Unit: Technical Assessment Unit

Public assessment report for biological products

Hiberix

Administrative information:

Trade name of the medicinal product:	Hiberix
INN (or common name) of the active substance(s):	Haemophilus influenza type b polysaccharide 10 µg Conjugated to Tetanus toxoid as carrier protein Approximately 25 µg.
Manufacturer of the finished product	GlaxoSmithKline Biologicals SA Parc de la Noire Epine Rue Fleming, 20 B-1300 Wavre, Belgium. GlaxoSmithKline Biologicals Rue des Aulnois, 637 F-59230 Saint-Amand-Les-Eaux, France. - Manufacturer of solvent: Novo Nordisk Production Belgium SA Font saint Landry, 10 1120 Brussels Belgium
Marketing Authorization holder	Glaxo Smith kline Biologicals S.A. 89 Rue de l' inistitut 1330 Rixensart -Belgium
Applied Indication(s):	- Active immunization of all infants from the age of six weeks against the infection caused by Haemophilus influenza type B. - Hiberix does not provide protection against illness caused by other types of Haemophillus influenza nor against meningitis caused by other organisms.
Pharmaceutical form(s) and strength(s):	- Powder and solvent for solution for injection -10µg/0.5ml
Route of administration	- Intramuscular -Subcutaneous in patients suffering from thrombocytopenia or hemorrhaging
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

DTPa	diphtheria, tetanus, and acellular pertussis
GMT	Geometric mean titer
Hib	Haemophilus influenzae type b
IPV	Inactivated Poliovirus Vaccine
PRP	polyribosyl-ribitol-phosphate

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1. **General introduction about the product including brief description of the AI, its mode of action and indications**.
   - Hiberix™ is a lyophilized vaccine of purified polyribosyl-ribitol-phosphate capsular polysaccharide (PRP) of Hib, covalently bound to tetanus toxoid.
   - The Hib polysaccharide is prepared from Hib, strain 20,752 and after activation with cyanogen bromide and derivatisation with an adipic hydrazide spacer is coupled to tetanus toxoid via carbodiimide condensation. After purification the conjugate is lyophilized in the presence of lactose as stabilizer.
   - Hiberix™ meets the WHO requirements for the manufacture of biological substances and of Hib conjugated vaccines.
   - Each single dose of vaccine is formulated to contain 10 µg of purified capsular polysaccharide covalently bound to approximately 30 µg tetanus toxoid
2. **Quality aspects:**

   2.2.1 Introduction

   As mentioned in above general introduction.

   2.2.2 Drug Substance (Active ingredient)

   - **General information**

   The active ingredient of the Hib conjugate product consists of the capsular polysaccharide from Haemophilus influenzae type b covalently bound to tetanus toxoid (carrier protein). The average molecular weight (MW) of PRP-TT conjugates determined by multiple angle laser light scattering (MALLS) ranges from 4600 to 5200 kDa.

   - **Manufacture, process controls and characterization:**

   - **Manufacturer(s)**

-The active substance (PRP-tetanus toxoid conjugate) is prepared at:
GlaxoSmithKline Biologicals 10, Tuas South Avenue 8 Singapore 637421, Singapore
The intermediate Hib purified polysaccharide (PRP) is prepared at:
GlaxoSmithKline Biologicals 10, Tuas South Avenue 8 Singapore 637421, Singapore
-The intermediate tetanus toxoid is prepared at:
GSK Vaccines GmbH Emil-von-Behring-Str. 76 D-35041 Marburg, Germany
And at GlaxoSmithKline Biologicals Kft. Homoki Nagy István utca 1. 2100 Gödöllő, Hungary.

- **Description of Manufacturing Process and Process Controls.**

Summaries the manufacturing process and gives the time frame associated to the manufacturing of purified polysaccharide batches are well described in MA file.

- **Control of Materials.**

A working seed was prepared from the master seed and identified in MA file.
In 2003 at the request of the FDA, the seed system for the Hib polysaccharide production was revised. New master and working seeds were produced on non-bovine certified media.
The different seeds that have been produced and Control tests results are provided in MA file.
Raw materials used during PRP manufacture are listed in MA file. All raw materials meet standards appropriate for their intended use.

- **Controls of Critical Steps and Intermediates.**

The process steps for the manufacturing of the purified PRP-TT conjugates are detailed in MA file.

Quality Control tests are performed on all production intermediates and on the PRP-TT bulks according to GSK Bio Monographs.

Process controls are applied during the manufacturing process and are classified in two categories:

(1) in-process tests used to make the decision to proceed from one manufacturing step to the next; these tests have defined specifications, and

(2) monitoring tests used to monitor the process consistency and performance.

In-process controls as well as QC release tests on the production intermediates are described in MA file.

- **Process Validation**

The manufacturing process has been validated adequately. All process parameters were maintained and all CQA were achieved.

- Tests results of critical quality attribute and results for critical parameter attribute in each stage of DS manufacturing had been demonstrated, aligned with the pre-determined acceptance criteria and show production process consistency. The results showed that the manufacturing process is consistent using three consecutive batches.

- **Manufacturing Process Development**.

During development of Hib vaccines and since the registration, the production process of the Hib (PRP-TT) drug substance evolved and changes were introduced. These changes are described in details in MA file.

- **Characterization.**

The active ingredient of the Haemophilus influenzae type b bulk vaccine consists of the capsular polysaccharide from H. influenzae type b covalently bound to a carrier protein (tetanus toxoid).

The capsular polysaccharide (PRP) consists of repeating units of ribose and ribitol linked through phosphoryl ester bonds (polyriboseribitol phosphate, or PRP).

- **Specification**

Specifications of PRP-TT bulk conjugate drug substance are listed in GSK Biologicals monograph n° 200160 and are presented in MA file. These specifications are identical to the specifications of the PRP-TT bulk conjugate used in GSK Bio's commercialized Hib-containing vaccines.

- **Batch analysis.**

Upon evaluation of submitted batch analysis results, consistency of production was observed.

- **Reference Standards or Materials.**

All reference standards used during manufacturing are well described in the MA file

- **Container closure system**

Conjugated polysaccharide bulk is stored in 10L-glass bottles (type 1 glass, Ph. Eur.). The

closure system is of pharmaceutical grade. Compatibility between antigen bulks and primary packaging material has been demonstrated via stability studies.

- **Stability of drug substance**

The results of stability studies for three production batches of each DS component support the claimed shelf-life when stored in its proper container.

-Based on the stability data obtained, the approved shelf-life of the PRP-TT conjugate bulk manufactured with TT from GSK Bio Kft is 6 months when stored at +2 to +8□C.

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**

The PRP-TT conjugate is made of the purified capsular polysaccharide of Haemophilus influenzae type b conjugated to Tetanus toxoid. The PRP-TT active ingredient in the Hib non-adsorbed 10µg complies with the requirements as indicated in the Ph. Eur. and WHO monographs on Haemophilus type b conjugate vaccines.

GSK Bio Hib non-adsorbed 10 µg vaccine is supplied as a lyophilized preparation to be reconstituted with the diluent (saline solution) or the liquid vaccine.
The nominal amount of capsular polysaccharide (10 µg) and the polysaccharide to protein ratio (0.30-0.50) is in line with the Ph. Eur. and WHO monographs on Haemophilus influenzae type b conjugate vaccines.
Lactose is used as a stabilizer for the Hib lyophilization procedure.

- Pharmaceutical Development including brief description on Components of drug product.
- **Physicochemical and Biological Properties**
Hib vaccine is indicated for active primary immunization against disease caused by Haemophilus influenzae type b in infants. The candidate vaccine will thus trigger the immune memory and induce the production of antibodies against Haemophilus influenzae type b.
- **Manufacturing Process Development.**
No developmental studies were performed on the finished product manufacturing process. No changes on the finished product manufacturing have been implemented between clinical lots formulation and that intended for commercial purpose
- Container closure system and their compatibility.
The neutral glass (type I) vials and the butyl rubber stoppers used for Hib 10µg vaccine are identical to those used for other licensed GSK Bio lyophilized vaccines. The compatibility of the vaccine with the container components has been demonstrated by stability studies.
- **Microbiological Attributes.**
It can be seen that all precautions are taken during the preparation of Hib vaccine to ensure the sterility of the final product.

Final bulk vaccine and vaccine final containers are tested for sterility according to European Pharmacopoeia requirements.

- Compatibility.

Vaccine compatibility with the liquid component used for reconstitution (saline diluent or liquid vaccine) is validated by clinical evaluation of Hib non-adsorbed 10µg vaccine.

- **Manufacture of the drug product:**

Manufacture(s) responsible for QC testing / batch release

GlaxoSmithKline Biologicals SA,Rue de l'Institut 89, B-1330 Rixensart, Belgium.

GlaxoSmithKline Biologicals SA, Parc de la Noire Epine, Rue Fleming, 20, B-1300 Wavre, Belgium.

GlaxoSmithKline Biologicals,Rue des Aulnois, 637, F-59230 Saint-Amand-Les-Eaux, France.

- Description of manufacturing process and process controls along with manufacturers and responsibilities.

For the manufacture of the Hib conjugate antigen in final containers, bulks of PRP-TT conjugate is mixed with a lactose solution. The corresponding final bulk is filled in 3ml vials and subsequently lyophilised. Flow diagrams of the vaccine formulation, filling and lyophilisation processes are provided in MA file.

A description of the manufacturing process is provided in MA file.

- Control of critical steps and intermediates

There is no intermediate produced between the final bulk conserved at 2°C to 8°C and the end of lyophilization.

Controls are performed at the final bulk stage and on the vaccine in final container. These QC tests are performed for release of the vaccine. The specifications and analytical methods are detailed in MA file.

- Process validation and / or evaluation.

All the manufacturing steps and procedures in the manufacturing have been validated.

The results showed that the manufacturing process is consistent using three consecutive batches.

Validation data provided in MA file.

- **Product specification:**

- Specifications for the release of Hib commercial lots are detailed in GSK monographs 200893 for final bulk and 200077 for final containers. Those specifications are presented in MA file for (final bulk) and (final container).
- Justification of the DP specifications at the release and during stability studies are provided.
-The analytical procedures, principles and validity criteria used for control testing of the vaccine were provided
- Upon evaluation of the submitted batch analysis results, consistency of production was reflected. And all the batch results were satisfactory and comply with acceptance criteria.

- **Reference Standards or Materials.**

Reference standards used for testing are suitable and fully described in the MA file.

- **Container closure system.**

The Hib lyophilised component is supplied in 3 ml vials, stoppered with rubber closures and capped with flip-off caps. The colour of the flip-off cap is purple.
Glass vials meet Ph. Eur. Requirements for "Glass containers for pharmaceutical use".
Vaccines, diluents and adjuvants are filled in 3 ml vials, uncoloured glass, 13 mm diameter, 31 mm height (drawn glass, type I).
Tests and specifications for glass vials are given in GSK Bio Monograph 10074901.

- **Stability of the drug product.**

Based on overall stability data,
the approved shelf-life of the Hib non-adsorbed 10µg vaccine is 36 months **(3 years)**
-Approved Storage Conditions:

- ✓ Store in refrigerator 2-8°C
- ✓ Protect from light
- ✓ The powder is not affected by freezing
- ✓ Do not freeze the solvent

3. Non –clinical aspect:

Given the extent of human experience with Hiberix, nonclinical data were not required and no new nonclinical data was submitted to support marketing authorization of the candidate vaccine.

4. Clinical aspect:

Clinical Development Program

The clinical development program for Hiberix comprised a comprehensive set of pivotal and supportive studies conducted in healthy infants and young children to evaluate immunogenicity, safety, booster responses, immune memory, lot-to-lot consistency, and compatibility with routine pediatric vaccines. The initial marketing authorization was supported by seven pivotal studies conducted between 1993 and 1995, which assessed primary and booster vaccination schedules, immunogenicity and reactogenicity following administration alone or in combination with DTPa-containing vaccines, manufacturing consistency, and comparability with licensed Hib conjugate vaccines.
Additional Phase II and Phase III studies conducted across Europe, North America, Asia, Australia, and Latin America provided further evidence on the immunogenicity and safety of HIBERIX when co-administered with routinely recommended pediatric vaccines. These studies also evaluated long-term immune persistence, immune memory, booster responses, lot consistency, and comparative immunogenicity versus licensed Hib-containing vaccines, including ActHIB and Pentacel.
Collectively, the pivotal studies (HIB-002, HIB-005, HIB-006, HIB-012, HIB-017, DTPa-BV-005, and DTPa-BV-007) and subsequent supportive studies, including the large multicenter Phase III study HIB-097, established a consistent immunogenicity and safety profile for HIBERIX and supported its use within routine childhood immunization programs.

Clinical Efficacy

As efficacy against invasive Hib disease was established through validated immunological correlates of protection, clinical efficacy was demonstrated through achievement of protective anti-PRP antibody levels and induction of immunological memory.

Primary Vaccination

The primary vaccination studies consistently demonstrated high seroprotection rates following completion of the recommended vaccination schedule.

In Study HIB-005, all vaccine regimens induced substantial immune responses against Hib and co-administered antigens. Although anti-PRP responses were somewhat lower when Hib vaccine was mixed with DTPa compared with separate administration, protective antibody responses were achieved and all vaccine combinations were considered immunogenic.

Study HIB-012 demonstrated successful immunogenicity following a three-dose primary vaccination course administered at 2, 4, and 6 months of age. No clinically meaningful differences in immune responses were observed among the three vaccine lots tested.

The large Phase III study HIB-097 further confirmed the efficacy profile by demonstrating non-inferiority of Hiberix compared with ActHIB based on accepted anti-PRP serological endpoints. Lot-to-lot consistency was also demonstrated.

Booster Vaccination

Study HIB-002 evaluated Hiberix as a booster dose in previously primed children. One month after booster vaccination:

- 100% of subjects achieved anti-PRP concentrations ≥0.15 µg/mL.
- 100% achieved anti-PRP concentrations ≥1.0 µg/mL.
- Anti-PRP GMT increased from 0.824 µg/mL pre-booster to 73.684 µg/mL post-booster.

These findings demonstrate a robust booster response indicative of effective long-term protection.

Clinical Immunogenicity

Hiberix consistently induced strong humoral immune responses and immunological memory.

Anti-PRP Antibody Response

Across the primary vaccination studies, high proportions of subjects achieved anti-PRP antibody concentrations above accepted protective thresholds. Following completion of vaccination schedules, anti-PRP GMTs increased substantially from baseline levels.

Immune Memory

The clinical program demonstrated persistence of anti-PRP antibodies and strong anamnestic responses following booster administration. In HIB-002, all subjects mounted a marked booster response with substantial increases in anti-PRP antibody concentrations.

Lot-to-Lot Consistency

Study HIB-012 and the pivotal Phase III study HIB-097 demonstrated consistency of immune responses among different manufacturing lots, supporting manufacturing reliability and product quality.

Concomitant Administration

Clinical studies demonstrated that Hiberix may be administered concomitantly with DTPa-containing vaccines, hepatitis B vaccines, IPV, pneumococcal conjugate vaccines, and rotavirus vaccines without clinically significant interference with immune responses to co-administered antigens.

Clinical Safety

Reactogenicity

The most frequently reported solicited adverse events were:

- Injection-site pain
- Injection-site redness
- Injection-site swelling
- Fever
- Irritability/restlessness

Most reactions were mild to moderate in severity and resolved spontaneously without sequelae.

Unsolicited Adverse Events

Across studies, unsolicited adverse events occurred at frequencies expected in the pediatric population and were generally unrelated or only possibly related to vaccination. Most events were transient and self-limiting.

Serious Adverse Events

- In HIB-005, twelve serious adverse events were reported; all were assessed as unrelated or probably unrelated to vaccination.
- In HIB-012, ten serious adverse events were reported and none were considered vaccine-related.
- In DTPa-HBV-005, seven serious adverse events were reported and none were considered related to vaccination.

No clinically significant safety signals were identified during the clinical development program.

Benefit- Risk Analysis

The clinical data demonstrate that Hiberix induces robust protective immune responses against Hib disease and generates effective booster responses. The safety profile is acceptable and consistent with established pediatric conjugate vaccines. The identified risks are minor and manageable, whereas the benefits include prevention of severe invasive Hib disease. Therefore, the overall benefit-risk balance remains favorable.

Overall Conclusion

The submitted clinical evidence supports the efficacy, immunogenicity, and safety of Hiberix for active immunization against *Haemophilus influenzae* type b disease. The vaccine consistently induces protective anti-PRP antibody responses, demonstrates immune memory through booster responses, and exhibits an acceptable safety profile with no clinically significant safety concerns. Manufacturing consistency and compatibility with routine pediatric immunization schedules have also been demonstrated.

Based on the totality of available clinical evidence, Hiberix maintains a positive benefit–risk profile and remains suitable for continued use in the prevention of invasive Hib disease in infants and young children.

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.