ImmunoGam process was performed concurrently, at the manufacturing scale.

Elucidation of structure has been conducted using the drug product, ImmunoGam, which is essentially the same as drug substance. The ImmunoGam manufacturing process is continuous, and the only significant steps carried out during drug product manufacture are final filtration and filling.

Identity and Purity demonstrated that the electrophoretic mobility of the drug product is consistent with that of gamma globulin. The determination of the Molecular Weight revealed for ImmunoGam the known molecular weight of human plasma IgG immunoglobulin. The IgG Subclass distribution for ImmunoGam is comparable to normal plasma.

Initially the applicant applied for intravenous and intramuscular use of ImmunoGam. The product did not completely conform to the requirements of Ph. Eur. for immunoglobulins for intravenous use. As the applicant withdrew the indications where intravenous administration was required, this was no longer applicable as it does not apply to the use of ImmunoGam for intramuscular administration.

Potential impurities in ImmunoGam may include species carried over from the donor plasma or reagents from the purification process. The in-process testing for impurities were summarized and data from representative batches showing that most of these process related impurities are controlled.

The purification process potentially enriches Factor XI from a plasma concentration. During the procedure the applicant provided results of suitable control tests on different lots of ImmunoGam. Since the plasma used in these experiments were not within the specification for the assay, it cannot be totally concluded that there is no activated FXI in the product. The applicant has committed to repeat these experiments using plasma that is within specification.

Purity of the drug substance is verified by drug product release testing. The analytical methods and the validation for testing ImmunoGam drug substance are the same as those used for testing the drug product.

The claimed stability for the drug substance is adequately validated with real time / real temperature data.

Medicinal Product

ImmunoGam is a clear to slightly opalescent and colourless or pale yellow liquid containing 5% (50 mg/ml) purified gamma globulin (IgG), antibodies to Hepatitis B surface antigen (HBsAg), stabilized with maltose and Polysorbate 80. ImmunoGam is supplied in single-dose glass vials with bromobutyl rubber stoppers, aluminum seals and plastic flip-off caps. ImmunoGam is intended for intramuscular administration only.

The commercial product is available in two vial sizes: 1.0 mL and 5.0 mL. Both sizes contain 312 IU/mL.

An overage is provided for both sizes of ImmunoGam to ensure that drug product will meet the acceptance criterion of 312 IU/mL throughout the entire shelf life of the product.

Drug product manufacture includes sterile filtration, filling, capping, labelling and packaging. A description of the manufacturing process for ImmunoGam drug product was provided and critical steps were indicated.

Validation of the manufacturing process for ImmunoGam was demonstrated.

A description of the procedure for shipping qualification was provided.

The applicant confirmed that ImmunoGam will not be reprocessed during the manufacturing process.

ImmunoGam is retested upon receipt in Europe for European batch release and importation testing. All retesting performed in Europe follows the same test methods as those performed in Canada.

Initially, the release specification did not fully comply with all the Ph Eur requirements. Some of the non compliant specifications were only related to the intravenous IgG. During the procedure the applicant has revised the specifications.

The final product specifications for the drug product are suitable for the control of the drug product and comply with the requirements of Ph. Eur for Immunoglobulins for intramuscular administration. ImmunoGam is intended for intramuscular administration only.

The ImmunoGam lots were produced from ImmunoGam Drug substance. The data of the batch analysis were provided.

The primary reference standard for ImmunoGam and in house qualified standard were described as were the standards of the other tests.

ImmunoGam is filled in 3 ml or 6 ml vials depending on the fill volume.

The stability of ImmunoGam has been evaluated at the recommended storage conditions of 2 to 8°C and under accelerated conditions. The shelf life of ImmunoGam (36 months at 2 to 8°C) was established based on real time stability studies using the current container closure system based on samples taken from commercial scale production.

The recommended storage temperature of ImmunoGam vials is 2 to 8°C and the expiration period is 36 months after the date of manufacture. The date of manufacture begins from date of the sterile filtration of drug substance.

All studies supporting drug product stability were conducted using the current commercial container closure system and at commercial formulation and strength.

Facilities and equipment are adequately described.

Adventitious Agents safety Evaluation

The applicant confirms that the excipients, raw materials, and reagents used in the manufacture of ImmunoGam are not of animal origin and that ImmunoGam is prepared in compliance with the current Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, EMEA/410/01 rev.2.

The applicant has provided adequate data to show that the nanofiltration will also remove significant quantities of spiked TSE agent. To get more confidence on the capacity of the production process of ImmunoGam to remove TSE agents, the applicant committed to perform a product specific investigational study to analyse the prion removal capacity of the anion chromatography column step.

ImmunoGam is produced from human plasma which is obtained from blood centres located in the USA and Canada. Donors are excluded with respect to vCJD risk according to European Directives or guidelines and US-regulations.

Regarding adventitious viruses, two main viral removal/inactivation steps were studied. The applicant has used the scale down models developed for WinRho. This is an acceptable approach if the manufacturing method for WinRho at the time that this scale down validation was done is the same for the current manufacturing method for ImmunoGam. The applicant has confirmed that these models also accurately model the ImmunoGam process.

Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted data, the marketing authorisation application for ImmunoGam is recommended for approval based on quality grounds. Overall, information on manufacture and control

of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important quality characteristics.

2.3 Non-clinical aspects

Introduction

ImmunoGam, a human hepatitis B immunoglobulin (HBIG) preparation, is a sterile solution of purified gamma globulin (IgG) fraction of human plasma containing antibodies to hepatitis B surface antigen (anti-HBs). ImmunoGam is manufactured from plasma collected from healthy, screened donors with high titres of anti-HBs which is purified by an anion-exchange column chromatography method.

In line with the Note for Guidance on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (CPMP/ICH/302/95, ICH S6), the principles of which may also be applied to plasma-derived products, no non-clinical studies have been conducted specifically with ImmunoGam due to its immunoglobulin nature. The applicant has provided a literature review of non-clinical data for the excipients as well as the solvent and detergent used in the viral clearance steps including a discussion of their projected intakes. In addition, data was provided from toxicology studies conducted with another hyperimmune product, WinRho, which is already marketed by the applicant. Both products are IgG preparations and are prepared using an identical manufacturing process except for the final formulation steps.

Pharmacology

- Primary pharmacodynamics and secondary pharmacodynamics

The mechanism of action of HBIG 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. HBIG also undergoes endocytosis by hepatocytes and binds to HBsAg within cells already infected, thereby decreasing viral secretion.

Primary pharmacodynamic effects have been established in clinical trials. There were no adverse effects of human immunoglobulins independent of primary pharmacodynamic effects that have been observed to warrant secondary pharmacodynamic studies in an animal model. Furthermore, no adverse pharmacodynamic effects were described in a study conducted for WinRho, another hyperimmune product manufactured by Cangene, containing residual amounts of TNBP and Triton X-100. In addition, the solvent-detergent component (TNBP/Triton X-100) is widely used in parenteral medicinal products.

Pharmacodynamic and safety pharmacology effects of polysorbate 80 were considered and sufficiently discussed. Cardiovascular effects of polysorbate 80 were observed in a variety of animal models only at very high doses, which are clinically not relevant. Toxic effects on the cardiovascular, respiratory and central nervous system are not expected with HBIG. The applicant argued that in addition to the available data further preclinical pharmacodynamic and safety pharmacology studies were not considered necessary. This justification was considered acceptable by the CHMP.

Pharmacokinetics

The active ingredient of ImmunoGam is the human IgG, a protein molecule that follows classical absorption, distribution, metabolism and excretion pathways in any species. Therefore, it is assumed that ImmunoGam will be degraded into small peptides and component amino acids via catabolic pathways that are typically associated with endogenous IgG. Pharmacokinetic studies in animals were not performed for ImmunoGam or its components as information regarding metabolism, excretion, pharmacokinetic drug interactions and other pharmacokinetic studies are available from published scientific literature. Furthermore, as a human protein its immunogenic properties in non-human

species would make the interpretation of animal data questionable and animal distribution studies would not predict the distribution in humans accurately. The pharmacokinetic profile of ImmunoGam after i.m. administration was established in two clinical biopharmaceutical studies in healthy volunteers. Therefore, the justification for the absence of non-clinical pharmacokinetic studies was acceptable for the CHMP.

The applicant has provided documentation on the metabolic fate of TNBP, polysorbate 80 and maltose in animal models including a discussion of the literature with respect to pharmacokinetics. Studies collectively suggest that TNBP is metabolised rapidly and the kidney plays a major role in its metabolism. The level of TNBP present in the maximum intended dose of ImmunoGam is low (approximately 0.6µg/kg) and in view of fast metabolism and excretion of TNBP, ImmunoGam is considered safe for human use. Published results on maltose suggest that it is metabolised to maltotetraose, maltotriose and glucose and that the kidney plays a major role in this metabolism.

The literature results indicate that polysorbate 80 is eliminated in faeces similarly to natural neutral fats. A very small portion of polyoxyethylene moiety is absorbed and eliminated in urine. There are no specific pharmacokinetics/metabolism data available for Triton X-100. However, in view of the low residual levels in ImmunoGam (≤ 10 ppm) and the fact that it is widely used in other pharmaceutical products, it is considered that such data are not crucial to the overall safety assessment.

Toxicology

Toxicology studies in animals were not performed with ImmunoGam or its components by the applicant. Information regarding repeat-dose toxicity, genotoxicity, carcinogenicity and reproductive/developmental toxicity of the excipients was provided from published literature.

- **Single dose toxicity**

The toxicology data obtained from a related lyophilised product WinRho have been applied to ImmunoGam. One single-dose toxicity study and two immunotoxicity studies were performed with WinRho, which contains residual amounts of TNBP and Triton X-100.

In the GLP-compliant acute toxicity study, ten mice (5 males and 5 females) were each given a single 75 µg intravenous dose of product and observed for 14 days. At the end of the observation period, the mice were killed and gross necropsy was performed. No deaths and no intolerance reactions occurred. All mice gained weight during the 14-day observation period. Gross necropsy revealed no gross pathological findings. The intravenous LD₅₀ exceeded 3750µg Anti-D Human Immune Globulin/kg bw (>233 mg IgG/kg). Considering that immunoglobulins are normal constituents of the human body, conducting only limited acute preclinical studies was considered acceptable.

- **Repeat dose toxicity (with toxicokinetics)**

No repeat dose toxicity studies were conducted with ImmunoGam and, subsequently, no toxicokinetic data are available. Given the potential for antigenicity following administration of a human protein to an animal species, the absence of repeated-dose toxicity studies is also justified for this product. Furthermore, ImmunoGam is intended for single use.

- **Genotoxicity**

Genotoxicity studies were not conducted for ImmunoGam as human immunoglobulins are not expected to interact directly with DNA or other chromosomal material. This is in accordance with the Note for Guidance on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals.

- **Carcinogenicity**

Carcinogenicity studies were not conducted, as administration of ImmunoGam is not likely to exceed a period of 6 months. This is in line with the Note for Guidance on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals.

- Reproduction Toxicity

Reproduction toxicity studies were not conducted with ImmunoGam. This was acceptable as for human plasma-derived immunoglobulin products such studies are not required.

- Local tolerance

Based on i.m. studies with a comparable product WinRho and on the available clinical experience with ImmunoGam, no adverse injection site reactions beyond some discomfort at the injection site are to be expected from i.m. administration of ImmunoGam. Further non-clinical testing for local tolerance was not considered justified or ethical since the tests are unlikely to extend the scientific knowledge of local tolerance in this case. The absence of any specific non-clinical local tolerance studies is acceptable.

- Other toxicity studies

A literature review on the toxicity of the excipients has been presented with respect to the maximum dose exposure from ImmunoGam administration. Published polysorbate 80 toxicology studies in rats indicate that the compound is relatively non-toxic by oral or i.p. administration. Consistent carcinogenic adverse effects and pheochromocytomas in adult male rats were found at a dose of 5,000 ppm/kg bw. The level of polysorbate 80 present in the maximum intended dose of ImmunoGam is far below the recommended daily consumption and the no adverse effect levels (NOAEL) in mice and rats. Collectively, the data presented suggest that the amount of polysorbate 80 in ImmunoGam presents a negligible toxic and carcinogenic risk to humans.

Other immunoglobulin products also contain maltose, some with a maximum dose exceeding that in ImmunoGam. Both maltose and polysorbate 80 are of compendial quality.

The concentration of Triton X-100 in the ImmunoGam formulation is estimated to result in a maximum daily exposure of 5µg/kg/day following a single administration (up to 35 ml/patient). This is far below the NOAEL seen in rats given Triton X-100 repeatedly for 90 days and also far below the level of Triton X-100 that caused developmental toxicity in rats. For Triton X-100, the margin on an applied dose basis over the NOAEL for general toxicity is 4,700 and for the dose at which effects were seen on developmental toxicity it is 8,300. Therefore, it is unlikely to present a risk of toxicity to humans.

The consistent toxic effects seen with TNBP are in the form of hyperplasia of the urinary bladder epithelium at high dose levels. The level of TNBP present in the maximum clinical dose of ImmunoGam is ≤10ppm; this is far below the NOAEL in mice and rats. For TNBP, the margin over the no adverse effect levels (NOAELs) on an applied dose basis for general toxicity in mice is 5,300 and for rats, it is 2,100 based on the maximum daily exposure of 5µg/kg/day. For embryo-fetal development, it is 80,000. If the dosage for rats is roughly applicable to humans, development of toxic symptoms in humans would result only from a very large exposure to TNBP. Collectively, the data presented suggest that the trace amounts of TNBP (≤10ppm) in ImmunoGam present negligible risk to humans.

Ecotoxicity/environmental risk assessment

The applicant argued that ImmunoGam could be exempt from the requirement for an environmental risk assessment on the grounds that its active substance, human hepatitis B immunoglobulin, is a naturally occurring, highly purified antibody from blood plasma. ImmunoGam's excipients include maltose (a disaccharide sugar), and polysorbate 80 which is a common surfactant or emulsifier present in food, cosmetics, household products and pharmaceuticals and are both compendial. The applicant's

justification was in accordance with the applicable guideline (CHMP/SWP/4447/00) and the absence of an environmental risk assessment was acceptable.

2.4 Clinical aspects

Introduction

The initial application for marketing authorisation for ImmunoGam included a claim for two indications associated with two different routes of administrations, namely: ImmunoGam for intramuscular (i.m.) use for the immunoprophylaxis of hepatitis B; and for intravenous (i.v.) use for the prevention of hepatitis B virus recurrence after liver transplantation in HBsAg-positive patients. Following a number of issues raised during the assessment procedure the applicant withdrew the intravenous use indication for prevention of hepatitis B virus recurrence from the application.

The approved indication for ImmunoGam is:

Immunoprophylaxis of Hepatitis B

- In case of accidental exposure in non-immunised subjects (including persons whose vaccination is incomplete or status unknown).
- In haemodialysed patients, until vaccination has become effective.
- In the newborn of a hepatitis B virus carrier-mother.
- In subjects who did not show an immune response (no measurable hepatitis B antibodies) after vaccination and for whom a continuous prevention is necessary due to the continuous risk of being infected with hepatitis B.

Consideration should also be given to other official guidance on the appropriate use of human hepatitis B immunoglobulin for intramuscular use.

The clinical development of ImmunoGam for immunoprophylaxis of hepatitis B included two biopharmaceutical studies (HB-002 and HB-008) to examine the pharmacokinetics and bioavailability in healthy adults, and an efficacy study (HB-004). In the healthy volunteer studies ImmunoGam pharmacokinetics and safety was compared to two other HBIG products licensed in North America. An overview of the clinical studies submitted in support of the claimed indication is provided in Table 1.

Table 1 Overview of clinical studies with ImmunoGam

Study ID	No. of study centres / locations	Design	Study Posology/ Route	Study Objective/ Comparator	Subjects Number	Duration
HB-002	1 center in Canada	Randomized, single-blind parallel arm study	Single dose Test: 50 mg/ml 0.06 ml/kg (19 IU/kg) / IM	1. To comparatively assess the pharmacokinetic characteristics of ImmunoGam and BayHep B 2. Safety / BayHep B (Bayer, Talecris)	Normal healthy volunteers: 70 enrolled, 61 received and 60 completed (30 per arm)	84 days
HB-008	1 center in USA	Double-blind randomized with 2 parallel arms	Single dose in 7 dosing cohorts. 0.06 ml/kg (19 IU/kg) / IM	1. To establish comparative PK of ImmunoGam and Nabi-HB 2. Safety / Nabi-HB (Nabi, Baxter)	Normal healthy volunteers: 80 enrolled, 75 completed and 5 discontinued	84 days
HB-004	Vertical: Multicentre (India); Horizontal:	Open-label, non-randomized historically controlled	Infants: Single dose: 0.5 ml within 12 h of birth; Adults:	Safety and efficacy of ImmunoGam used in combination with Hepatitis B vaccine, for the prevention of Hepatitis B infection /	253 infants enrolled and dosed. 178 completed and included in PP analysis. 75 infants excluded. All 253 were	Up to one year post-treatment for infants;

	Multicentre (Canada, Brazil)	study.	Single dose: 0.06 mL/kg within 48 hours of potential exposure / IM	N/A	in the safety analysis. Adults: 42 subjects enrolled and dosed. 23 compl. subjects as PP analysis. 19 excluded. All 42 subjects were in safety analysis.	180 days post-exposure in adults.
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Current recommendations for immunoprophylaxis of hepatitis B are based on national guidelines, which rely on published studies and clinical practice. It is noteworthy that the recommendations on doses of HBIG for immunoprophylaxis of hepatitis B are based on the Core SPC recommendations with consideration given to national official guidance in individual EU countries.

The clinical development program for ImmunoGam was essentially designed for approval by the FDA (USA) and Health Canada, respectively. There are several CHMP guidance documents, but those of specific relevance to hepatitis B immunoglobulin products became available some time after the applicant had initiated the development program. The guideline on the Core SPC for human plasma derived hepatitis B immunoglobulin for intramuscular use (CPMP/BPWG/4222/02) has been in effect since November 1, 2006. Other CHMP guidelines that have been taken into account during the evaluation provide a general framework for the efficacy and safety assessment, e.g. guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004). Of note, no guideline for the clinical development of hepatitis B immunoglobulin products is currently available in the EU. No separate paediatric development has been described by the applicant.

GCP

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

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The EMEA conducted routine GCP inspections of several sites involved in the clinical trials submitted in the initial application for marketing authorisation:

- The results of the inspection of selected sites from the HB-004 study in India were satisfactory and the study was deemed to be acceptable for assessment purposes.
- The inspection at the site of the pivotal HB-005 study (Turkey) in support of the originally claimed intravenous use indication for prevention of hepatitis B virus recurrence identified a series of observations, including a critical finding on the reliability of the study. Data from this site was deemed unreliable for the assessment purpose.

Pharmacokinetics

ImmunoGam solution for injection is intended for intramuscular administration for the immunoprophylaxis of hepatitis B. In the submitted dossier, the applicant provided two comparative bioavailability studies (study HB-002 and study HB-008, Table 1). In both studies, the bioavailability of ImmunoGam after IM injection in healthy volunteers was compared to two hepatitis B immunoglobulin products licensed in North America. The primary differences between the HB-002 and the HB-008 studies were the choice of anti-HBs assays and the comparator products.

In the PK development program three different analytical techniques were employed for the estimation of serum levels of anti-HBs immunoglobulins and the potency in the investigated drug-products: In study HB-002 two different anti-HBs assays were employed one in-house for drug-product potency and one commercial kit for anti-HBs serum levels. In study HB-008 a commercial kit was used for the estimation of serum levels as well as for the measurement of drug-product potency. The applicant provided a validation report and justification for the potency correction factors utilised in the studies.

- Absorption / Distribution / Elimination

Single-dose studies:

Both PK studies provide an acceptable picture of the anti-HBs Ig of the tested products. The anti-HBs Ig is adequately absorbed after i.m. injection. The results of both HB-002 and HB-008 indicate that despite some differences in PK parameters due to difference in the product potency and use of different analytical techniques across studies, ImmunoGam has PK properties of a typical immunoglobulin product intended for intramuscular use with C_{max} well above 100 mIU/mL, half-life of 22-25 days and T_{max} of 4-5 days. These results are broadly in line with those seen with other intramuscular immunoglobulin products. The maximum plasma level is reached 3-6 day after injection. The anti-HBs Ig is slowly cleared with an elimination half-life of around 3 to 4 weeks. Low inter-subjects variability of PK parameters was observed in both studies (around or less than 20 %). Two months (56 days) after single injection of approximately 21 IU/kg (study 1) or \approx 40 IU/kg (study 2), the serum levels of anti-HBs Ig is higher than the protective 10 mIU/ml in all subjects.

The main findings of study HB-002 are tabulated below:

Parameter (unit)	Mean \pm SD Treatment T (n=30)	Mean \pm SD Treatment R (n= 30)	Ratio T/R (90% Confidence Interval)
AUC _{last} (mIU*.day/mL)	7521 \pm 1550	5418 \pm 1255	140% [126%, 154%]
AUC (mIU*.day/mL)	8477 \pm 1937	6209 \pm 1415	136% [123%, 151%]
C_{max} (mIU/mL)	215.6 \pm 41.1	157.2 \pm 35.4	138% [126%, 151%]
t_{max} (day)	5.4 \pm 2.4	6.6 \pm 2.6	-
$T_{1/2}$ (day)	24.5 \pm 4.6	24.4 \pm 5.2	-

T : Test (NP-002); R : Reference (BayHep B)

Repeat-dose investigations:

No PK repeat-dose studies were performed. There is no current requirement for the conduct of such studies and extrapolation proposed by the applicant based on the modelling approach is considered sufficient.

Modelling for single dose immunoprophylaxis in adults and children

To determine if the proposed posology is sufficient to maintain titres above the protective level of 10 mIU/mL, 10,000 patients were simulated by the applicant using the distributions of pharmacokinetic parameters. The simulations took into consideration different scenarios, utilizing the variable dose of 0.06 mL/kg and a fixed dose of 1.6 mL (500 IU). In addition both the label-claim potency and the potency of the lots of ImmunoGam administered in the clinical studies were utilized. In addition, clinical trial lot potencies were compared to production lot potencies for sensitivity analysis. The modelling data supports that an immunoprophylaxis dose in children and adults will provide protective titres of 10 mIU/mL beyond 30 days after dosing. Using the minimum label claim potency of 312 IU/mL and the actual potencies within the manufacturing capabilities, all modelled patients have protective titres of \geq 10 mIU/mL at 30 days post-dosing and 60 – 93 % of modelled patients achieve \geq 10 mIU/mL at 60 days post-dosing.

Modelling for continuous (repeat-dose) immunoprophylaxis in adults and children

The applicant originally proposed a dose of 19 IU/mL in children based on the North American guidelines. This dose of 19 IU/mL is lower than the newborn dose of 156 IU. However, the Core SPC also recommends a lower dose, 8 IU/kg every 2 months, as compared to the birth dose of 30-100 IU/kg. This dosing discrepancy is explained by both the intensity of exposure, which is anticipated to be very high in the case of a neonate exposed to a hepatitis B positive carrier mother during birth, and the duration of sustaining protective anti-HBs levels, which for a newborn may be up to completion of the vaccination series.

The modelling in adults predicted that with nominal potency of ImmunoGam of 312 IU/ml at least 98.3% and 60% of adults will have >10 mIU/mL levels of anti-HBs at Day 30 and 60, respectively.

To investigate the adequacy of an 8 IU/kg dose in children, a pharmacokinetic modelling and simulation study was conducted. To predict the pharmacokinetic behaviour of ImmunoGam in children, the model created for adult patients was scaled allometrically by weight. The results were used to predict PK outcomes for non-neonate paediatric (older than one year) patients in the weight range of 10 to 50 kg. First, a sampling of weights was created, using a uniform distribution between the 10 and 50 kg limits. When the 8 IU/kg dose is modelled, >99.8% of simulated patients have protective levels of anti-HBs greater than 10 mIU/mL at 30 days after ImmunoGam administration. Sixty days after ImmunoGam administration, modelling demonstrates that 46– 89% of children are predicted to have an anti-HBs antibody level ≥ 10 mIU/mL, based on minimum (312 IU/ml label claim) or actual trended potencies.

- Dose proportionality and time dependencies

Dose proportionality was not investigated. As only single-dose studies were performed, no information regarding time dependency could be drawn from the investigations carried out by the applicant.

- Special populations

No studies were performed in special populations; however it is reasonable to extrapolate the efficacy of ImmunoGam from other available evidence (PK studies HB-002, HB-008 and study HB-004). In addition, the immunoprophylaxis duration will be guided by levels of anti-HBs estimated during monitoring of patients. Based on modelling simulations provided by the applicant, it is reassuring that the level of anti-HBs >10 mIU/mL is predicted in >98% of adults and children at Day 30 following the administration of HBIG.

- Pharmacokinetic interaction studies

No interaction studies have been conducted. Current WHO recommendations include combination of the vaccination against hepatitis B along with passive immunoprophylaxis in cases of acute post-exposure prophylaxis in high risk groups, e.g. healthcare personnel.

- 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 (PD) study for ImmunoGam conducted by the applicant. This is appropriate for this type of product as the efficacy of HBIG products was previously well studied and published in evidence-based literature. The mechanism of action of HBIG 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. Refer to section Non-clinical aspects for details on the mechanism of action of HBIG.

Clinical efficacy

The clinical development of ImmunoGam for immunoprophylaxis of hepatitis B included one efficacy study (HB-004). The study was conducted in two immunoprophylaxis populations - accidental exposure in adults (horizontal exposure) and neonatal exposure to HBsAg-positive mothers (vertical exposure). Study HB-004 was originally designed for the horizontal (adult to adult) exposure to hepatitis B but it was later amended to include a vertical (mother to infant) population. The horizontal arm was prematurely terminated due to poor recruitment. Conclusions regarding the efficacy of ImmunoGam in post-exposure prophylaxis are based on the results of the vertical arm and the results

for the horizontal arm, which are presented in a supplemental report (HB-004s), and are intended to provide supportive evidence of efficacy.

It should be noted that none of the clinical studies has been conducted with the intended commercial product using the 20 nm viral filter however, comparability studies using the clinical trial material (35 nm) and the commercial product were accepted.

- Dose response study

There were no dose finding studies conducted for this submission. Posology differences persist in the national recommendations of the Centers for Disease Control and Prevention (CDC) (USA) and CHMP (EU), and the applicant's submission was acceptable.

- Main study(ies)

Study HB-004 - Immunoprophylaxis of Hepatitis B (horizontal and vertical arm)

METHODS

Study Participants

In the **vertical arm** pregnant women were screened for HBsAg status. Following consent from pregnant women at 5-9 months of gestation, a rapid HBsAg test was performed. A positive HBsAg test was verified by ELISA. Following delivery, all healthy infants identified as eligible received a HBIG and Hepatitis B vaccine within 12 hours from delivery.

Inclusion Criteria allowed normal healthy newborn infants within 12 hours of birth negative for IgM anti-HBc*, HBsAg* and anti-HBs*, whose mother must be HBsAg-positive. The serology status of the infant may not have been known at time of dosing (delayed entry criteria). Since the results for certain tests (*) may have taken longer than 12 hours, the infant was enrolled into the study and treated, in the interest of infant's safety. If the test results indicated that the subject was positive for any of the exclusion criteria, the subject was considered as "not evaluable", and was excluded from the PP analysis.

Most important Exclusion Criteria: infants for whom HBsAg data was not available from the mother; concurrent viral or other systemic infections, requirements antiviral therapy; under weight (<2.0 kg) or pre-term (<37 weeks gestation) infant; evidence of clinically significant medical conditions including, but not limited to hepatic, renal, cardiac insufficiency, haematological or neoplastic diseases; mother positive for HCV or HIV*.

In the **horizontal arm**, healthy males and females of 18-55 years of age were included who were potentially exposed to HBV in the 48 hours prior to dosing (accidental, sexual, or household). Main exclusion criteria included history of hypersensitivity to blood or blood products, history of exposure in past 6 months to viral hepatitis other than hepatitis B, HBV, HIV or HCV positive tests.

Treatments

Enrolled infants of HBsAg-positive mothers were administered a single dose 0.5 ml of ImmunoGam (312 IU/ml) along with the hepatitis B vaccine (Engerix B) intramuscularly within 12 hours of birth. Infants received a 0.5 ml injection of ImmunoGam in the anterolateral thigh as well as a 0.5 ml injection of hepatitis B vaccine at a different IM site. The infants also received follow-up injections of hepatitis B vaccine at Day 30 and Day 180, as directed in the vaccine labelling. An additional vaccine dose was administered at Day 270 for those infants who did not have sufficient anti-HBs at Day 180.

Subjects enrolled in the horizontal arm who were potentially exposed to HBV were administered a single dose of ImmunoGam (0.06 ml/kg) and hepatitis B vaccine (Recombivax HB or Engerix- B) intramuscularly within 48 hours of exposure. ImmunoGam and hepatitis B vaccine were given at

different intramuscular (IM) sites. The subjects also received follow-up injections of hepatitis B vaccine at Day 30 and Day 180, as directed in the vaccine product information.

Objectives

The study objectives were to assess safety and efficacy of ImmunoGam used in combination with hepatitis B vaccine, for the prevention of hepatitis B infection following vertical or horizontal exposure to the HBV.

Outcomes/endpoints

The primary endpoint of HB-004 study was the overall protection rate provided by ImmunoGam in combination with hepatitis B vaccine. The failure to protect from hepatitis B infection is measured by the appearance of HBsAg at any time point following ImmunoGam administration. The protection rate is defined as the proportion of infants/subjects who do not develop a positive HBsAg result.

Secondary endpoints included:

- Proportion of infants or adults and time to development of a positive HBeAg result at any time during the study period after baseline was calculated (HBeAg was only measured to Day 90 as per protocol);
- Time to development of detectable HBsAg in serum (HBV occurrence in days);
- Proportion of vaccine responders.

Sample size

Study HB-004 was originally designed in a horizontal (adult to adult) exposure population but it was later amended to include a population that was vertically (mother to infant) exposed to hepatitis B. It was anticipated that approximately 200 and 175 subjects would be enrolled into the vertical and horizontal arms of the study, respectively, in order to attain 155 evaluable subjects in one of the study arms. The population (vertical or horizontal) achieving the recruitment goal first would be analyzed for efficacy, while the other arm would provide supportive data only.

Assuming a true protection rate of 97%, 155 subjects provide 80% power to show non-inferiority, where non-inferiority is declared if the lower limit of a 95% two-sided confidence interval using the exact binomial distribution is greater than 92% (i.e. a type I error of 2.5% was assumed).

Randomisation / Blinding (masking)

The study design was a single arm, open label trial; therefore, no randomisation or blinding procedures did apply.

Statistical methods

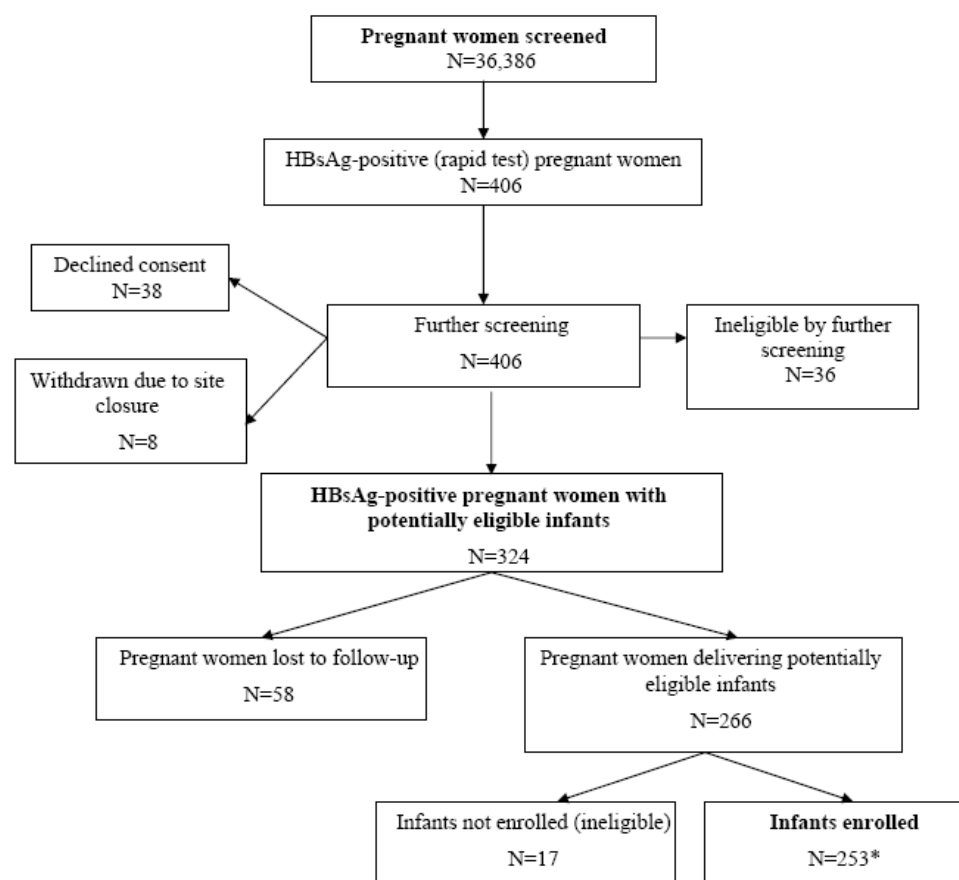
The study was described by the applicant as an uncontrolled non-randomized open trial comparing the protective efficacy of combined HBIG and vaccine use during the vertical transmission of HBV against historical reference data. The pre-specified reference of a protective level of 97% was based on data from a study on the vertical transmission of HBV from HBsAg-positive/HBeAg-positive mothers to infants in Thailand and the protection rate of around 95% afforded with a combined administration of HBIG and vaccination schedule of Engerix B (at 0, 1 and 6 months) (Poovorawan *et al.*, 1997). Proportions and two-sided 95% confidence intervals were calculated using the exact binomial distribution. The confidence interval for the primary endpoint was compared to the reference protection rate of 0.97 with the margin of equivalence set at 0.05.

RESULTS (VERTICAL ARM)

As discussed in both the protocol and the SAP, since the horizontal arm of study HB-004 did not meet the target enrolment, the efficacy analyses were performed but no conclusions regarding efficacy of NP-002 were based on these analyses. All efficacy conclusions for study HB-004 are based on the

results from the vertical arm which are presented in a separate clinical study report. Therefore, the results of the horizontal arm which are considered supportive in this application and results from both arms are presented separately in this report.

Participant flow



* 4 sets of twins

Figure 1 Participant flow – Pregnant women (HB-004)

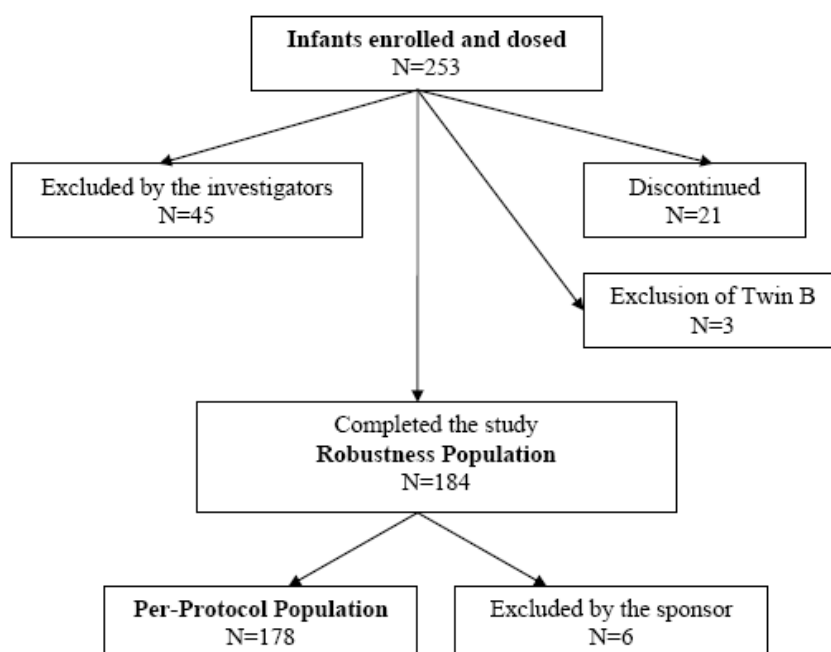


Figure 2 Participant flow – Infants (HB-004)

Recruitment

In the vertical arm, the first infant was dosed on November 17, 2003 and the last infant completed on July 3, 2006.

Conduct of the study

Substantial changes have been made in the statistical analysis plan of this HB-004 study. The horizontal arm of this study was terminated prematurely following recruitment failure. There was an interim analysis planned in the study but the applicant stated that it has not been carried out.

Baseline data

A summary of the overall demographic characteristics in both arms is presented in Table 2 and 3. All infants were born between November 16, 2003 and July 16, 2005 and were dosed within 12 hours of birth. All of 249 mothers were tested positive for HBsAg at baseline.

Table 2 Summary of infant demographics (vertical arm)

Characteristic	Variable	
Gender	Male	137 (54.2%)
	Female	116 (45.8%)
Race/Ethnicity	Asian	253 (100%)
Age of Mother (years)	Mean (SD)	24.0 (4.1)
	Range	16.4 – 36.9
Weight (kg)	Mean (SD)	2.8 (0.4)
	Range	2.0 – 4.5

Numbers analysed

Two analysis populations were used: per-protocol (PP) and safety populations. The safety population in the vertical arm (n=253) was used for all safety assessments and includes all infants who received ImmunoGam, including infants who did not complete the study. The PP population consisted of 178 infants who received ImmunoGam and completed the study as per protocol and was the population used for the primary analysis and to generate the study conclusions. Efficacy data was also available from 6 infants who were ineligible to enter the study. In addition, three infants (one from each of the three sets of twins) were excluded in order to maintain an independent population for all statistical analyses. Data from all 184 infants who completed the study (excluding the three twins) were included in the robustness analysis.

Outcomes and estimation

Primary efficacy analysis:

The primary endpoint for this study was the overall protection rate provided by ImmunoGam in combination with hepatitis B vaccine. The protection rate is defined as the proportion of infants who do not develop a positive HBsAg result (at any time during the study period) following vertical exposure to hepatitis B. The summary of the HBsAg results in the vertical arm is presented in Table 3.

Table 3 Summary of Infant Serology Results over Time – PP population

Viral Marker	Visit	N*	Positive (%)
HBsAg	Baseline	178	0 (0.0)
	Day 30	178	0 (0.0)
	Day 90	174	0 (0.0)
	Day 180**	178	3 (1.7)

	Day 270**	175	2 (1.1)
	Day 365	178	0 (0.0)
HBeAg	Baseline	162	1 (0.6)
	Day 30	177	0 (0.0)
	Day 90	171	0 (0.0)

* N=Total Number of Infants with Test Result at Each Visit WD Day 180 and WD Day 365 are Reported with the Corresponding Scheduled Visit Day 180 and Day 365. WD = Withdrawal

**Note: 1 patient had 2 HBsAg-positive test results (1 at Day 180 and 1 at Day 270)

An overall summary of the results is presented below by analysis population.

Table 4. Summary of Overall ImmunoGam Protection Rate (vertical arm).

Population	N	Protection Rate	95% Confidence Interval*
Per-Protocol	178	0.978	(0.944, 0.994)
Robustness	184	0.978	(0.945, 0.994)

*Exact confidence interval limits for the binomial proportion using the *F* distribution method

For both PP and robustness analyses four infants became HBeAg positive at any point in the study, thus the overall protection rate achieved was 0.98 (174/178) with a corresponding 95% confidence interval of (0.94, 0.99). The lower 95% confidence bound for the calculated protection rate is greater than 0.92 and therefore the study objectives were achieved.

Secondary efficacy analysis

- Appearance of HBeAg

The proportion of infants with detectable HBeAg (at any time after baseline) was computed along with a 95% confidence interval. None of the infants in the study became HBeAg-positive, therefore the proportion was 0% (0/178). A summary of the HBeAg results by study visit is presented in the Table 3.

Of note, one infant included in the PP population was HBeAg positive at birth (prior to NP-002 dosing). The infant likely became HBeAg positive from his mother who was also HBeAg-positive at birth. The infant had no evidence of infection *in utero* or during the course of the study. HBeAg has been demonstrated to cross placenta *in utero*. All subsequent HBeAg results were negative for this subject, and hence this subject was not regarded as an endpoint for HBeAg.

- Time to Occurrence of HBsAg and HBeAg

The secondary endpoints of time-to-occurrence of HBsAg and HBeAg are based on the first detectable serum HBsAg (or HBeAg) result. The time to occurrence (in days) was calculated for infants from the date of birth to the actual date of the first positive HBsAg (or HBeAg) result. A summary of the HBsAg and HBeAg results by study visit is presented in Table 3. All infants who did not develop detectable HBsAg (or HBeAg) were censored at their last study visit. As only 4 infants of the 178 infants evaluated developed detectable HBsAg (Days 179, 181, 185 and 270) and none of the 178 infants developed detectable HBeAg, the median time to occurrence and 95% confidence interval were not calculable. All occurrences happened between 179 and 270 days while all censoring took place between 346 and 460 days.

- Anti-HBe, Anti-HBc, and Anti-HBs Levels

Additional hepatitis B markers were tabulated as part of secondary endpoints. Summary statistics for anti-HBe, anti-HBc (total) and anti-HBc (IgM) antibodies over time were calculated.

Summary statistics for anti-HBs over time are presented in Table 5.

Infants acquire anti-HBe or anti-HBc (IgG) antibodies passively from their mothers either *in utero* or through breast-feeding. In addition, infants may develop their own anti-HBe from exposure to maternal HBeAg, which can cross the placenta. Anti-HBe results available for Days 180, 270, and 365 visits demonstrated that 71% of the infants were anti-HBe-positive at Day 180 and by Day 365 only 26% were positive. Anti-HBc (total) was positive in the vast majority of infants until Day 180 (89-99%), and began to decline with 11% positive at Day 365. The decline in anti-HBe and anti-HBc (total) by the end of the study likely corresponds to a decrease in breast feeding. Anti-HBc (IgM), indicating a new HBV infection, was detected in one of the four HBsAg-positive infants and not detected in any of the other infants enrolled.

Anti-HBs levels indicate long-term immunity. The mean anti-HBs increased from baseline over the course of the study in a biphasic fashion. (Table 5). The first increase was seen at Day 30, likely due to ImmunoGam administration, followed by a decrease as ImmunoGam was cleared from the body and subsequent gradual increase due to HBV vaccination providing long-term immunity.

Table 5 Summary of Anti-HBs Results Over-time – PP Population

Visit	N	Mean (SD) (mIU/ml)	Range ¹
Baseline	178	0.3 (1.1)	0.0 – 7.6
Day 30	178	217.1 (163.5)	15.9 – 2260.0
Day 90	174	92.7 (152.2)	15.0 – 1307.0
Day 180	178	216.8 (369.0)	0.0 – 2000.0
Day 270	175	853.0 (723.4)	0.0 – 2000.0
Day 365	178	630.4 (650.4)	0.0 – 2000.0

¹ Undetectable levels (<3.0) were set to 0.0 for summary purposes.

Ancillary analyses

As efficacy data was available for 6 infants who did not meet all inclusion/exclusion criteria, a robustness analysis was performed where these infants were included. It can be seen that the results for the per-protocol and robustness populations are nearly identical.

This confirms that the effect of excluding this subset of infants from the PP population on the study results is negligible.

RESULTS (HORIZONTAL ARM)

Participant flow

Of 42 subjects enrolled and dosed in the horizontal arm, ten subjects discontinued, nine were excluded by the investigators and 23 subjects completed the study (per-protocol population).

Recruitment

The first subject in the horizontal arm was dosed on November 1, 2002 and the last subject completed on December 4, 2003.

Baseline data

Table 6 Summary of demographics in horizontal arm

Characteristic	Variable	
Gender	Male	17 (40.5%)
	Female	25 (59.5%)
Race/Ethnicity	Asian	1 (2.4%)
	Black	3 (7.1%)
	Caucasian	27 (64.3%)
	Hispanic	6 (14.3%)

	Native	1 (2.4%)
	Other	4 (9.5%)
Age (years)	Mean (SD)	37.8 (10.3)
	Range	20.5 - 57.4

Numbers analysed

In the horizontal arm, the PP population consisted of 23 subjects who received ImmunoGam and completed the study as per protocol and is the population used for the primary efficacy analysis. Nine subjects were excluded from the efficacy analysis by the investigators and an additional 10 subjects either withdrew from the study or were lost to follow-up. The safety population (n=42) is used for all safety assessments and includes all subjects who received ImmunoGam, including subjects who did not complete the study.

Outcomes and estimations

In the horizontal arm, none of the subjects became HBsAg positive during the study. Thus, a 1.0 (23/23) protection rate was achieved with a corresponding 95% confidence interval of (0.85, 1.00) using the exact binomial method. None of the subjects in the horizontal arm became HBeAg positive, therefore the proportion was 0 (0/23) with a corresponding 95% confidence interval of (0.00, 0.18). Summary statistics for anti-HBe, anti-HBc (IgG) and anti-HBc (IgM) antibodies over time in the horizontal arm were calculated.

Table 7 Summary of Serology Results over Time - Safety Population (horizontal arm)

Viral Marker	Visit	N	Positive (%)
HBsAg	Baseline*	42	1 (2.4)
	Day 30*	30	1 (3.3)
	Day 90	27	0 (0.0)
	Day 180	23	0 (0.0)
	Early WD*	8	1 (12.5)
HBeAg	Baseline	162	1 (0.6)
	Day 30	177	0 (0.0)
	Day 90	171	0 (0.0)

WD = Withdrawal

* Three HBsAg-positive results were from 1 patient who was HBsAg-positive at baseline (i.e. HBV infection prior to entry into study HB-004S). This patient was withdrawn as soon as the entry criterion violation was detected.

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

A meta-analysis of historical clinical data from studies with HBIG products has been provided by the applicant (Lee et al. (2006)).

This meta-analysis found that hepatitis B immunoglobulin alone or when added to hepatitis B vaccine decreased the risk of hepatitis B infection (0.52, 0.44 to 0.63). Conclusively, the current immunisation advice remains that HBIG are “immediately effective and seem protective for several months, after which the efficacy wanes”.

- Clinical studies in special populations

No studies were performed with ImmunoGam in special populations.

Clinical safety

- Patient exposure

The overall extent of exposure to ImmunoGam in the applied for indication is presented in Table 8.

Table 8 Overall extent of exposure in post-exposure prophylaxis.

Study	Study Population	Number of Subjects	ImmunoGam Dose and Route
PK Study 1	Healthy adults	30	0.06 ml/kg IM
Efficacy Study	Neonates born to HBsAg-positive mothers (vertical arm)	253	0.5 ml IM
Efficacy Study-Supplement	Adults potentially exposed to HBV (horizontal arm)	42	0.06 ml/kg IM
PK Study 2	Healthy adults	40	0.06 ml/kg IM

- Adverse events / Serious adverse events / deaths

Study	Number of AEs	Number of subjects with AEs	SAEs/ subjects	Deaths
PK Study 1	43 (25 in ImmunoGam; 18 in comparator)	23 (12 in ImmunoGam; 11 in comparator)	0	0
PK Study 2	12	11	0	0
Efficacy Study-	531	159	43/38*	1
Efficacy Study-Supplement	69	25	0	0

* Some cases contained multiple SAE terms within a single case.

In the PK studies a total of 55 AEs were reported in 34 patients irrespective of treatment; of those AEs 47 were mild and 8 were moderate. No serious adverse events were reported in both studies. The most common adverse events after ImmunoGam administration were headaches and nasopharyngitis. A total of 30 adverse events were reported by 17 (24%) of the subjects who were administered ImmunoGam in both studies. Eleven (37%) subjects who were administered BayHep B reported 18 adverse events and 6 (15%) subjects who were administered Nabi-HB reported 7 adverse events.

In both the ImmunoGam and the Nabi-HB group, the organ system with the highest occurrence of adverse events was the nervous system disorders. In the BayHep B group, respiratory, thoracic and mediastinal disorders was the system organ class with the highest number of adverse events. Only one adverse event, nausea, was reported to be related to the study drug, in a subject who was administered ImmunoGam in PK study 2.

In the Efficacy study, a total of 531 adverse events were reported from 159 of the infants (63%) over the duration of the study. 478 of the adverse events were mild, 40 were moderate and 12 were severe. A total of 43 serious adverse events terms were captured on CRFs for 38 infants. The most common adverse events amongst infants in this study were diarrhoea (57 events) and pyrexia (52 events). Only one adverse event was regarded as possibly related to ImmunoGam; the adverse event was indurations in right and left thighs. No action was taken and the adverse event was resolved after 2 days. One infant death was reported in this study and considered to be unrelated to ImmunoGam. Amongst SAEs in infants the majority of events included gastroenteritis, infections, sepsis, and neonatal jaundice unrelated to ImmunoGam.

In the horizontal arm of the study, a total of 69 adverse events were reported by 25 subjects (60%) over the duration of the study. The most common adverse event amongst adults in this study was headache which was reported by 9 subjects. Nausea, pyrexia, arthralgia and myalgia were also AEs which were experienced by more than 5% of subjects in this study. A total of 46 adverse events were mild, 14 were moderate and 1 headache was categorized as severe. Related adverse events included

nausea, fatigue, malaise, pain, pyrexia, hypersensitivity, arthralgia, back pain, myalgia, headache, and dizziness. No SAEs were reported during this study.

- Laboratory findings

In the IM route immunoprophylaxis studies, most of laboratories findings were within normal range.

- Safety in special populations

Studies in special populations were not conducted with ImmunoGam.

- Safety related to drug-drug interactions and other interactions

No data on drug-drug interactions is available specifically for ImmunoGam. Information on potential interactions of immunoglobulins in general, such as a potential interference with the development of an immune response to live attenuated virus vaccines, is included in the SPC.

- Discontinuation due to adverse events

One subject was withdrawn from the study due to experiencing a facial rash which was reported on study day 7. The rash was assessed as moderate in intensity and assessed by investigator to be unlikely caused by ImmunoGam administration.

- Post marketing experience

As of June 25, 2008, there have been two post-marketing adverse event reports from use of ImmunoGam in North America, which were both expected adverse events: dyspepsia (Gastrointestinal disorders) and back pain (Musculoskeletal and connective tissue disorders). These adverse events are described in the SPC.

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 MAH submitted a risk management plan.

Safety concern	Proposed Pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
<u>Important potential risks (product specific)</u>		
Blood Glucose False Positive Hypoglycaemia (Masked hypoglycaemia) Hypoglycaemia (Life threatening hypoglycaemia)	<ul style="list-style-type: none"> • Routine Pharmacovigilance Signal detection Investigation of possible confounding condition that precipitate or	<u>Labelling information</u> SPC section 4.5: Interaction with other medicinal products and other forms of interaction “Some types of blood glucose testing systems (for example, those based on the glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase methods) falsely interpret the maltose contained in ImmunoGam as glucose. This may result in falsely elevated glucose readings and consequently in

Safety concern	Proposed Pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	exacerbate potential complications	the inappropriate administration of insulin, resulting in life-threatening hypoglycaemia. Also, cases of true hypoglycaemia may go untreated if the hypoglycaemic state is masked by falsely elevated glucose readings. Accordingly, when administering ImmunoGam or other parenteral maltose-containing products, the measurement of blood glucose must be done with a glucose-specific method. The product information of the blood glucose testing systems, including that of the test strips, should be carefully reviewed to determine if the system is appropriate for use with maltose-containing parenteral products".
Important potential risks (class related)		
Hypersensitivity	<ul style="list-style-type: none"> Routine Pharmacovigilance 	<p><u>Labelling information</u></p> <p>4.3 Contraindications</p> <p>Hypersensitivity to any of the components.</p> <p>Hypersensitivity to human immunoglobulins, especially in very rare cases of IgA deficiency when the patient has antibodies against IgA.</p> <p>4.4 Special warnings and precautions for use</p> <p>Ensure that ImmunoGam is not administered into a blood vessel, because of the risk of shock.</p> <p>True hypersensitivity reactions are rare.</p> <p>ImmunoGam contains a small quantity of IgA (less than 40 micrograms/ml). Individuals who are deficient in IgA have the potential for developing IgA antibodies and may have anaphylactic reactions after administration of blood components containing IgA. The physician must therefore weigh the benefit of treatment with ImmunoGam against potential risk of hypersensitivity reactions.</p> <p>Rarely, human hepatitis B immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who have tolerated previous treatment with immunoglobulin.</p> <p>Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the injection. In case of shock, standard medical treatments for shock should be implemented.</p>
Transfusion-related Acute Lung Injury (TRALI) Acute Acute Respiratory Distress Syndrome (ARDS)	<ul style="list-style-type: none"> Routine Pharmacovigilance 	None

Safety concern	Proposed Pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Aseptic meningitis	<ul style="list-style-type: none"> Routine Pharmacovigilance 	None
Renal impairment	<ul style="list-style-type: none"> Routine Pharmacovigilance 	None
Embolism (pulmonary embolism, deep vein thrombosis)	<ul style="list-style-type: none"> Routine Pharmacovigilance 	None
Haemolytic anaemia	<ul style="list-style-type: none"> Routine Pharmacovigilance 	None

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

ImmunoGam 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.

The applicant has demonstrated adequately the consistency and robustness of the manufacturing process. The results of tests carried out for the control of the drug substance and drug product indicate satisfactory consistency and uniformity of important quality characteristics.

Non-clinical pharmacology and toxicology

As immunoglobulins are normal constituents of the human body, and in the absence of a suitable animal model in which to test ImmunoGam, the lack of a full toxicology programme was considered acceptable. The use of the single-dose toxicity and immunotoxicity data from WinRho another hyperimmune IgG product manufactured by an almost identical process, was accepted as a reasonable approach and there is no reason to assume that the different immunoglobulin will influence the toxicity. The absence of local tolerance data is acceptable and no further studies were considered necessary. The review of the toxicity data on the excipients, solvent and detergent is satisfactory.

For TNBP, the margin over the NOAELs on an applied dose basis for general toxicity in mice is 5,300 and for rats it is 2,100 based on the maximum daily exposure of 5 µg/kg/day; for embryo-fetal development, it is 80,000. For Triton X-100, the margin on an applied dose basis over the NOAEL for general toxicity is 4,700 and for the dose at which effects were seen on developmental toxicity it is 8,300. Although different routes of administration are involved, these margins indicate that any risks from traces of the solvent and detergent will be negligible.

Given the clinical experience with ImmunoGam, for which marketing licence was first granted January 2006 in the USA, the information provided on toxicology is sufficient.

Efficacy

ImmunoGam provides passive immunisation for individuals exposed to the hepatitis B virus. According to the WHO and national European guidelines, human hepatitis B immunoglobulin remains an essential component of the passive immunisation protection of infants during vertical transmission following birth and of any subjects following accidental exposure to hepatitis B (sexual, and

percutaneous route of transmission) when the concomitant administration with vaccine allows the maintenance of a reasonable level of protective anti-HBs antibodies (>10 IU/l) while the host is initiating an immunological response to vaccine.

A level of anti-HBsAg of 10 IU/L is usually accepted as the lower limit that still confers protection. Therefore, in order to make comparisons to historical data and infer evidence of efficacy, characterisation of PK is of importance. The PK profile of ImmunoGam after single administration was determined using a product manufactured by the 35 nm filter process, which is different to the product to be marketed (20 nm filtration). The comparability between different versions of the product was sufficiently demonstrated.

The applicant has conducted pharmacokinetic studies HB-002 and HB-008, which have demonstrated that ImmunoGam has PK properties of a typical immunoglobulin product intended for intramuscular use. The anti-HBs Ig is slowly cleared with an elimination half-life of around 3 to 4 weeks. Despite the fact that the drug products investigated in studies HB-002 and HB-008 are different from the product to be marketed, the applicant provided comparability data between batches produced using 35 nm and 20 nm filters which reassure that the finally marketed product will have a similar PK profile to the one observed in the HB-002 and HB-008 studies. The release specifications for the finally manufactured product comply with Ph. Eur for intramuscular immunoglobulin products. The applicant is asked to provide some PK data with the commercial product from a limited subset of patients as a follow-up measure.

To determine if a dose evaluated in studies HB-002 and HB-008 can be effectively bridged to the posology proposed by the CHMP Core SPC in terms of the maintenance of titres above the protective level of 10 mIU/mL, 10,000 patients were simulated by the applicant using the distributions of pharmacokinetic parameters. The simulations took into consideration different scenarios, utilizing the variable dose of 0.06 mL/kg and doses proposed by CHMP Core SPC. The modelling data supports an immunoprophylaxis dose in children and adults that will provide protective titres of 10 mIU/mL beyond 30 days after dosing in single dose and continuous (repeat use) settings. Using the minimum label claim potency of 312 IU/mL and the actual potencies within the manufacturing capabilities, all modelled patients have protective titres of ≥ 10 mIU/mL at 30 days post-dosing and 60% of modelled patients achieve ≥ 10 mIU/mL at 60 days post-dosing.

The application included the results of one Phase 3 efficacy trial. Study HB-004 contained a vertical and a horizontal arm which enabled it to produce clinical data in both infants and adults. The study was open and non-randomized in nature and compared protection rates to the published historical reference. The endpoints for both vertical and horizontal arms were the same and the choice of endpoints in the study was acceptable, except for one secondary endpoint, HBeAg, which was not monitored beyond Day 90 as per protocol.

In relation to the immunoprophylaxis in infants, the combined efficacy of ImmunoGam and vaccination was demonstrated using PP analysis and protective rates were comparable to those seen in Poovorawan *et al.* studies and published in meta-analysis by Lee *et al.* (2006). There were no subjects with HBsAg+ amongst adults, although the number of adults in the study was extremely small and the horizontal arm was terminated prematurely and therefore without statistically significant results.

The historical reference of protection rate 97% based on data from study on the vertical transmission of HBV from HBsAg-positive/HBeAg-positive mothers to infants in Thailand and the protection rate of around 95% afforded with a combined administration of HBIG and vaccination schedule of Engerix B (at 0, 1 and 6 months) (Poovorawan *et al.*, 1997) with 5% margin were selected. The conduct of a study with HBIG alone (without concurrent vaccination) is not considered to be ethical as it would provide inferior protection (around 70-85%) and potentially may expose children and adults to a greater risk. Also, the efficacy of HBIG products was previously well studied and reported in numerous studies (see Cochrane meta-analysis by Lee *et al.*, 2006). Therefore the approach selected by the applicant is acceptable. The applicant commented that the study is not interpreted as a non-inferiority study but rather as an uncontrolled non-randomized open trial. Confidence intervals for protective rates were presented and compared to historical rates observed in Poovorawan *et al.* studies.

In the per-protocol analysis only 4 infants became HBsAg positive at any point in the study, thus the overall protection rate achieved was 0.98 (174/178) with a corresponding 95%CI of (0.94, 0.99). The historical reference protection rate is 0.97, therefore the protection rate provided by ImmunoGam in combination with the Hepatitis B vaccine is comparable to the protection rates seen in the historical reference from the literature.

In the horizontal arm none of the subjects became HBsAg positive during the study. Thus, a 1.0 (23/23) protection rate was achieved with a corresponding 95% confidence interval of (0.85, 1.00). The confidence interval for the protection rate from the horizontal arm was wide due to an insufficient sample size. Although statistical significance was not achieved for the horizontal arm of the study, the point estimate of the protection rate was 1.0; all subjects in the PP population were protected from possible infection with HBV. These results provide strong support for the conclusions which were drawn for the vertical arm of the study that ImmunoGam in combination with hepatitis B vaccine provides a protection rate that is not inferior to the protection rates seen in the literature.

Despite the limitations in this study, it is considered to be conducted in conservative settings (only a single dose of HBIG was provided without repeat doses given) and therefore it is supportive of the claimed indication. The overall proportion of non-responders (anti-HBs of <10 mIU/mL) was only 5.6%. Considering the challenging circumstances of conducting a study in horizontal transmission settings, the extrapolation of data from the vertical arm is possible. In addition the modelling results from the PK studies are supportive of the protective efficacy of ImmunoGam in immunoprophylaxis. Therefore the approach selected by the applicant is acceptable and results of the Efficacy study can be considered supportive of the efficacy in the immunoprophylaxis indication.

Overall, the conclusions from the Efficacy study are sufficient to demonstrate the efficacy of ImmunoGam in combination with HBV vaccine in immunoprophylaxis settings in children and adults following vertical and horizontal transmission of the HBV.

No studies were performed in special populations; however, it is reasonable to extrapolate the efficacy of ImmunoGam from other available evidence (PK studies and Efficacy study). In addition, the immunoprophylaxis duration will be guided by levels of anti-HBs estimated during monitoring of patients. Based on modelling simulations provided by the applicant, it is reassuring that the level of anti-HBs >10 mIU/mL is predicted in >98% of adults and children at Day 30 following the administration of HBIG.

Safety

The safety profile of ImmunoGam appears to be acceptable. The proportion of local reactions observed with the intramuscular administration of ImmunoGam was low.

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

- User consultation

A user consultation on the package leaflet has been performed. Based on satisfactory results of the user test, it is possible to conclude that the PIL for ImmunoGam is acceptable to convey the necessary patient information on use of the product in immunoprophylaxis settings. The PIL is presented in a useful and readable format and can be utilized as a good educational material for patients.

Risk-benefit assessment

The risk-benefit ratio for ImmunoGam for the indication of immunoprophylaxis of hepatitis B in children and adults is positive. From the physician's point of view, an administration of HBIG should provide an adequate passive immunisation while the vaccine response is developing or if the vaccine

response failed. All proposed posology for ImmunoGam is aligned with the CHMP Core SPC requirements.

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

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of ImmunoGam in the immunoprophylaxis of Hepatitis B in the following settings (Intramuscular use):

“Immunoprophylaxis of Hepatitis B:

- In case of accidental exposure in non-immunised subjects (including persons whose vaccination is incomplete or status unknown).
- In haemodialysed patients, until vaccination has become effective.
- In the newborn of a hepatitis B virus carrier-mother.
- In subjects who did not show an immune response (no measurable hepatitis B antibodies) after vaccination and for whom a continuous prevention is necessary due to the continuous risk of being infected with hepatitis B.

Consideration should also be given to other official guidance on the appropriate use of human hepatitis B immunoglobulin for intramuscular use.”

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