

PRODUCT MONOGRAPH

INFANRIX-IPV/Hib
HIBERIX reconstituted with INFANRIX-IPV

Combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis,
Haemophilus influenzae type b vaccine

Sterile suspension for injection

Single dose pre-filled syringe INFANRIX-IPV (suspension for injection)
and
Single dose vial HIBERIX (lyophilized powder for injection)

Active immunizing agent

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INFANRIX-IPV/Hib

combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis,
Haemophilus influenzae type b vaccine

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular injection	Sterile suspension for injection/ not less than 25 limit of flocculation (Lf) [30 International Units (IU)] of diphtheria toxoid; 10 Lf (40 IU) of tetanus toxoid; 25 µg of pertussis toxoid; 25 µg of filamentous haemagglutinin; 8 µg of pertactin; 40 D-antigen units (DU) of type 1 poliovirus; 8 DU type 2 poliovirus; 32 DU type 3 poliovirus; 10 µg of purified polyribosyl-ribitol-phosphate capsular polysaccharide of <i>Haemophilus Influenzae</i> type B covalently bound to 25 µg of tetanus toxoid per 0.5 mL dose.	lactose, sodium chloride, aluminum adjuvant (as aluminum salts), Medium 199 (as stabilizer including amino acids, mineral salts and vitamins) and water for injection, residual formaldehyde, polysorbate 80, potassium chloride, disodium phosphate, monopotassium phosphate, glycine and trace amounts of neomycin sulphate and polymyxin B sulphate.

DESCRIPTION

INFANRIX-IPV/Hib (combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b vaccine) contains diphtheria toxoid, tetanus toxoid, three purified pertussis antigens [pertussis toxoid (PT), filamentous haemagglutinin (FHA), and pertactin (69 kiloDalton outer membrane protein)] adsorbed onto aluminum salts, inactivated poliovirus types 1, 2, and 3, and contains purified polyribosyl-ribitol-phosphate capsular polysaccharide (PRP) of *Haemophilus influenzae* type b (Hib), covalently bound to tetanus toxoid.

INDICATIONS AND CLINICAL USE

Pediatrics:

Primary Immunization

INFANRIX-IPV/Hib (combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b vaccine) is indicated for:

- active primary immunization in infants from the age of 6 weeks against diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenzae* type b.

The administration of the primary vaccine course should be given at 2, 4, and 6 months as stated in the Canadian Immunization Guide. However, other vaccine schedules (such as 2, 3, 4 months; 3, 4, 5 months; 3, 5, 11 months) have been studied in different countries.

INFANRIX-IPV/Hib has not been evaluated in the Canadian Native Population.

Booster Vaccination

The administration of the booster dose should be given at 18 months as stated in the Canadian Immunization Guide.

INFANRIX-IPV/Hib is also indicated as:

- a booster dose in the second year of life for children who have previously been immunised with diphtheria, tetanus, pertussis (DTaP), polio and Hib antigens.

Where passive protection is required, Tetanus Immune Globulin and/or Diphtheria Antitoxin may also be administered at separate sites. Because of the substantial risks of complications from pertussis disease, completion of a primary series of vaccine early in life is strongly recommended.

CONTRAINDICATIONS

INFANRIX-IPV/Hib (combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b vaccine):

- should not be administered to subjects with known hypersensitivity to any component of the vaccine (see DOSAGE FORMS, COMPOSITION AND PACKAGING) or to subjects having shown signs of hypersensitivity after a previous dose of this vaccine or any injection containing diphtheria, tetanus, pertussis, poliovirus, or *Haemophilus influenzae* type b.
- is contraindicated in patients who previously experienced an immediate anaphylactic reaction temporally associated with a previous dose of this vaccine or any injection containing diphtheria, tetanus, pertussis, poliovirus, or

Haemophilus influenzae type b. Because of the uncertainty to which component of the vaccine might be responsible, no further vaccination with any of these components should be given. Alternatively, because of the importance of tetanus vaccination, such individuals may be referred to an allergist for evaluation.

- should not be administered to persons 5 years of age or older.
- is contraindicated if the infant has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with a pertussis containing vaccine. In these circumstances, pertussis vaccination should be discontinued and the vaccination should be continued with diphtheria-tetanus, polio, and Hib vaccines.

Elective immunization of individuals over 6 months should be deferred during an outbreak of poliomyelitis.

WARNINGS AND PRECAUTIONS

General

INFANRIX-IPV/Hib (combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b vaccine) should under no circumstances be administered intravenously.

As for all diphtheria, tetanus and pertussis vaccines, each injection should be given deep intramuscularly, in the anterolateral aspect of the thigh, and each injection of the immunization series should be made at a different site.

As with other injectable vaccines, epinephrine injection (1:1000) and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur. For this reason, the vaccinee should remain under medical supervision for 30 minutes after immunization. Refer to “Anaphylaxis: Initial Management in Non-Hospital Settings”, in the Canadian Immunization Guide, 7th ed.

As with other vaccines, the administration of INFANRIX-IPV/Hib should be postponed in subjects suffering from moderate or severe illness with or without fever. The presence of minor illnesses with or without a low-grade fever 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.

As with any other vaccine, every individual may not receive 100% protection from each component of INFANRIX-IPV/Hib. This product is not recommended for treatment of actual infections.

If any of the following events occur in temporal relation to administration of whole-cell DTP or acellular DTP vaccine, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered.

- Temperature of $\geq 40.0^{\circ}\text{C}$ (rectal) within 48 hours of vaccination 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 high incidence of pertussis, in which the potential benefits outweigh possible risks, particularly since these events have not been proven to cause permanent sequelae.

The Hib component of the vaccine does not protect against diseases due to capsular serotypes other than type b of *Haemophilus influenzae* or against meningitis caused by other organisms. Excretion of capsular polysaccharide antigen in the urine has been described following administration of Hib vaccines, and therefore antigen detection may not have a diagnostic value in suspected Hib disease within 1-2 weeks of vaccination.

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.

Hematologic

INFANRIX-IPV/Hib should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following intramuscular administration to these subjects. Firm pressure should be applied to the injection site (without rubbing) for at least 2 minutes.

Immune

INFANRIX-IPV/Hib is not contraindicated for use in individuals with HIV infection. The expected immunological response may not be obtained after vaccination of immunosuppressed patients e.g. patients on immunosuppressive therapies.

Neurologic

Experience with INFANRIX (DTaP) and other INFANRIX based combinations has not revealed any cases of encephalopathy or permanent neurologic damage causally linked to vaccination. While acute encephalopathy and permanent neurologic damage have not been reported to be causally linked nor in temporal association with administration of INFANRIX-IPV/Hib, data are limited at this time.

In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it is better to defer pertussis (Pa or Pw) immunization 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 for INFANRIX-IPV/Hib, an acellular DTP vaccine.

Studies suggest that, when given whole-cell DTP vaccine, infants and children with a history of convulsions in first-degree family members (i.e. siblings and parents) have a 2.4-fold increased risk for neurologic events compared to those without such histories.

Respiratory

Although a moderate or severe febrile illness with or without fever is a reason to defer vaccination, minor illnesses such as mild upper respiratory infections with or without low-grade fever are not a contraindication.

Special Populations

Pregnant Women: INFANRIX-IPV/Hib is not intended for use in adults.

Nursing Women: INFANRIX-IPV/Hib is not intended for use in adults.

Pediatrics: INFANRIX-IPV/Hib should not be administered to persons 5 years of age or older.

The potential risk of apnea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunization series to very premature infants (born \leq 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinical trial data from approximately 6100 doses administered for primary immunization, and approximately 2900 doses administered as a booster during the second year of life, have shown that INFANRIX-IPV/Hib (combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b vaccine) is generally well tolerated.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The local and systemic symptoms reported after administration of the combined DTaP-IPV/Hib vaccine when used for primary vaccination during clinical trials using an infant immunization schedule of 2, 4, 6 months and booster are shown in Table 1.

Table 1: Signs and Symptoms Reported After Administration of the Combined DTaP-IPV/Hib Vaccine

Event	INFANRIX-IPV/Hib Primary		INFANRIX-IPV/Hib Booster	
	2, 4, 6 months (Doses = 2023)	All Schedules (Doses = 6109)	2, 4, 6 months (Doses = 332)	All Schedules (Doses = 2940)
Local	%		%	
Pain, any	14.5	14.9	37.0	33.3
Pain, severe	0.2	0.4	0.9	1.9
Redness, any	20.6	30.6	48.2	45.4
Redness, > 20 mm	1.3	1.3	26.5	14.2
Swelling, any	14.6	15.3	36.7	33.0
Swelling, > 20 mm	2.0	1.7	16.6	10.3
Systemic	%		%	
Temperature ≥ 38°C	14.0	14.3	31.0	29.6
> 39.5°C	0.4	0.4	1.8	2.4
Diarrhea any	9.8	9.1	16.0	14.7
Grade 3	0.2	0.2	1.5	1.3
Eating/Drinking less than usual, any	16.2	15.1	27.4	19.8
Grade 3	0.3	0.4	3.3	1.9
Irritability/Fussiness, any	38.8	31.8	36.7	22.4
Grade 3	1.3	1.7	3.0	2.2
Unusual crying for more than 1 hour, any	16.2	17.6	23.8	11.7
Grade 3	0.7	1.3	1.5	1.7
Vomiting, any	7.8	7.9	6.3	5.5
Grade 3	0.1	0.2	0.9	0.8

Grade 3 = Severe Adverse experience which prevents normal everyday activities.

The safety profile presented below is based on data from more than 3500 subjects.

As has been observed for DTaP and DTaP-containing combinations, an increase in local reactogenicity and fever was reported after booster vaccination with INFANRIX-IPV/Hib with respect to the primary course.

Other symptoms which have been reported during the studies are nervousness, anorexia, somnolence and fatigue.

Very common: ≥ 10%

Appetite lost, irritability, crying abnormal, restlessness, somnolence, injection site reactions such as pain and redness, local swelling at the injection site (≤ 50 mm), fever ($\geq 38.0^\circ\text{C}$)

Common: ≥ 1% and < 10%

Diarrhea, vomiting, injection site reactions including induration, local swelling at the injection site (> 50 mm)¹

Uncommon: ≥ 0.1% and < 1%

Upper respiratory tract infection, lymphadenopathy, cough, bronchitis, rhinorrhea, rash, urticaria, fever² $> 39.5^\circ\text{C}$, fatigue, diffuse swelling of the injected limb, sometimes involving the adjacent joint¹

Rare: ≥ 0.01% and < 0.1%

Pruritus, dermatitis

Post-Market Adverse Drug Reactions

Respiratory, thoracic and mediastinal disorders

Apnea³ [see section “Warnings and Precautions” for apnea in very premature infants (≤ 28 weeks of gestation)]

Blood and lymphatic system disorders

Thrombocytopenia⁴

Immune system disorders

Allergic reactions (including anaphylactic³ 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 oedema³, petechiae/purpura

General disorders and administration site conditions

Swelling of the entire injected limb¹, injection site vesicles³, oedema peripheral

¹Children 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.

²Common with booster vaccination

³Reported with GSK's DTaP containing vaccines

⁴ Reported with D and T vaccines

DRUG INTERACTIONS

Overview

INFANRIX-IPV/Hib (combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b vaccine) should not be mixed with any other vaccines in the same syringe.

It is current practice in pediatric vaccination to co-administer different vaccines during the same session, where injectable vaccines should be given at different injection sites. Clinical trials have shown that INFANRIX-IPV/Hib can be administered concomitantly with Hepatitis B vaccine.

Drug-Drug Interactions

Anticoagulants

As with other intramuscular injections, INFANRIX-IPV/Hib should not be given to infants or children on anticoagulant therapy unless the potential benefit clearly outweighs the risk of administration (see WARNINGS AND PRECAUTIONS).

Measles-Mumps-Rubella vaccine

The simultaneous administration of INFANRIX-IPV/Hib and Measles-Mumps-Rubella vaccine has not been studied. However, it is generally accepted that Measles-Mumps-Rubella vaccine may be given, simultaneously, but at different sites, with inactivated combination vaccines.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose

Primary Immunization

The primary immunization course is 3 doses of INFANRIX-IPV/Hib 0.5 mL (combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b vaccine), given intramuscularly at 2, 4 and 6 months of age.

Booster Immunization

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.

Missed Dose

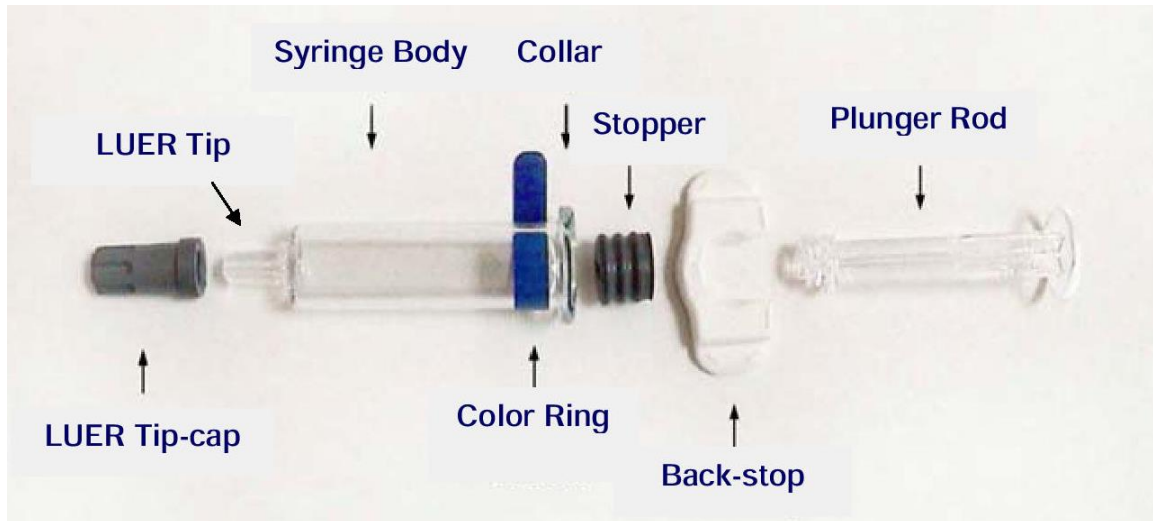
Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved with INFANRIX-IPV/Hib. There is no need to start the series over again regardless of the time elapsed between doses.

Administration

Preparation for Administration

INFANRIX-IPV/Hib is prepared by adding the entire liquid contents, INFANRIX-IPV (diphtheria toxoid, tetanus, acellular pertussis and inactivated poliomyelitis vaccine), of the syringe, to the vial containing the HIBERIX (*Haemophilus influenzae* type b), a lyophilized powder. The vaccine should not be mixed with other vaccines.

Do not remove the white back-stop from the syringe. Prior to administration, ensure that the plunger rod is firmly attached to the rubber stopper by turning the plunger clockwise until slight resistance is felt. **Do not** over tighten. Remove syringe LUER Tip-cap and needle cap. Attach needle by pressing and twisting in a clockwise rotation until secured to the syringe.



All parenteral drug products should be inspected visually for particulate matter or discoloration prior to administration. Upon storage, a white deposit and clear supernatant may be observed in the liquid component in the syringe; this does not constitute a sign of deterioration. Shake the syringe well before use. With thorough agitation, the liquid component should become a homogenous white turbid suspension. Discard if it appears otherwise. After the addition of the liquid to the powder, the mixture should be well shaken until the powder is completely dissolved. The vaccine is ready to use without dilution.

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. Discard if it appears otherwise.

The product should be used immediately after reconstitution. However stability of the vaccine has been demonstrated for 8 hours at +21°C after reconstitution.

After removal of the 0.5 mL dose, any vaccine remaining in the vial should be discarded.

INFANRIX-IPV/Hib should be administered by intramuscular injection. The preferred site is the anterolateral aspects of the thigh. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk. Before injection, the skin at the injection site should be cleaned and prepared with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

Do not administer this product subcutaneously or intravenously.

OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Diphtheria

Diphtheria is a serious communicable disease, primarily a localized and generalized intoxication caused by diphtheria toxin, an extracellular protein metabolite of toxigenic strains of *Corynebacterium diphtheriae*. The disease occurs most frequently in unimmunized or partially immunized individuals. The incidence of diphtheria in Canada has decreased from 9,000 cases reported in 1924 to extremely low levels. Only one or two cases have been reported annually in recent years. The case fatality rate remains 5% to 10%, with the highest death rates in the very young and elderly. If immunization levels are allowed to fall and adults do not receive booster doses, disease re-emergence may appear as demonstrated in the Commonwealth of Independent States (former Soviet Union), where tens of thousands of cases with substantial mortality have been reported. Protection against disease is due to the development of neutralizing antibodies to the diphtheria toxin. Following adequate immunization with diphtheria toxoid, it is thought that protection persists for at least 10 years. Serum antitoxin levels of at least 0.01 antitoxin units per mL by *in vivo* neutralization assay are generally regarded as protective.

This significantly reduces both the risk of developing diphtheria and the severity of clinical illness. Immunization with diphtheria toxoid does not, however, eliminate carriage of *C. diphtheriae* in the pharynx, nose or on the skin.

Tetanus

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin released by *Clostridium tetani*. Immunization is highly effective, provides long-lasting protection and is recommended for the whole population. Only 1 to 7 with an average of 5 cases of tetanus are now reported annually in Canada while no deaths recorded since 1995. The disease continues to occur almost exclusively among persons who are unvaccinated, or inadequately vaccinated or whose vaccination histories are unknown or uncertain.

Spores of *C. tetani* are ubiquitous. Naturally acquired immunity to tetanus toxin does not occur. Thus, universal primary immunization and timed booster doses to maintain adequate antitoxin levels are necessary to protect all age groups. Protection against disease is due to the development of neutralizing antibodies to the tetanus toxin. Tetanus

toxoid is a highly effective antigen and a completed primary series generally induces serum antitoxin levels of at least 0.01 antitoxin units per mL by *in vivo* neutralization assay, a level which has been reported to be protective. It is thought that protection persists for at least 10 years.

Pertussis

Pertussis (whooping cough) is a disease of the respiratory tract caused by *Bordetella pertussis*. Pertussis is highly communicable (attack rates in unimmunized household contacts of up to 90% have been reported) and can affect individuals of any age; however, severity is greatest among young infants. Precise epidemiologic data do not exist, since bacteriological confirmation of pertussis can be obtained in less than half of the suspected cases. Most reported illness from *B. pertussis* occurred in infants and young children in whom complications can be severe. Older children, adolescents and adults, in whom classic signs are often absent, may go undiagnosed and may serve as reservoirs of disease. Pertussis epidemics are cyclic and occur every 3 to 4 years. Pertussis has been controlled in Canada through immunization. During the last 40 years, the incidence of pertussis has decreased by > 90% although outbreaks continue to occur.

A recent study was conducted in Germany to assess the efficacy of pertussis vaccine after partial and completed primary vaccination series for preventing hospitalizations due to pertussis under field conditions. Data was acquired by a nationwide, hospital based, active surveillance system. After one dose of the vaccine, vaccine effectiveness was as high as 68%, increasing to 91.8% after receipt of the second dose. Vaccine effectiveness of 3 and 4 doses of acellular vaccine were estimated to be 99.8% and 98.6%, respectively.

Antigenic components of *B. pertussis* believed to contribute to protective immunity include: pertussis toxin (PT); filamentous hemagglutinin (FHA); and pertactin. Although the role of these antigens in providing protective immunity in humans is not well understood, clinical trials which evaluated candidate acellular DTP vaccines manufactured by GlaxoSmithKline supported the efficacy of 3-component INFANRIX (DTaP). Recently published data suggests a higher importance of the PT and pertactin components in providing protection against pertussis.

INFANRIX, which contains three pertussis antigens (PT, FHA and pertactin), has been shown to be effective in preventing World Health Organization (WHO)-defined pertussis as well as clinically milder disease in two published clinical trials when administered as a primary series.

A double-blind, randomized, placebo (DT)-controlled trial conducted in Italy, sponsored by the U.S. National Institutes of Health (NIH), assessed the absolute protective efficacy of INFANRIX when administered at 2, 4 and 6 months of age. A total of 15,601 infants were immunized with 1 of 2 tri-component acellular DTP vaccines (containing inactivated PT, FHA and pertactin), or with a whole-cell DTP vaccine manufactured by Sanofi Pasteur, or with DT vaccine alone. The mean length of follow-up was 17 months, beginning 30 days after the third dose of vaccine. The population used in the primary

analysis of vaccine efficacy included 4,481 INFANRIX vaccinees, 4,348 whole-cell DTP vaccinees and 1,470 DT vaccinees. After 3 doses, the protective efficacy of INFANRIX against WHO-defined typical pertussis (21 days or more paroxysmal cough with infection confirmed by culture and/or serologic testing) was 84% (95% CI: 76% to 89%) while the efficacy of the whole-cell DTP vaccine was 36% (95% CI: 14% to 52%). When the definition of pertussis was expanded to include clinically milder disease with respect to type and duration of cough, with infection confirmed by culture and/or serologic testing, the efficacy of INFANRIX was calculated to be 71% (95% CI: 60% to 78%) against > 7 days of any cough and 73% (95% CI: 63% to 80%) against \geq 14 days of any cough. A longer follow-up of the Italian trial showed that after three doses, the absolute efficacy of INFANRIX against WHO-defined pertussis remained as high as 84% among children up to 4 years of age.

A prospective, blinded efficacy trial was also conducted in Germany employing a household contact study design. In preparation for this study, 3 doses of INFANRIX were administered at 3, 4 and 5 months of age to more than 22,000 children living in 6 areas of Germany in a large safety and immunogenicity trial. Infants who did not participate in this trial could have received whole-cell DTP vaccine (manufactured by Chiron Behring, Germany) or DT vaccine. Calculation of vaccine efficacy was based on attack rates of pertussis in household contacts classified by vaccination status. Of the 173 unvaccinated household contacts, 96 developed WHO-defined pertussis (21 days or more of paroxysmal cough with infection confirmed by culture and/or serologic testing), as compared to 7 of 112 contacts vaccinated with INFANRIX and 1 of 75 contacts vaccinated with whole-cell DTP vaccine. The protective efficacy of INFANRIX was calculated to be 89% (95% CI: 77% to 95%), with no indication of waning of immunity up until the time of the booster. The protective efficacy of the whole-cell DTP vaccine was calculated to be 98% (95% CI: 83% to 100%). When the definition of pertussis was expanded to include clinically milder disease, with infection confirmed by culture and/or serologic testing, the efficacy of INFANRIX against \geq 7 days of any cough was 67% (95% CI: 52% to 78%) and against \geq 7 days of paroxysmal cough was 81% (95% CI: 68% to 89%). The corresponding efficacy rates of INFANRIX against \geq 14 days of any cough or paroxysmal cough were 73% (95% CI: 59% to 82%) and 84% (95% CI: 71% to 91%), respectively.

Poliomyelitis

Poliovirus is an enterovirus that belongs to the picornavirus family. Three serotypes of poliovirus have been identified (types 1, 2 and 3). Poliovirus is highly contagious with the predominant mode of transmission being person-to-person via the fecal-oral route. Infection may be spread indirectly through contact with infectious saliva or feces or by contaminated water or sewage.

Replication of poliovirus in the pharynx and intestine is followed by a viremic phase where involvement of the central nervous system can occur. While poliovirus infections are asymptomatic or cause non-specific symptoms (low-grade fever, malaise, anorexia and sore throat) in 90% to 95% of individuals, 1% to 2% of infected persons will develop paralytic disease.

Following the introduction of inactivated poliovirus vaccines (IPV) in Canada in 1955, the indigenous disease has been eliminated. Since 1980, 12 paralytic cases have been reported in Canada, 11 of which were determined to be vaccine-associated paralytic poliomyelitis (VAPP), with Oral Polio Vaccine (OPV). The last reported case of VAPP occurred in 1995.

Forty seven studies involving over 19,000 infants and children have been conducted in developed and developing countries with GlaxoSmithKline's enhanced inactivated poliovirus components as trivalent IPV vaccine or as a part of DTaP-IPV based combinations.

Haemophilus influenzae type b

Haemophilus influenzae type b (Hib) was the most common cause of bacterial meningitis and a leading cause of other serious invasive infections in young children prior to the introduction of other Hib vaccines. About 55% to 65% of affected children had meningitis while the remainder had epiglottitis, bacteremia, cellulitis, pneumonia or septic arthritis. The case fatality rate of meningitis is about 5%. Severe neurologic sequelae occur in 10% to 15% of survivors and deafness in 15% to 20% (severe in 3% to 7%).

Before the introduction of Hib conjugate vaccines in Canada in 1988, there were approximately 2,000 cases of Hib disease annually. Since then the overall incidence has fallen by more than 99%. The majority of cases occur now in children too old to have received primary vaccination. In 1998, only 15 cases were reported in children < 5 years of age.

STORAGE AND STABILITY

The HIBERIX component and the INFANRIX-IPV component must be stored at 2° to 8°C.

Do not use after expiration date shown on the label.

After reconstitution: immediate use is recommended. However stability of the vaccine has been demonstrated for 8 hours at +21°C after reconstitution.

Do not freeze. Discard if the vaccine has been frozen.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms:

Syringe and Vial

HIBERIX (*Haemophilus influenzae* type b) vaccine is supplied as a lyophilized white powder in a glass vial.

INFANRIX-IPV (diphtheria, tetanus, acellular pertussis and inactivated poliomyelitis vaccine) is supplied as a turbid white suspension in a pre-filled (0.5 mL) syringe. Upon storage, a white deposit and clear supernatant may be observed in the liquid component of the syringe; this does not constitute a sign of deterioration.

The vials and prefilled syringes are made of neutral glass type 1, which conforms to European Pharmacopoeia requirements.

The vial is sealed with a butyl rubber stopper. The syringes are presented with or without needles and fitted with butyl rubber plunger stoppers and tip caps or rubber shields.

Composition

Each 0.5 mL dose is formulated to contain not less than: 25 limit of flocculation (Lf) [30 International Units (IU)] diphtheria toxoid, 10 Lf (40 IU) tetanus toxoid, 25 µg PT, 25 µg FHA, 8 µg pertactin, 40 D-antigen Units (DU) of type 1 poliovirus, 8 DU type 2 poliovirus, 32 DU type 3 poliovirus, 10 µg of purified capsular polysaccharide of Hib (PRP) covalently bound to 25 µg of tetanus toxoid.

Each 0.5 mL dose also contains 12.6 mg lactose (as stabilizer), 4.5 mg sodium chloride, aluminum adjuvant (as 0.5 mg aluminum salts), Medium 199 (as stabilizer) and water for injection. The vaccine contains residual formaldehyde, polysorbate 80, potassium chloride, disodium phosphate, monopotassium phosphate, glycine, and trace amounts of neomycin sulphate and polymyxin B sulphate.

Packaging

Pack sizes of :

10 doses: 10 syringes INFANRIX-IPV suspension x 10 vials lyophilized HIBERIX.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b vaccine

Product Characteristics

INFANRIX-IPV/Hib (combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b vaccine) contains diphtheria toxoid, tetanus toxoid, three purified pertussis antigens [pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (69 kiloDalton outer membrane protein)] adsorbed onto aluminum salts, inactivated poliovirus types 1,2 and 3, and contains purified polyribosyl-ribitol-phosphate capsular polysaccharide (PRP) of *Haemophilus influenzae* type b (Hib), covalently bound to tetanus toxoid.

CLINICAL TRIALS

Study Results

Immune Response to INFANRIX-IPV/Hib Administered as a Three-Dose Primary Series

Over 6,000 doses of INFANRIX-IPV/Hib (combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b vaccine) have been administered to infants from 2 months of age and up as a primary series of clinical studies. These studies have investigated the tolerability and immunogenicity of the vaccine in various schedules (i.e. 2, 4, 6 months; 2, 3, 4 months; 3, 4, 5 months; 3, 5, 11 months). Immunological results are obtained in all of the clinical studies for each of the components are summarized below:

DTaP component:

Immunological data:

One month after the 3-dose primary vaccination course, more than 99% of infants vaccinated with INFANRIX-IPV/Hib, had antibody titres of ≥ 0.1 IU/mL by ELISA for 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 titres of ≥ 0.1 IU/mL for both tetanus and diphtheria.

One month after the 3-dose primary vaccination course with INFANRIX-IPV/Hib, more than or equal to 99.8% of infants were seropositive for the three pertussis components, and the overall response rate for each of the three individual pertussis antigens (PT, FHA, pertactin) was 98.4%, 97.6% and 98.4%, respectively.

Following administration of a 4th dose of INFANRIX-IPV/Hib in the second year of life, a booster response was seen in 98.6%, 97.6% and 97.9% of vaccinated infants against the respective pertussis antigens. All subjects were seropositive one month after this dose. Since a serological correlation for protection against pertussis disease does not exist, the efficacy of the pertussis component presently relies on efficacy trials described below:

Protective efficacy data:

The efficacy of the DTaP component, against WHO-defined typical pertussis (≥ 21 days of paroxysmal cough) was demonstrated in two studies.

The first was a prospective blinded household contact study performed in Germany (3, 4, 5 months vaccination 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%.

The second was a National Institutes of Health (NIH) sponsored efficacy study performed in Italy (2, 4, 6 months vaccination schedule). The vaccine efficacy was found to be 84%. In a follow-up of the same cohort, efficacy was confirmed up to 60 months after completion of primary vaccination without administration of a booster dose of pertussis.

The immune response to pertussis antigens following INFANRIX-IPV/Hib administration is equivalent to that of INFANRIX.

IPV component:

One month after the primary vaccination, the overall seroprotection rates for each of the three serotypes (types 1, 2 and 3) were 99.6%, 98.4% and 99.9%, respectively.

Following administration of the booster dose in the second year of life, 100% of infants were seroprotected for the three serotypes.

Hib component:

One month after completion of the primary vaccination course, a titre of ≥ 0.15 $\mu\text{g/mL}$ was obtained in $> 98\%$ of infants.

One month after the booster dose was administered in the second year of life, a titre of ≥ 0.15 $\mu\text{g/mL}$ was obtained in 99.7% of all infants, and in $> 98.3\%$ of infants, a titre of 1 $\mu\text{g/mL}$ was reached.

Induction of immunological memory has been shown to be an important and intrinsic part of the protective immune response following administration of Hib conjugate vaccines.

Children primed with INFANRIX-IPV/Hib had an anamnestic response (defined as a rapid and substantial increase in antibody level) on subsequent exposure to the antigen.

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

The effectiveness of the GlaxoSmithKline Hib component (when combined with DTaP or DTaP-IPV) has been investigated through an extensive post-marketing surveillance study in Germany. Over a 2 year follow-up period, the effectiveness of three primary doses of DTaP/Hib or DTaP-IPV/Hib was 98.8%.

The immune response to each of the antigens contained in INFANRIX-IPV/Hib were evaluated in sera obtained after the third dose of vaccine using an administration schedule of 2, 4, 6 months. The results are shown in Table 2 below.

Table 2 : Antibody Responses to Each Antigen Following INFANRIX-IPV/Hib Administration Using 2, 4, 6, Primary Immunization Schedule (One Month After Administration of Dose 3)

	INFANRIX-IPV/Hib (N=328-591)
Anti-Diphtheria % \geq 0.1 IU/mL GMT (95% C.I.)	99.3 1.852 (1.696-2.022)
Anti-Tetanus % \geq 0.1 IU/mL GMT (95% C.I.)	99.8 2.484 (2.314-2.667)
Anti-PT % positive GMT (95% C.I.)	100 60.4 (56.5-64.6)
Anti-FHA % positive GMT (95% C.I.)	100 217.3 (205.3-229.9)
Anti-Pertactin % positive GMT (95% C.I.)	100 165.3 (151.2-180.7)
Anti-Polio 1 % positive GMT (95% C.I.)	99.5 344.6 (303.8-390.8)
Anti-Polio 2 % positive GMT (95% C.I.)	98.8 310.8 (268.7-359.4)
Anti-Polio 3 % positive GMT (95% C.I.)	100 894.0 (793.9-1006.7)
Anti-PRP % \geq 0.15 mcg/mL % \geq 1.0 mcg/mL GMT (95% C.I.)	98.5 76 2.438 (2.209-2.691)

GMT = Geometric mean antibody titre.

(95% C.I.) = 95% Confidence Interval

N = the range of the cumulative number of blood samples tested for the different antigens, from all studies using a primary administration schedule at 2, 4 and 6 months.

PT = Pertussis Toxoid

FHA = Filamentous Haemagglutinin

Polio = Poliovirus

PRP = Polyribosyl-ribitol-phosphate

DETAILED PHARMACOLOGY

Not applicable.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Not applicable.

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PART III: CONSUMER INFORMATION**INFANRIX-IPV/Hib**

combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis and *Haemophilus influenzae* type b vaccine

This leaflet is part III of a three-part "Product Monograph" published for INFANRIX-IPV/Hib (combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis and *Haemophilus influenzae* type B vaccine), approved for sale in Canada, and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about INFANRIX-IPV/Hib. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

INFANRIX-IPV/Hib is a vaccine used in children for protection against diphtheria, tetanus (lockjaw), pertussis (whooping cough), poliomyelitis (polio) and *Haemophilus influenzae* type b diseases.

Vaccination is the best way to protect against these diseases.

What it does:

INFANRIX-IPV/Hib works by helping the body make its own protection (antibodies) which protect your child against these diseases.

When it should not be used:

INFANRIX-IPV/Hib should not be used:

- in children with known allergy to any component of the vaccine (see "What the important nonmedicinal ingredients are" section) or children having shown signs of an allergic reaction after a previous dose of this vaccine or any injection containing diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenzae* type b. Signs of an allergic reaction may include shortness of breath and swelling of the face or tongue.
- if your child has an infection or a high temperature (over 38°C). A minor infection such as a cold should not be a problem, but talk to your doctor first.
- vaccination should not be received if your child's defences against infections (immunity mechanisms) are impaired.
- in persons 5 years of age or older.
- in infants who experienced problems of the nervous system within 7 days following previous vaccination with a pertussis (whooping cough) vaccine.

What the medicinal ingredient is:

INFANRIX-IPV/Hib contains the following medicinal ingredients: combined diphtheria and tetanus toxoids, three purified pertussis antigens [pertussis toxoid, filamentous haemagglutinin and pertactin (69 kiloDalton outer membrane protein)], inactivated polio virus types 1, 2 and 3, and conjugated *Haemophilus influenzae* type b.

None of the components in the vaccine are infectious. You cannot get the diseases from the INFANRIX-IPV/Hib vaccine.

What the important nonmedicinal ingredients are:

INFANRIX-IPV/Hib contains the following nonmedicinal ingredients: lactose, sodium chloride, aluminum salts, Medium 199 and water for injection, residual formaldehyde, polysorbate 80, potassium chloride, disodium phosphate, monopotassium phosphate, glycine, and trace amounts of neomycin sulphate and polymyxin B sulphate.

What dosage forms it comes in:

INFANRIX-IPV/Hib is supplied as a cloudy suspension for injection in a pre-filled glass syringe. The HIBERIX portion is supplied as a powder in a glass vial.

The 2 components are mixed together before they are given to your child.

WARNINGS AND PRECAUTIONS

Before you use INFANRIX-IPV/Hib talk to your doctor or pharmacist if:

- your child had any problems (such as high fever, collapse or shock-like state or persistent crying lasting 3 hours or more) within 48 hours or fits (with or without a fever) within 3 days of vaccination with INFANRIX-IPV/Hib or another vaccine against pertussis (whooping cough).
- you have a family history of convulsions.
- your child is suffering from neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy (disease of brain).
- your child has a bleeding problem or bruises easily. INFANRIX-IPV/Hib should be given with caution since bleeding may occur following vaccination.
- your child has an infection, or a temperature over 38°C, or both.
- your child has any known allergies.
- your child is taking any other medicine or has recently received any other vaccine.
- your child has any serious health problem.
- if your child has breathing difficulties, please contact your doctor. This may be more common in the first

three days following vaccination if your child is born prematurely (before or at 28 weeks of pregnancy).

- Please tell your doctor if your child has had an allergic reaction to neomycin or polymyxin (antibiotics).

Fainting can occur following, or even before, any needle injection; therefore, tell the doctor or nurse if your child fainted with a previous injection.

INTERACTIONS WITH THIS MEDICATION

INFANRIX-IPV/Hib can be given at the same time as hepatitis B vaccine. Measles-Mumps-Rubella vaccine may be given simultaneously with INFANRIX-IPV/Hib, but at different sites, with inactivated combination vaccines.

INFANRIX-IPV/Hib should not be given to children on anticoagulant (medicine that prevents blood from clotting) therapy unless the benefits clearly outweigh the risks.

PROPER USE OF THIS MEDICATION

Usual dose:

Your child will receive a total of 4 injections. Each injection will be given intramuscularly (into a muscle) at 2, 4 and 6 months of age. A booster should be given at 18 months.

Missed Dose:

If your child misses a scheduled injection, talk to your doctor and arrange another visit.

Make sure your child finishes the complete vaccination course. If not your child may not be fully protected against infection.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all vaccines, INFANRIX-IPV/Hib may occasionally cause unwanted effects.

As with other vaccines in any age group, allergic reactions may occur very rarely (in less than 1 in 10,000 doses of the vaccine). This can be recognised by symptoms such as itchy rash of the hands and feet, swelling of the eyes and face and difficulty in breathing or swallowing and a sudden drop in blood pressure and loss of consciousness. Such reactions will

usually occur before leaving the doctor's office. However, you should seek immediate treatment in any event.

See your doctor straight away if your child has any of the following serious side effects:

- collapse
- times when they lose consciousness or have a lack of awareness
- fits – this may be when they have a fever

These side effects have happened very rarely with other vaccines against whooping cough. They usually happen within 2 to 3 days after vaccination.

Other side effects:

Very common side effects (in more than 1 in 10 doses of the vaccine) after having INFANRIX-IPV/Hib are loss of appetite, irritability, unusual crying, restlessness, pain, redness and swelling at injection site, fever more than 38°C and sleepiness.

Common side effects (in more than 1 in 100 doses of the vaccine) after having INFANRIX-IPV/Hib are vomiting, diarrhea, swelling larger than 5 cm at injection site and a hard lump at injection site.

Uncommon side effects (in more than 1 in 1,000 doses of the vaccine) after having INFANRIX-IPV/Hib are upper respiratory tract infection, swollen glands in the neck, armpit or groin, cough, bronchitis, runny nose, rash, hives, fever more than 39.5°C, feeling tired and swelling occurring over a large area of the injected limb.

Rare side effects (in more than 1 in 10,000 doses of the vaccine) after having INFANRIX-IPV/Hib are itching and skin rash.

Very rare side effects (in less than 1 in 10,000 doses of the vaccine) after having INFANRIX-IPV/Hib are bleeding or bruising more easily than normal, temporarily stopping breathing, in babies born very prematurely (at or before 28 weeks of gestation) longer gaps than normal between breaths may occur for 2-3 days after vaccination, swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing, discoloured skin, swelling of the legs, swelling of the entire injected limb and blisters at the injection site.

If these symptoms continue or become severe, tell the doctor or nurse.

If the child develops any other symptom within days following the vaccination, tell the doctor as soon as possible.

Do not be alarmed by this list of possible side effects. It is possible that your child will have no side effects from vaccination.

This is not a complete list of side effects. For any unexpected effects while taking INFANRIX-IPV/Hib, contact your doctor or pharmacist.

HOW TO STORE IT

Store INFANRIX-IPV/Hib at 2° to 8°C. **Do not freeze.** Discard if the vaccine has been frozen. Store in the original package in order to protect from light.

After reconstitution immediate use is recommended.

Do not use after expiration date shown on the label. The date for last use corresponds to the last day of the month mentioned.

Store all vaccines out of the reach and sight of children.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.

For health care professionals:

If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local Health Unit in [your province/territory](#).

For the General Public:

Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada:

By toll-free telephone: 1-866-844-0018

By toll-free fax: 1-866-844-5931

By email: caefi@phac-aspc.gc.ca

At the following website:

<http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php>

By regular mail:

The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road
Ottawa, Ontario
K1A 0K9 Address Locator 6502A

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

MORE INFORMATION

This document plus the full INFANRIX-IPV/Hib monograph, prepared for health professionals can be found at:

<http://www.gsk.ca> or by contacting the sponsor,
GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4
1-800-387-7374

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