INFANRIX IPV Hib

1. NAME OF THE MEDICINAL PRODUCT

INFANRIX IPV Hib
powder and suspension for suspension for injection

Diphtheria (D), tetanus (T), pertussis (acellular component) (Pa), poliomyelitis (inactivated) (IPV) and Haemophilus influenzae type b (Hib) conjugate vaccine (adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

A 0.5 ml dose of vaccine contains:

Diphtheria toxoid[1]	not less than 30 International Units (IU) (25 Lf)
Tetanus toxoid[1]	not less than 40 International Units (IU) (10 Lf)
Bordetella pertussis antigens	
Pertussis toxoid (PT) [1]	25 µg
Filamentous haemagglutinin(FHA) [1]	25 µg
Pertactin (PRN)[1]	8 µg
Poliovirus (inactivated) (IPV)	
type 1 (Mahoney strain)[2]	40 D-antigen unit
type 2 (MEF-1 strain)[2]	8 D-antigen unit
type 3 (Saukett strain)[2]	32 D-antigen unit
Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate) (PRP)	10 µg
conjugated to tetanus toxoid as carrier protein	approximately 25 µg
[1]Adsorbed on aluminium hydroxide, hydrated	0.5 milligrams Al^{3+}
[2]Propagated in VERO cells	

The vaccine may contain traces of formaldehyde, neomycin and polymyxin which are used during the manufacturing process (see section 4.3).

Excipients with known effect
The vaccine contains para-aminobenzoic acid < 0.07 nanograms per dose and phenylalanine 0.036 micrograms per dose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and suspension for suspension for injection.
The diphtheria, tetanus, acellular pertussis and inactivated poliomyelitis (DTPa-IPV) component is a turbid white suspension.
The lyophilised *Haemophilus influenzae* type b (Hib) component is a white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

INFANRIX IPV Hib is indicated for active immunisation in infants from the age of 2 months to 5 years**,** against diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenzae* type b.

INFANRIX IPV Hib is also indicated as a booster dose for children who have previously been immunised with DTP, polio and Hib antigens.

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 2 months. An interval of at least 1 month should be respected between subsequent doses.

A booster dose is recommended in the second year of life with an interval of at least 6 months after completion of primary vaccination schedule.

Method of administration

INFANRIX IPV Hib is for deep intramuscular injection, in the anterolateral aspect of the thigh.

It is preferable that each subsequent dose is given into alternating limbs.

INFANRIX IPV Hib should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects. Firm pressure should be applied to the injection site (without rubbing) for at least two minutes.

INFANRIX IPV Hib should under no circumstances be administered intravascularly.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 or formaldehyde, neomycin or polymyxin .

Hypersensitivity after previous administration of diphtheria, tetanus, pertussis, polio or Hib vaccines.

INFANRIX IPV Hib is contra-indicated if the child has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine.

As with other vaccines, the administration of INFANRIX IPV Hib should be postponed in subjects suffering from an acute severe febrile illness. The presence of a minor infection, however, is not a contraindication.

4.4 Special warnings and precautions for use

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.
If any of the following events have occurred in temporal relation to receipt of any DTP-containing vaccine, the decision to give subsequent doses of vaccine containing a pertussis component should be carefully considered.

- Temperature of ≥ 40.0 °C (rectal) within 48 hours, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination.
- Convulsions with or without fever, occurring within 3 days of vaccination.

There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks, particularly since the events are not associated with permanent sequelae. According to available clinical data, the risk of such reactions is lower with acellular pertussis vaccines than with whole cell pertussis vaccines.

As for any vaccination, the risk-benefit of immunising with INFANRIX IPV Hib or deferring this vaccination should be weighed carefully in an infant or in a child suffering from a new onset or progression of a severe neurological disorder.

The Hib component of the vaccine does not protect against diseases due to other types of *Haemophilus influenzae* nor against meningitis caused by other organisms.

A history of febrile convulsions, a family history of convulsions, a family history of Sudden Infant Death Syndrome (SIDS) and a family history of an adverse event following DTP, IPV and/or Hib vaccination do not constitute contra-indications to administration of INFANRIX IPV Hib.

Human Immunodeficiency Virus (HIV) infection is not considered to be a contraindication to administration of INFANRIX IPV Hib.

The expected immunological response may not be obtained after vaccination of immunosuppressed patients, e.g. patients on immunosuppressive therapy.

Excretion of capsular polysaccharide antigen in the urine has been described following receipt of Hib vaccines. Therefore false positive antigen detection test results are possible within 1-2 weeks of vaccination.

Administration of INFANRIX IPV Hib should be recorded in the patient's International Vaccination Certificate.

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 the 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.

Excipients with known effect

INFANRIX IPV Hib contains para-aminobenzoic acid. It may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.
The vaccine contains 0.036 microgram phenylalanine in each dose. Phenylalanine may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

The vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.
The vaccine contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially 'potassium-free'.

Traceability

In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded. It is recommended to record the batch number as well.

4.5 Interaction with other medicinal products and other forms of interaction

If INFANRIX IPV Hib is to be given at the same time as another injectable vaccine(s), the 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 Fertility, pregnancy and lactation

As INFANRIX IPV Hib is not intended for use in adults, information on the safety of the vaccine when used during pregnancy or lactation is not available.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

- Clinical trials

Summary of the safety profile
The safety profile presented below is based on data from more than 3500 subjects.
As has been observed for DTPa and DTPa-containing combinations, an increase in local reactogenicity and fever was reported after booster vaccination with INFANRIX IPV Hib with respect to the primary course.

List of adverse reactions
Frequencies per dose are defined as follows:

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)

Infections and infestations
Uncommon: upper respiratory tract infection

Blood and lymphatic system disorders
Uncommon: lymphadenopathy

Metabolism and nutrition disorders
Very common: appetite lost

Psychiatric disorders
Very common: crying abnormal, irritability, restlessness

Nervous system disorders
Very common: somnolence

Respiratory, thoracic and mediastinal disorders
Uncommon: bronchitis, cough, rhinorrhoea

Gastrointestinal disorders
Common: diarrhoea, vomiting

Skin and subcutaneous tissue disorders
Uncommon: urticaria, rash

Rare: pruritus, dermatitis

General disorders and administration site conditions
Very common: fever (≥38.0°C), injection site reactions such as pain and redness, local swelling at the injection site (≤50 mm)
Common: injection site reactions including induration, local swelling at the injection site (>50 mm)[1]
Uncommon: diffuse swelling of the injected limb, sometimes involving the adjacent joint[1], fever[2]>39.5°C, fatigue

- Post-marketing surveillance

Immune system disorders
Allergic reactions (including anaphylactic[3] and anaphylactoid reactions)

Nervous system disorders
Collapse or shock-like state (hypotonic-hyporesponsiveness episode), convulsions (with or without fever)

Respiratory, thoracic and mediastinal disorders
Apnoea[3] [see 4.4 for apnoea in very premature infants (≤ 28 weeks of gestation)]

Skin and subcutaneous tissue disorders
Angioneurotic oedema[3]

General disorders and administration site conditions
Swelling of the entire injected limb[1], injection site vesicles[3]

[1]Children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. These reactions resolve over an average of 4 days.
[2]common with booster vaccination
[3]reported with GSK's DTPa containing vaccines

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il.

Additionally, you should also report to GSK Israel (il.safety@gsk.com).

4.9 Overdose

Some cases of overdose have been reported during post-marketing surveillance. Adverse events, when reported following overdosage, were similar to those observed after administration of the recommended dose of INFANRIX IPV Hib.

5. PHARMACOLOGICAL PROPERTIES.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bacterial and viral vaccines combined, ATC code: J07CA06

Results obtained in the clinical studies for each of the components are summarised in the tables below:

Percentage of subjects with antibody titres ≥ assay cut-off after primary vaccination with INFANRIX IPV Hib:

Antibody (cut-off)	**3-5 months N= 86 (1 trial) %**	**1.5-3.5-6 months N= 62 (1 trial) %**	**2-3-4 months N= 337 (3 trials) %**	**2-4-6 months N= 624 (6 trials) %**	**3-4-5 months N= 127 (2 trials) %**	**3-4.5-6 months N=198 (1 trial) %**
Anti-diphtheria (0.1 IU/ml)*	94.1	100	98.8	99.3	94.4	99.5
Anti-tetanus (0.1 IU/ml)*	100.0**	100	99.7	99.8	99.2	100
Anti-PT (5 EL.U/ml)	99.5**	100	99.4	100	98.4	100
Anti-FHA (5 EL.U/ml)	99.7**	100	100	100	100	100
Anti-PRN (5 EL.U/ml)	99.0**	100	100	100	100	100
Anti-Polio type 1 (1/8 dilution)*	93.0	ND	99.1	99.5	100	100
Anti-Polio type 2 (1/8 dilution)*	95.3	ND	95.7	99.0	99.2	100
Anti-Polio type 3 (1/8 dilution)*	98.8	ND	100	100	99.2	99.4
Anti-PRP (Hib) (0.15 µg/ml)*	83.7	100	98.5	98.5	100	98.4
Anti-PRP (Hib) (1.0 µg/ml)	51.2	87.1	68.5	76.0	97.6	81.2

* cut-off accepted as indicative of protection
** Post dose 2 results from studies where DTPa-HBV-IPV+Hib was administered in a schedule 3, 5 and 11 months of age.
N = number of subjects
ND = not determined

Percentage of subjects with antibody titres ≥ assay cut-off after booster vaccination with INFANRIX IPV Hib:

Antibody (cut-off)	**Booster vaccination at 11/12 months of age following a 3-5 months primary course N =184 (1 trial) %**	**Booster vaccination during the second year of life following a three dose primary course N = 1326 (9 trials) %**
Anti-diphtheria (0.1 IU/ml)*	100	99.8
Anti-tetanus (0.1 IU/ml)*	99.9**	99.9
Anti-PT (5 EL.U/ml)	99.9**	99.7
Anti-FHA (5 EL.U/ml)	99.9**	100
Anti-PRN (5 EL.U/ml)	99.5**	99.9
Anti-Polio type 1 (1/8 dilution)*	99.4	99.9

Anti-Polio type 2 (1/8 dilution)*	100	100
Anti-Polio type 3 (1/8 dilution)*	99.4	100
Anti-PRP (Hib) (0.15 µg/ml)*	100	100
Anti-PRP (Hib) (1.0 µg/ml)	96.7	99.2

* cut-off accepted as indicative of protection
** Post dose 3 results from studies where DTPa-HBV-IPV+Hib was administered in a schedule 3, 5 and 11 months of age.
N = number of subjects

The effectiveness of the Hib component (when combined with DTPa, DTPa-IPV or DTPa-HBV-IPV) was investigated via an extensive post-marketing surveillance study conducted in Germany. Over a 4.5 year follow-up period, the effectiveness of DTPa+Hib or DTPa-IPV+Hib vaccines was 96.7% for a full primary series and 98.5% for a booster dose (irrespective of priming). Over a seven year follow-up period, the effectiveness of the Hib components of two hexavalent vaccines was 89.6% for a full primary series and 100% for a full primary series plus booster dose (irrespective of the Hib vaccine used for priming).

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety, specific toxicity and compatibility of ingredients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hib powder:
Lactose

DTPa-IPV suspension:
Sodium chloride
Medium 199 (as stabilizer containing amino acids (including phenylalanine), mineral salts (including sodium and potassium), vitamins (including para-aminobenzoic acid) and other substances)
Water for injections

For adjuvants, see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

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

After reconstitution, the vaccine should be injected immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should normally not be longer than 8 hours at 2°C to 8°C (in a refrigerator).

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Store in the original package, in order to protect from light.

For storage conditions after reconstitution of the medicinal product, please section 6.3.

6.5 Nature and contents of container

Powder in a vial (type I glass) containing 1 dose with a stopper (butyl rubber) and
0.5 ml of suspension in a pre-filled syringe (type I glass) with a plunger stopper (butyl rubber) and with a rubber tip cap.

The tip cap and rubber plunger stopper of the pre-filled syringe and the stopper of the vial are made with synthetic rubber.

Pack sizes of 1 and 10 doses, with or without needles.

6.6 Special precautions for disposal and other handling

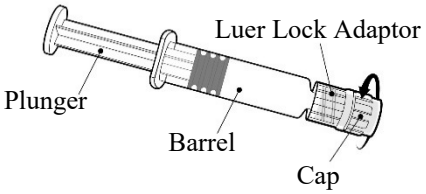
Upon storage of the DTPa-IPV suspension, a white deposit and clear supernatant can be observed in the syringe. This is not a sign of deterioration.

The pre-filled syringe should be well shaken to obtain a homogeneous suspension. The DTPa-IPV suspension in the pre-filled syringe, the Hib powder in the vial and the reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either is observed, the vaccine should be discarded.

The vaccine is reconstituted by adding the entire contents of the pre-filled syringe of DTPa-IPV suspension to the vial containing the Hib powder. The mixture should then be injected immediately. The full reconstitution instructions are:

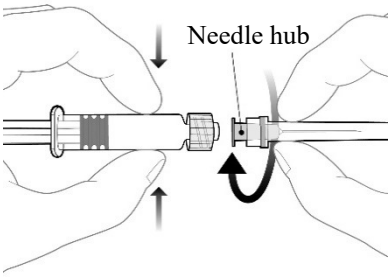
1. Shake the pre-filled syringe containing the DTPa-IPV suspension
2. Attach a needle to the pre-filled syringe of DTPa-IPV and inject the contents of the syringe into the Hib vial.
3. With the needle still inserted, shake the Hib vial vigorously and examine for complete dissolution.
4. Withdraw the entire mixture back into the syringe.
5. Replace the needle with an appropriate size needle for injection and administer the vaccine.
6. If the vaccine is not administered immediately, shake the solution vigorously again before injection.

Instructions for the pre-filled syringe



Hold the syringe by the barrel, not by the plunger.

Unscrew the syringe cap by twisting it anticlockwise.



To attach the needle, connect the hub to the Luer Lock Adaptor and rotate a quarter turn clockwise until you feel it lock.

Reconstitute the vaccine as described above.

Do not pull the syringe plunger out of the barrel. If it happens, do not administer the vaccine.

Disposal

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

7. MANUFACTURER

Glaxo Smith Kline Biologicals S.A., Rixensart, Belgium

8. LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva

9. LICENSE NUMBER

112-53-29413

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