Hiberix™

1. NAME OF THE MEDICINAL PRODUCT

Hiberix™

Haemophilus influenzae type b (Hib) vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 ml) contains:

Haemophilus influenzae type b polysaccharide	10 micrograms
conjugated to tetanus toxoid as carrier protein	approximately 25 micrograms

Hiberix™ is a white powder.

The solvent is a clear and colourless liquid.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hiberix™ is indicated for active immunisation of all infants from the age of 6 weeks against disease caused by Hib.

Hiberix™ does not protect against disease due to other types of *H. influenzae* nor against meningitis caused by other organisms.

4.2 Posology and Method of Administration

Posology

The primary vaccination schedule consists of three doses in the first 6 months of life and can start from the age of 6 weeks.

To ensure a long term protection, a booster dose is recommended in the second year of life.

Infants between the ages of 6 and 12 months previously unvaccinated should receive 2 injections, given with an interval of one month, followed by a booster in the second year of life. Previously unvaccinated children aged 1-5 years should be given one dose of vaccine.

As vaccination schemes vary from country to country, the schedule for each country may be used in accordance with the different national recommendations.

Method of administration

The reconstituted vaccine is for **intramuscular** injection. However, it is good clinical practice that in patients with thrombocytopenia or bleeding disorders the vaccine should be administered subcutaneously.

4.3 Contraindications

Hiberix™ should not be administered to subjects with known hypersensitivity to any component of the vaccine, or to subjects having shown signs of hypersensitivity after previous administration of Hib vaccines.

4.4 Special Warnings and Precautions for Use

As with other vaccines, the administration of **Hiberix™** should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, is not a contra-indication for vaccination. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine. For this reason the vaccinee should remain under medical supervision for 30 minutes after immunisation.

Human Immunodeficiency Virus (HIV) infection is not considered as a contra-indication for **Hiberix™**.

Although limited immune response to the tetanus toxoid component may occur, vaccination with **Hiberix™** alone does not substitute for routine tetanus vaccination.

Excretion of capsular polysaccharide antigen in the urine has been described following receipt of Hib vaccines, and therefore antigen detection may not have a diagnostic value in suspected Hib disease within 1-2 weeks of vaccination.

Hiberix™ should under no circumstances be administered intravenously.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Hiberix™ can be administered either simultaneously or at any time before or after a different inactivated or live vaccine.

Hiberix™ can be mixed in the same syringe with GlaxoSmithKline vaccines **Infanrix™** (DTPa vaccine), or **Tritanrix™ HB** (DTPw-HB vaccine). Other injectable vaccines should always be administered at different injection sites.

As with other vaccines it may be expected that in patients receiving immunosuppressive therapy or patients with immunodeficiency, an adequate response may not be achieved.

4.6 Pregnancy and Lactation

As **Hiberix™** is not intended for use in adults, human data on use during pregnancy or lactation and adequate animal reproduction studies are not available.

4.7 Effects on Ability to Drive and Use Machine

Not applicable.

4.8 Undesirable Effects

Clinical trial data

The following frequencies were based on the analysis of approximately 3,000 infants enrolled in study Hib-097 and of approximately 1,200 infants enrolled in study DTPa-HBV-IPV-011.

Adverse reactions reported are listed according to the following frequency:

Very common	≥ 1/10
Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1,000 to < 1/100
Rare	≥ 1/10,000 to < 1/1,000
Very rare	< 1/10,000

Metabolism and nutrition disorders

Very common: loss of appetite

Psychiatric disorders

Very common: crying, irritability, restlessness

Nervous system disorders

Very common: somnolence

Rare: convulsions (including febrile convulsions)

Gastrointestinal disorders

Very common: diarrhoea

Common: vomiting

General disorders and administration site conditions

Very common: fever, swelling, pain and redness at the injection site

Post marketing data

Immune system disorders

Very rare: allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema

Nervous system disorders

Very rare: hypotonic-hyporesponsive episode, syncope or vasovagal responses to injection

Respiratory, thoracic and mediastinal disorders

Very rare: apnoea [see section "4.4 Special Warnings and Precautions for Use" for apnoea in very premature infants (≤ 28 weeks of gestation)]

Skin and subcutaneous tissue disorders

Very rare: urticaria, rash

General disorders and administration site conditions

Very rare: extensive swelling of vaccinated limb, injection site induration

4.9 Overdose

In general, the adverse event profile reported following overdosage was similar to that observed after administration of the recommended dose of **Hiberix™**.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmaco-therapeutic group: Bacterial vaccines, ATC code J07AG01.

Primary vaccination

Table 1 presents the immunogenicity results from 4 clinical trials in which infants in the United States, Europe, South America and South-East Asia received a 3-dose primary vaccination with **Hiberix™** in the first 6 months of life starting from 6 weeks of age. Varying vaccination schedules were evaluated and **Hiberix™** was co-administered with other routinely recommended vaccines.

Hiberix™ was immunogenic in all 3-dose schedules studied. Anti-PRP concentration of ≥ 0.15 µg/ml (a level indicative for short-term protection) was obtained in 96.6-99.4% of infants one month after the completion of the vaccination course.

Table 1: Percentage of subjects with antibody concentration ≥ 0.15 µg/ml one month after primary vaccination with Hiberix™.

Study	**Age at primary vaccination**	**N**	**Co-administered vaccines**	**% subjects with anti-PRP ≥ 0.15 µg/ml (95% CI)**
Hib-097	2-4-6 months	1,590	DTPa-HBV-IPV PCV13 HRV	96.6 (95.6;97.4)
DTPw-HBV-Hib-008 PRI	2-4-6 months	171	DTPw-HBV	99.4 (96.8;100)
DTPa-HBV-IPV-005	3-4-5 months	410	DTPa-HBV-IPV or DTPa-HBV-IPV + OPV (at 3rd dose)	99.0 (97.5;99.7)
DTPw-HBV=Hib Kft-001	6-10-14 weeks	175	DTPw-HBV	99.4 (96.9;100)

CI: Confidence Interval

DTPw-HBV: combined Diphtheria, Tetanus, Pertussis (whole cell) and Hepatitis B Vaccine

DTPa-HBV-IPV: combined Diphtheria, Tetanus, Pertussis (acellular), Hepatitis B and Poliomyelitis Vaccine

HRV: Human Rotavirus Vaccine

N: number of subjects in the according to protocol (ATP) cohort (except for DTPw-HBV-Hib-008: Total Vaccinated Cohort)

OPV: Oral Polio Vaccine

PCV13: 13-valent Pneumococcal Conjugate Vaccine

PRP: Polyribosylribitol phosphate

In addition, in unprimed toddlers aged 22-26 months (study Hib-036) who received a single dose of **Hiberix™** co-administered with DTPa, 100% of subjects [N= 54, 95 % CI (93.4;100)] achieved anti-PRP concentrations ≥ 1.0 µg/ml one month after vaccination. These data support a single dose of **Hiberix™** in children aged from 1 year and above.

Booster vaccination

Antibody responses to booster vaccination with **Hiberix™** after a 3 dose priming schedule are presented in Table 2. One month after the booster dose, all children had anti-PRP concentrations ≥ 0.15 µg/ml and at least 99.1% had anti-PRP concentrations ≥ 1.0 µg/ml, a concentration correlated with long term immunity to Hib (Table 2).

Table 2: Percentage of subjects with antibody concentration ≥ 1.0 µg/ml one month after booster vaccination with Hiberix.

Study	N	Age at primary vaccination	Age at booster vaccination	Co-administered vaccines at booster	% of subjects with anti-PRP ≥ 1.0 µg/ml (95% CI)
Hib-097	336	2-4-6 months	15-18 months	DTPa	99.1 (97.4;99.8)
DTPw-HBV-Hib-008 BST	161	2-4-6 months	18 months	DTPw-HBV	99.4 (96.6;100)
DTPw-HBV=Hib Kft-003	74	6-10-14 weeks	15-18 months	DTPw-HBV	100% (95.1;100)

CI: Confidence Interval

N: number of subjects in the ATP cohort

DTPa: combined Diphtheria, Tetanus, Pertussis (acellular) vaccine

DTPw-HBV: combined Diphtheria, Tetanus, Pertussis (whole cell) vaccine and Hepatitis B Vaccine

PRP: Polyribosylribitol phosphate

5.2 Pharmacokinetic Properties

Evaluation of pharmacokinetic properties is not required for vaccines.

Clinical studies

See section 5.1 Pharmacodynamic Properties

5.3 Preclinical Safety Data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lyophilised Hib vaccine: Lactose

Solvent: Sterile saline solution

6.2 Incompatibilities

Hiberix™ can be mixed in the same syringe with GlaxoSmithKline vaccines **Infanrix™** (DTPa vaccine), or **Tritanrix™ HB** (DTPw-HB vaccine). Other injectable vaccines should always be administered at different injection sites.

Hiberix™ should not be mixed with other vaccines in the same syringe (except for authorised combinations).

6.3 Shelf Life

The expiry date of the vaccine is indicated on the label and packaging.

6.4 Special Precautions for Storage

The lyophilised vaccine has to be stored at +2^{O}C to +8^{O}C and has to be protected from light. The lyophilised vaccine is not affected by freezing.
The solvent can be stored in the refrigerator (+2^{O}C to +8^{O}C) or at ambient temperatures (up to 25 ^{O}C) and should not be frozen.

6.5 Nature and Contents of Container

The lyophilised vaccine is presented as a white powder in a glass vial.
The sterile solvent (saline) is clear and colourless and presented in a glass vial (US manufactured), ampoule or pre-filled syringe.
The vials, ampoules and pre-filled syringes are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.

6.6 Instructions for Use, Handling

How to use Hiberix™

The solvent and reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of appearance prior to administration. If either is observed, do not administer the vaccine.

<u>Instructions for reconstitution of the vaccine with solvent presented in vials (US manufactured) or ampoules</u>

Hiberix™ must be reconstituted by adding the entire contents of the supplied vial of solvent to the vial containing the powder. After the addition of the solvent to the powder, the mixture should be well shaken until the powder is completely dissolved**.**

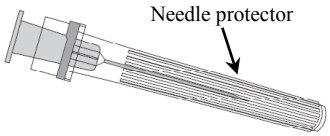
The reconstituted vaccine is a clear to opalescent and colourless solution.
When using a multidose vial, each dose should be taken with a sterile needle and syringe. As with other vaccines, a dose of vaccine should be withdrawn under strict aseptic conditions and precautions taken to avoid contamination of the contents.
After reconstitution, the vaccine should be used promptly.
A new needle should be used to administer the vaccine.
Withdraw the entire contents of the vial.

Instructions for reconstitution of the vaccine with the solvent presented in pre-filled syringe

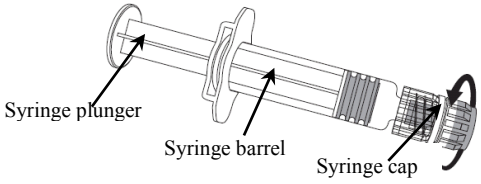
Hiberix™ must be reconstituted by adding the entire content of the pre-filled syringe of solvent to the vial containing the powder.

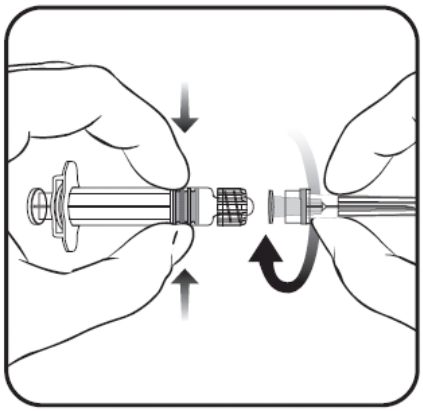
To attach the needle to the syringe, refer to the drawing below. However, the syringe provided with **Hiberix™** might be slightly different than the syringe described in the drawing.

Needle



Syringe





1. Holding the syringe barrel in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.
2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock. (see picture)
3. Remove the needle protector, which on occasion can be a little stiff.

Add the solvent to the powder. After the addition of the solvent to the powder, the mixture should be well shaken until the powder is completely dissolved.

The reconstituted vaccine is a clear to opalescent and colourless solution.

After reconstitution, the vaccine should be used promptly.

A new needle should be used to administer the vaccine.

Withdraw the entire contents of the vial.

To mix Hiberix™ with Tritanrix™ HB or Infanrix™

Hiberix™ vaccine may be reconstituted either with **Tritanrix™ HB** or with **Infanrix™** for simultaneous administration via one injection.

Tritanrix™ HB and **Infanrix™** are presented as suspensions. Upon storage, a white deposit and clear supernatant may be observed. The vaccine should be well shaken in order to obtain a homogeneous turbid white suspension and visually inspected for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, discard the vaccine.

Discard the sterile solvent provided with **Hiberix™**.

The combined DTPw-HB-Hib or DTPa-Hib vaccines must be reconstituted by adding the entire contents of either a **Tritanrix™ HB** or **Infanrix™** monodose container to the monodose vial containing the white **Hiberix™** powder. After the addition of **Tritanrix™ HB** or **Infanrix™** to the **Hiberix™** powder, the mixture should be well shaken until the **Hiberix™** powder is completely dissolved in either the **Tritanrix™ HB** or **Infanrix™** suspension.

The reconstituted combined vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspects prior to administration. In the event of either being observed, discard the reconstituted vaccine.

After reconstitution, the vaccine should be used promptly.

A new needle should be used to administer the vaccine. Withdraw the entire contents of the vial.

Any unused product or waste material should be disposed of in accordance with local requirements

Presentations

Pack of a 0.5 ml monodose vial and 10 dose vial.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Thailand) Ltd.

8. MARKETING AUTHORISATION NUMBER (S)

1C 288/41 (N)

9. DATE OF FIRST AUTHORISATION

2 Dec 1998 (conditional license)

9 Aug 2001 (unconditional license)

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Version number: [GDSv09/IPI07] / Date of issue: [23/Jun/2015]
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