NEW ZEALAND DATA SHEET

1. PRODUCT NAME

INFANRIX-IPV+Hib Combined diphtheria-tetanus-acellular pertussis (DTPa) enhanced inactivated polio and *Haemophilus influenzae* type b suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

INFANRIX-IPV+Hib contains diphtheria toxoid, tetanus toxoid, three purified pertussis antigens (PT, FHA and pertactin) adsorbed on aluminium salts. It contains three types of inactivated polio viruses (type 1: Mahoney strain; type 2: MEF-1 strain; type 3: Saukett strain) and contains purified polyribosyl-ribitol-phosphate capsular polysaccharide (PRP) of *Haemophilus influenzae* type b (Hib), covalently bound to tetanus toxoid.

The diphtheria and tetanus toxoids obtained from cultures of *Corynebacterium diphtheriae* and *Clostridium tetani* are inactivated and purified. The acellular pertussis vaccine components (PT, FHA and pertactin) are prepared by growing phase I *Bordetella pertussis* from which the PT, FHA and pertactin are extracted and purified. FHA and pertactin are treated with formaldehyde, PT is treated with glutaraldehyde and formaldehyde, and irreversibly inactivated.

The three polioviruses are cultivated on a continuous VERO cell line, purified and inactivated with formaldehyde.

The Hib polysaccharide is prepared from *Haemophilus influenzae* type b, strain 20,752 and is coupled to tetanus toxoid. After purification the conjugate is lyophilised in the presence of lactose as stabiliser.

INFANRIX-IPV+Hib meets the World Health Organisation requirements for the manufacture of biological substances, of diphtheria, tetanus, pertussis and combined vaccines, of inactivated poliomyelitis vaccines and Hib conjugate vaccines.

After reconstitution, 1 dose (0.5 mL) of the 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[1] (PT)	25 micrograms
Filamentous haemagglutinin[1] (FHA)	25 micrograms
Pertactin[1] (PRN/69 kiloDalton (kDa) outer membrane protein)	8 micrograms
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 micrograms
conjugated to tetanus toxoid as carrier protein	approximately 25 micrograms
[1]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$)	0.5 milligrams Al^{3+}

[2]propagated in VERO cells

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

INFANRIX-IPV+Hib is presented as Hib vaccine (lyophilised) for reconstitution with the INFANRIX-IPV vaccine (suspension) for injection.

The Hib component of the vaccine is a white powder in a glass vial.

The INFANRIX-IPV component of the vaccine is a turbid white suspension presented in a prefilled syringe. Upon storage, a white deposit and clear supernatant can be observed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

INFANRIX-IPV+Hib is indicated as a booster dose for children aged 15 months and older who have previously been immunised with DTP, polio and Hib antigens.

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

4.2 Dose and method of administration

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

Method of administration

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

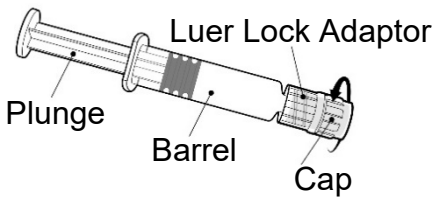
It is preferable that each subsequent dose is given at alternate sites.

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.

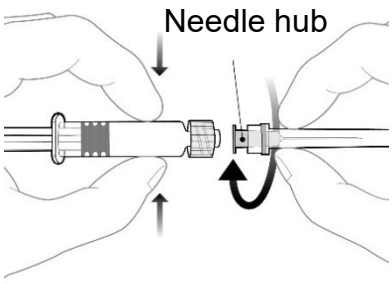
INFANRIX-IPV+Hib should under no circumstances be administered intravenously.

For instructions on reconstitution of the medicine before administration, see section 6.6 Special precautions for disposal and other handling.

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 in section 6.6 Special precautions for disposal and other handling.

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

4.3 Contraindications

INFANRIX-IPV+Hib 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 diphtheria, tetanus, pertussis, inactivated polio or Hib vaccines.

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

4.4 Special warnings and precautions for use

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

It is good clinical practice that vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

If any of the following events occur in temporal relation to receipt of DTP-containing vaccine, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered. 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 benefit ratio of acellular pertussis vaccine is better than the risk benefit ratio of whole cell pertussis vaccine. The following events were previously considered contra-indications for DTPw and can now be considered precautions:

- 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

In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it is better to defer pertussis (Pa or Pw) immunisation until the condition is corrected or stable. However, the decision to give pertussis vaccine must be made on an individual basis after careful consideration of the risks and benefits.

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 contraindications.

Human Immunodeficiency Virus (HIV) infection is not considered as a contraindication.

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

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.

INFANRIX-IPV+Hib contains traces of neomycin and polymyxin. The vaccine should be used with caution in patients with known hypersensitivity to one of these antibiotics.

The use of INFANRIX-IPV+Hib in persons over five year of age is not recommended.

As with all diphtheria, tetanus, and pertussis vaccines, the vaccine should be given by deep intramuscular injection. The vaccine should be given in the anterolateral aspect of the thigh. It is preferable that each subsequent dose is given at alternate sites.

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.

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.

INFANRIX-IPV+Hib should under no circumstances be administered intravenously.

The vaccination should be recorded in the patient's immunisation record.

The potential risk of apnoea and the need for respiratory monitoring for 48-72 hours 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 Interactions with other medicines and other forms of interaction

It is current practice in paediatric vaccination to coadminister different vaccines during the same session, where injectable vaccines should always be given at different injection sites.

INFANRIX-IPV+Hib can be administered concomitantly with hepatitis B vaccine, the injections being applied 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, adequate 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 machines

Not applicable.

4.8 Undesirable effects

Tabulated list of adverse reactions

Clinical Trials

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.

Adverse reactions reported are listed according to the following frequency:

Very common: ≥ 1/10

Common: ≥ 1/100 to < 1/10

Uncommon: ≥ 1/1000 to < 1/100

Rare: ≥ 1/10000 to < 1/1000

Very rare: < 1/10000

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: irritability, crying abnormal, restlessness

Nervous system disorders

Very common: somnolence

Respiratory, thoracic and mediastinal disorders

Uncommon: cough, bronchitis, rhinorrhoea

Gastrointestinal disorders

Common: diarrhoea, vomiting

Skin and subcutaneous tissue disorders

Uncommon: rash, urticaria

Rare: pruritus, dermatitis

General disorders and administration site conditions

Very common: injection site reactions such as pain and redness, local swelling at the injection site (≤50 mm), fever (≥38.0°C)

Common: injection site reactions including induration, local swelling at the injection site (>50 mm)[1]

Uncommon: fever >39.5°C[2], fatigue, diffuse swelling of the injected limb, sometimes involving the adjacent joint[1]

Post-marketing Experience

Respiratory, thoracic and mediastinal disorders

Apnoea[3] [see section 4.4 Special warnings and precautions for use for apnoea in very premature infants (≤ 28 weeks of gestation)]

Blood and lymphatic system disorders

Thrombocytopenia[4]

Immune system disorders

Allergic reactions (including anaphylactic[3] and anaphylactoid reactions)

Nervous system disorders

Convulsions (with or without fever), collapse or shock-like state (hypotonic-hyporesponsiveness episode)

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

[4]Reported with D and T vaccines

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: https://nzphvc.otago.ac.nz/reporting.

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Bacterial and viral vaccines combined, ATC code J07CA06

Immune response to the DT components:

One month after a primary vaccination course more than 99% of infants vaccinated with INFANRIX-IPV+Hib had antibody titers of ≥0.1 IU/mL to both tetanus and diphtheria.

Following administration of a 4th dose of INFANRIX-IPV+Hib in the second year of life, more than 99.5 % of infants had antibody titers of ≥0.1 IU/mL for both tetanus and diphtheria.

Immune response to the Pa component:

One month after the 3-dose primary vaccination course with INFANRIX-IPV+Hib 100% of infants were seropositive for the three pertussis components (PT, FHA, pertactin), and the overall response rate for each of the three individual pertussis antigens was 98.4%, 97.7% and 97.3% respectively.

A booster response was seen in 97.6% - 99.0% - 98.5% of vaccinees against the respective pertussis antigens. All subjects were seropositive one month after this dose.

Protective efficacy of the Pa component:

As the immune response to pertussis antigens following INFANRIX-IPV+Hib administration is equivalent to that of INFANRIX, it can be assumed that the protective efficacy of the two vaccines will also be equivalent.

The protective efficacy of pertussis component of INFANRIX, against WHO-defined typical pertussis (≥ 21 days of paroxysmal cough) was demonstrated in:

- a prospective blinded household contact study performed in Germany (3, 4, 5 months schedule).

  Based on data collected from secondary contacts in households where there was an index case with typical pertussis, the protective efficacy of the vaccine was 88.7%. Protection against laboratory confirmed mild disease, defined as 14 days or more of cough of any type was 73% and 67% when defined as 7 days or more of cough of any type.

- a NIH (National Institute of Health - USA) sponsored efficacy study performed in Italy (2,4,6 months schedule). The vaccine efficacy was found to be 84%. When the definition of pertussis was expanded to include clinically milder cases with respect to type and duration of cough, the efficacy of INFANRIX was calculated to be 71% against >7 days of any cough and 73% against >14 days of any cough.

Immune response to the IPV component:

One month after the primary vaccination, the overall response rate for each of the three serotypes (type 1, 2 and 3) were 99.4%, 97.5% and 100% respectively. More than 99.5% of infants were

seropositive for the three serotypes. Following administration of a fourth dose of INFANRIX-IPV+Hib in the second year of life, 100 % of infants were seropositive for the three serotypes.

Immune response to the Hib component:

A titre of ≥0.15 µg/mL was obtained in ≥ 95% of infants one month after the primary vaccination course.

A titre of ≥1.0 µg/mL was obtained in all infants one month after the booster dose, and in 87.4% of them, a titre of ≥10 µg/mL was reached.

Induction of immunological memory was shown to be an intrinsic part of the mechanism of action of Hib conjugates vaccines. It was shown, with this vaccine, that the primed vaccinee responds with an anamnestic response to a subsequent exposure to the antigen (regardless of the level of measurable antibodies).

In a randomised comparative study**,** it was shown that INFANRIX-IPV+Hib was at least as immunogenic as a DTPw-IPV-Hib vaccine.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aluminium salts (as adjuvant), lactose, sodium chloride, Medium 199 (as stabiliser including amino acids, mineral salts and vitamins) and water for injections.

Residues:

Neomycin sulfate and polymyxin B sulfate.

6.2 Incompatibilities

INFANRIX-IPV+Hib should not be mixed with other vaccines in the same syringe.

6.3 Shelf life

3 years before reconstitution.

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

6.4 Special precautions for storage

The Hib component and the INFANRIX-IPV component have to be stored at +2°C to +8°C.

The INFANRIX-IPV component should not be frozen. Discard if it has been frozen.

6.5 Nature and contents of container

The DTPa-HBV-IPV component is presented as 0.5mL of suspension in a pre-filled syringe (type 1 glass) with a plunger stopper (butyl rubber) and a rubber tip cap.

The Hib component contains one dose and is presented as powder in a glass vial (type 1 glass) with a stopper (butyl rubber).

The tip cap and rubber plunger stopper of the pre-filled syringe and the stopper of the vial are not made with natural rubber latex.

Infanrix-IPV+Hib is supplied in pack sizes of 1 and 10.

Not all pack sizes may be distributed in New Zealand.

6.6 Special precautions for disposal and other handling

The Hib powder, the INFANRIX-IPV suspension and the reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, discard the vaccine. Since a white sediment may form during storage, the INFANRIX-IPV suspension should be shaken before reconstitution.

The vaccine must be reconstituted by adding the entire contents of the supplied container of the INFANRIX-IPV component to the vial containing the powder. Only the components of the vaccine should be mixed together and not with other vaccines or other batches of components. After the addition of the INFANRIX-IPV component to the Hib powder, the mixture should be well shaken.

The reconstituted vaccine presents as a slightly more cloudy suspension than the liquid component alone. This is normal and does not impair the performance of the vaccine. In the event of other variation being observed, discard the vaccine.

After reconstitution, the vaccine should be injected immediately.

Withdraw the entire contents of the vial.

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

GlaxoSmithKline NZ Ltd
Private Bag 106600
Downtown
Auckland
NEW ZEALAND

Phone: (09) 367 2900
Facsimile: (09) 367 2910

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 15 June 2000

10. DATE OF REVISION OF THE TEXT

30 March 2023

Summary table of changes:

Section changed	**Summary of new information**
4.2	Introduction of pictograms for the pre-filled syringe
6.5	Update to description of syringe and cap, including a statement that tip cap and rubber plunger stopper are not made of natural rubber latex

Version 8.0