PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Act-HIB®

Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate)

Each 0.5 mL dose contains 10 mcg of Purified Polyribosylribitol Phosphate Capsular Polysaccharide (PRP) of *Haemophilus influenzae* type b covalently bound to 18-30 mcg of Tetanus Protein

Reconstituted Product for Injection

Active Immunizing Agent

Haemophilus influenzae b, purified antigen conjugated

ATC code: J07AG01

Sanofi Pasteur Limited
Toronto, Ontario, Canada

Date of Initial Authorization:
Mar. 19, 1992

Date of Revision:
Apr. 4, 2023

Submission Control Number: 268415

RECENT MAJOR LABEL CHANGES

1 Indications, 1.1 Pediatrics, 1.2 Geriatrics	01/2023
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	01/2023
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Act-HIB® [Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate)] is indicated for:

- The active immunization of children 2 months of age and older for the prevention of invasive disease caused by *Haemophilus influenzae* type b.
- Routine immunization against invasive disease caused by *H. influenzae* type b in infants and children between 2 to 59 months of age.

For more information on this vaccine, refer to NACI recommendations[1].

1.1 Pediatrics (<2 months and >5 years)

- Safety and effectiveness of Act-HIB® have not been established in infants below the age of 2 months and children and adolescents 5 years of age and older.

1.2 Geriatrics

- No data are available from clinical trials to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use .

2 CONTRAINDICATIONS

Allergy to any component of Act-HIB® [Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate)] (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING), including tetanus protein, or an allergic or anaphylactic reaction to a previous dose of Act-HIB® are contraindications to vaccination. When Act-HIB® is reconstituted with Sanofi Pasteur Limited's TRIPACEL® or QUADRACEL® the contraindications for TRIPACEL® or QUADRACEL® must also be considered.

Immunization with Act-HIB® should be deferred in the presence of any acute illness, including febrile illness, to avoid superimposing adverse effects from the vaccine on the underlying illness or mistakenly attributing to the vaccine a manifestation of the underlying illness. A minor afebrile illness such as mild upper respiratory infection is not usually reason to defer immunization.

[1] The National Advisory Committee on Immunization (NACI) provides additional guidance on vaccines in Canada. Please refer to the published chapters on Haemophilus influenza Type B (HIB) and tetanus toxoid.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Each dose is a single injection of 0.5 mL given intramuscularly.

1. **Routine**: Act-HIB® [Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate)] is indicated for the routine immunization of all children between **2 and 59 months** of age. In infants, three injections are to be given intramuscularly at **2, 4 and 6 months** of age, followed by a booster at **18* months** of age (While an interval of 2 months between doses is recommended, an interval as short as 1 month is acceptable).

2. a) For infants between the age of **7 and 11 months**, two doses should be given at an interval of two months, followed by a booster at **18* months** of age.

   b) Children between **12 and 14 months** of age who have not previously received any *Haemophilus* b vaccine should receive one dose of the vaccine followed by a booster at or after **18 months*** of age.

   c) Unvaccinated children between **15 and 59 months** of age should receive a single dose of vaccine.

* The booster dose may be given as early as 15 months of age provided that at least 2 months have elapsed since the previous dose.

For more information, refer to NACI recommendations on Act-Hib vaccine[2].

4.3 Reconstitution

Reconstitution of Freeze-Dried Product and Withdrawal from Stoppered Vial.

Reconstitute the vaccine using only the diluent supplied, Sanofi Pasteur Limited's TRIPACEL® or QUADRACEL®. The use of any other vaccine or diluent to reconstitute Act-HIB® is **not** recommended.

Do not remove the stopper from the vial.

Apply a **sterile** piece of cotton moistened with a suitable antiseptic to the surface of the stopper of the vial of vaccine. Withdraw the diluent into a syringe. Holding the plunger of the syringe containing the diluent steady, pierce the center of the stopper in the vial and **slowly** inject the 0.5 mL of diluent into the freeze-dried vaccine. Do not try to force all of the diluent into the vial at once as this will create pressure. It is necessary to allow air to escape gradually into the syringe by intermittently aspirating air from the vial while injecting the diluent into the vial. Do not remove the needle from the stopper until the required volume of diluent has been injected. Shake the vial gently until a clear, colourless solution results. **Avoid foaming** since this will prevent withdrawal of the proper dose. Withdraw the entire contents of the reconstituted vaccine into the syringe and inject the total volume (about 0.5 mL). Aseptic technique must be used for withdrawal of each dose. (See 4.4 Administration).

When Sanofi Pasteur Limited's TRIPACEL® or QUADRACEL® is used for the reconstitution of Act-HIB®, **shake the single dose vial well** to distribute uniformly the suspension before withdrawing entire

[2] The National Advisory Committee on Immunization (NACI) provides additional guidance on vaccines in Canada. Please refer to the published chapters on *Haemophilus influenza* Type B (HIB) and tetanus toxoid.

contents (about 0.5 mL). Do not remove either the stopper or the metal seal holding it in place. Inject all the TRIPACEL® or QUADRACEL® into the vial of Act-HIB® vaccine. Swirl the vial until a cloudy, uniform suspension results. Avoid foaming since this will prevent withdrawal of the proper dose. Use a sterile needle and syringe to withdraw the entire contents for one dose.

Upon reconstitution the vaccine should be used immediately.

Administer the vaccine **intramuscularly**. The preferred site is into the anterolateral aspect of the mid-thigh (vastus lateralis muscle) or into the deltoid muscle. In children >1 year of age, the deltoid is the preferred site since use of the anterolateral thigh results in frequent complaints of limping due to muscle pain.

DO NOT INJECT INTRAVENOUSLY.

Each person who is immunized should be given a permanent personal immunization record. In addition, it is essential that the physician or nurse record the immunization history in the permanent medical record of each patient. This permanent office record should contain the name of the vaccine, date given, dose, manufacturer and lot number. If Act-HIB® is reconstituted with QUADRACEL® or TRIPACEL®, the lot numbers of both vaccines should be recorded.

4.4 Administration

Do not inject into a blood vessel.

Aseptic technique must be used. Use a separate sterile needle and syringe, or a sterile disposable unit, for each individual dose to prevent disease transmission. Needles should not be recapped and should be disposed of in accordance with biohazardous waste recommendations.

Sanofi Pasteur Limited's QUADRACEL® may be used for the reconstitution of lyophilized Act-HIB® in place of the saline diluent. This provides an efficient means of administering routine immunization against diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenzae* type b in a single injection at a single visit.

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4.5 Missed Dose

If a dose is missed, it can be given any time.

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular injection	Reconstituted product for injection. Each 0.5 mL dose of vaccine contains: 10 mcg purified polyribosylribitol phosphate capsular polysaccharide (PRP) of *Haemophilus influenzae* type b covalently bound to 18-30 mcg of tetanus protein.	Sucrose, Sodium Chloride solution* and Tris (hydroxymethyl) aminomethane * The sodium chloride comes from the Act-HIB® diluent and not the lyophilized product.

Description

Act-HIB® [Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate)] is a freeze-dried powder and diluent for intramuscular administration.

Act-HIB® is prepared from *Haemophilus influenzae* type b (Hib) strain cultures and *Clostridium tetani* cultures. Hib strains are precipitated with cetrimide and capsular polysaccharide (PRP) is extracted. PRP is then purified and activated. At the same time, the preparation of *C. tetani* strains is precipitated with ammonium sulphate and detoxified to obtain tetanus protein, which is concentrated. Activated PRP and concentrated tetanus protein are conjugated by carbodiimide group reaction to produce the drug substance (PRP-T), which is then formulated with excipients (final bulk product) that is then freeze-dried.

The diluent for reconstitution is a 0.4% saline solution. After reconstitution the vaccine appears clear and colourless and does not contain a preservative.

Each dose (0.5 mL) is contains: Purified Polyribosylribitol Phosphate Capsular Polysaccharide (PRP) of *Haemophilus influenzae* type b covalently bound to 18-30 mcg of Tetanus Protein (10 mcg)

The non-medicinal ingredients are as follows: Sodium chloride* (2.0 mg); Sucrose (42.5 mg) and tris (hydroxymethyl) aminomethane (0.6 mg)

* The sodium chloride comes from the Act-HIB® diluent and not the lyophilized product.

Packaging

Act-HIB® [Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate)] is available in packages containing five single dose vials of Act-HIB® and five x 0.5 mL (single dose vials of Sanofi Pasteur Limited's DILUENT, 0.4% Saline for reconstitution of Act-HIB®.

Act-HIB® is also supplied in packages containing five single dose vials of Act-HIB® and five x 0.5 mL (single dose) vial of Sanofi Pasteur Limited's QUADRACEL® to be used for reconstitution in place of the Act-HIB® diluent and sold under the tradename PENTACEL®.

Act-HIB® is also supplied in one or five dose packages containing either one or five single dose vials of Act-HIB® and one or five x 0.5 mL (single dose) vials of Sanofi Pasteur Limited's TRIPACEL® to be used for reconstitution in place of the Act-HIB® diluent and sold under the tradename ACTACEL®.

The stoppers of the vials containing Act-HIB® and the diluent (0.4% saline) do not contain latex (natural rubber).

7 WARNINGS AND PRECAUTIONS

General

As with any vaccine, immunization with Act-HIB® [Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate)] may not protect 100% of susceptible individuals.

Before administration, take all appropriate precautions to prevent adverse reactions. This includes a review of the patient's history concerning possible hypersensitivity to the vaccine or similar vaccine, previous immunization history, the presence of any contraindications to immunization, current health status.

Before administration of Act-HIB®, health-care providers should inform the patient, parent or guardian of the benefits and risks of immunization, inquire about the recent health status of the patient and comply with any local requirements regarding information to be provided to the patient before immunization and the importance of completing the immunization series.

Because the vaccine will not protect against non-typeable strains of *H. influenzae,* which cause recurrent upper respiratory disease, otitis media and sinusitis, the vaccine is not recommended for these conditions.

Carcinogenesis and Mutagenesis

No evaluation of Act-HIB® has been made with respect to its potential for carcinogenesis or mutagenesis.

Hematologic

Because of the risk of bleeding and hematoma formation following any intramuscular injection, Act-HIB® should be given with caution in persons with any bleeding disorder, such as hemophilia or thrombocytopenia, or persons on anticoagulant therapy.

Immune

As with other products, Epinephrine Hydrochloride Solution (1:1000) and other appropriate agents should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. Health-care providers should be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings, including proper airway management. For instructions on recognition and treatment of anaphylactic reactions, see the current edition of the Canadian Immunization Guide or visit the Health Canada website.

When Act-HIB® is reconstituted with Sanofi Pasteur Limited's TRIPACEL® or QUADRACEL®, the possibility of allergic reactions to the components of these vaccines must be evaluated.

Immunocompromised persons (whether from disease or treatment) may not obtain the expected immune response. If possible, consideration should be given to delaying routine vaccination until after the completion of any immunosuppressive treatment. However, the vaccination of subjects with chronic immunosupression, such as HIV infection, asplenia or sickle cell disease, is recommended even though there is a risk of suboptimal immune response.

In patients <10 years of age with functional or anatomic asplenia it may be prudent to verify the presence of antibodies directed against *H. influenzae* and re-immunize as needed.

Individuals who have received multiple doses of products containing tetanus toxoid show no differences in reaction rates when immunized with this vaccine.

Recipients of *Haemophilus* b vaccine are not protected against Hib disease in the week after vaccination, before the onset of the protective effects of the vaccine.

Neurologic
Syncope can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent falling and injury and to manage syncope.

Peri-Operative Considerations

Act-HIB® along with other recommended vaccines should be administered if possible at least 2 weeks before removal of the spleen.

7.1 Special Populations

7.1.1 Pregnant Women

Vaccination of adults against Hib is uncommon. Data on the use of this vaccine in pregnant women are limited, therefore, the administration of the vaccine during pregnancy is not recommended. Act-HIB® should be given to pregnant women only if clearly needed and following an assessment of the risks and benefits.

Animal reproduction studies have not been conducted with Act-HIB®. It is also not known whether Act-HIB® reconstituted with saline diluent can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

7.1.2 Breast-feeding

Vaccination of adults against Hib is uncommon. It is not known whether this vaccine is excreted in human milk; therefore, the risk and benefits should be carefully considered before administering Act-HIB® to a nursing mother.

It is recommended that breast-feeding women who have not received the recommended immunizations may safely be given vaccines[3].

[3] NACI provides additional information on the use of vaccines in pregnant women. Please refer to the current NACI recommendations for pregnant women.

7.1.3 Pediatrics

Children in whom invasive Hib disease develops before 24 months of age should still receive vaccine as recommended, since natural disease may not induce protection.

Premature infants whose clinical condition is satisfactory should be immunized with full doses of vaccine at the same chronological age and according to the same schedule as full-term infants, regardless of birth weight[4].

The potential risk of apnea and the need for respiratory monitoring for 48 – 72 hours should be considered when administering the primary immunization 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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Pain, redness, swelling or induration at the injection site, are seen in 5-30% of vaccinees. It is generally early, transient, and of moderate intensity. Systemic reactions including fever, irritability, drowsiness, prolonged or abnormal crying, anorexia and vomiting have occurred after immunization with Act-HIB® [Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate)] in conjunction with whole-cell or acellular DPT-containing vaccines. The rates of reactions observed were generally comparable to those usually reported following the concomitant vaccine given alone.

Adverse events presented in this section are listed using MedDRA terminology (system organ classes and terms). Within each system organ class, the adverse events are ranked under headings of frequency (most frequent reactions first), using the following convention:

Very common: ≥ 10%

Common: ≥ 1% and < 10%

Uncommon: ≥ 0.1% and < 1%

Rare: ≥ 0.01% and < 0.1%

Very rare: < 0.01%

Not known: cannot be estimated from the available data.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

[4] The National Advisory Committee on Immunization (NACI) provides additional guidance on vaccines in Canada. Please refer to the published chapters on *Haemophilus influenza* Type B (HIB) and tetanus toxoid.

Act-HIB® has been administered during clinical trials to over 110,000 infants and children in Canada, the United States, Finland, France, Chile, Israel, and the United Kingdom using local immunization schedules, almost always in conjunction with whole-cell or acellular DPT vaccines and has been used widely in immunization programs. In controlled studies, when Act-HIB® was administered in conjunction with DPT vaccines, the rate and type of subsequent systemic reactions were not different from those seen with DPT administered alone.

Adverse events, possibly related, observed during clinical studies in more than 1% patients after immunization (i.e., "common" to "very common") are presented in this section, categorized by frequency. They usually occur soon after the administration of the vaccine (within 6-24 hours), are transient, and have a mild to moderate intensity.

No increase in the incidence or severity of these events was seen with subsequent doses of the primary vaccination series.

The most common reactions occurring after Act-HIB® administration were local reactions at the injection site, fever and irritability.

Gastrointestinal disorders

- Vomiting: common

General disorders and application site conditions

- General disorders: pyrexia (fever): common (above 39°C: uncommon)
- Application site conditions: Injection site reactions such as pain, erythema, swelling and/or inflammation, induration: common to very common.

Psychiatric disorders

- Irritability: very common
- Crying (uncontrollable or abnormal): uncommon to common.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Local reactions: Pain, redness, swelling or induration are seen in 5-30% of vaccinees. It is generally early, transient, and of moderate intensity.

Systemic Reactions: In a randomized, placebo-controlled clinical trial, infants received either Act-HIB® and DPT given at separate sites or placebo and DPT given at separate sites at 2, 4 and 6 months of age. Table 2 shows the systemic reactions reported.

Table 2: Systemic Reactions (%) Within 24 Hours of Vaccination

GROUP	First Dose		Second Dose		Third Dose	
	PRP-T and DPT*	DPT	PRP-T and DPT*	DPT	PRP-T and DPT*	DPT
Any Systemic Reactions	77.8	81.8	87.7	75.0	76.5	68.8
Fever 38°C-38.9°C	27.7	17.5	27.1[@]	6.5[@]	16.4	12.1
Fever >39°C	4.1	0.0	2.9	1.6	1.5	3.0
Irritability	51.8	57.1	47.7	51.9	41.7	41.6
Drowsiness	43.2	41.6	44.4	28.6	33.3	26.0
Loss of Appetite	8.6	15.6	13.6	15.6	21.2	11.7
Vomiting	3.7	3.9	0.0	0.0	3.7	3.9
Diarrhea	0.0	1.3	2.5	6.5	6.2	6.5

* PRP-T vaccine and whole-cell DPT vaccine administered at two different sites.

@ P>0.001

Act-HIB® Reconstituted with QUADRACEL®

In clinical trials conducted in Canada, 215 infants received 3 doses of either Act-HIB® reconstituted with QUADRACEL® [Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine] or the same vaccines administered simultaneously at separate sites at 2, 4 and 6 months of age. An additional 186 18-month old children received a single dose of either Act-HIB® reconstituted with QUADRACEL® or the same vaccines administered simultaneously at separate sites. The rates of local and systemic reactions for the combination of Act-HIB® and QUADRACEL® were consistently lower than for the combination of Act-HIB® and whole-cell DPT-Polio Adsorbed. The incidence of local reactions at the QUADRACEL® site was lower when the vaccines are given separately, but severe local reactions are uncommon (<6% for any dose). Systemic reactions were comparable between the two groups. No hypotonic-hyporesponsive episodes following QUADRACEL® and Act-HIB® administration were reported during these trials. There were three reports of febrile seizures (6 days to 1 month following immunization with QUADRACEL® and Act-HIB®), all attributed to intercurrent febrile illness.

Act-HIB® Reconstituted with TRIPACEL®

In a clinical trial conducted in Canada, 17-19 month old children previously immunized with TRIPACEL® ($CP_{10/5/5/3}DT$) at 2, 4 and 6 months of age received either a single injection of TRIPACEL® used to reconstitute Act-HIB® (n = 33), or separate injections of TRIPACEL® and Act-HIB® reconstituted with diluent at the same visit (n = 33). All subjects received OPV at the same visit. There was no significant difference in rates of local or systemic reactions. No serious adverse events were observed during this study.

In a clinical trial conducted in Taiwan, 68 infants received a different formulation of TRIPACEL® ($CP_{20/20/5/3}DT$) used to reconstitute Act-HIB® and a control group of 67 received the same vaccines administered at separate sites at 2, 4 and 6 months of age. A fourth dose of the same vaccines was given at 18 months of age to 62 children who had received the combined vaccines and 66 who had received separate injections. No consistent differences in reaction rates were seen between the two methods of administration. Reaction rates were low in both vaccine groups; local reactions tended to be mild or moderate and systemic reactions tended to be mild. No serious adverse events were observed during this study.

8.5 Post-Market Adverse Reactions

The following additional adverse events have been spontaneously reported during the post-marketing use of Act-HIB® worldwide. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Decisions to include these events in labelling were based on one or more of the following factors: 1) severity of the event, 2) frequency of reporting, or 3) strength of causal connection to Act-HIB®.

General disorders and application site conditions

- Extensive limb swelling of the vaccinated limb (from the injection site beyond one or both joints)
- Large injection site reactions (>50 mm) such as pain, erythema, swelling and/or inflammation, or induration

- Edema of lower limbs:
  Edematous reaction affecting one or both lower limbs may occur following vaccination with *Haemophilus influenzae* type b containing vaccines. If this reaction occurs, it does so mainly after primary injections and is observed within the first few hours following vaccination. Associated symptoms may include cyanosis, redness, transient purpura and severe crying. All events resolve spontaneously without sequelae within 24 hours.

Immune system disorders

- Hypersensitivity reactions

Nervous system disorders

- Convulsions (with or without fever)

Skin and subcutaneous tissue disorders:

- Urticaria, rash generalized, rash, pruritus
- Face edema, laryngeal edema (suggestive of a possible hypersensitivity reaction).

Potential Adverse Events

Other adverse events reported with administration of other *Haemophilus influenzae* type b conjugate vaccines include renal failure and Guillain-Barré syndrome (GBS). A cause and effect relationship among any of these events and the vaccination has not been established.

When Act-HIB® is reconstituted with another vaccine, the product monograph of that other vaccine must be carefully reviewed.

Physicians should be familiar with the adverse reactions associated with whatever vaccine is used to reconstitute Act-HIB® and read carefully the direction leaflet which accompanies each such vaccine.

Physicians, nurses and pharmacists should report any adverse occurrences temporally associated with the administration of the product in accordance with local requirements (See PATIENT MEDICATION INFORMATION, Reporting Side Effects for Vaccines).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Act-HIB® [Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate)] may be reconstituted with the diluent provided or with QUADRACEL® or TRIPACEL®.

Once reconstituted, this vaccine must not be mixed with other vaccine or medicinal products.

Act-HIB® may be administered simultaneously with whole-cell DPT, DT, whole-cell DPT Polio, IPV, QUADRACEL® or TRIPACEL® at separate sites with separate syringes and with OPV.

Act-HIB® may also be given simultaneously with measles, mumps, rubella, hepatitis B, pneumococcal and meningococcal vaccines at separate sites with separate syringes.

Because simultaneous administration of common childhood vaccines is not known to affect the efficacy or safety of any of the routine recommended childhood vaccines, if the return of a vaccine recipient for further immunization is doubtful, simultaneous administration of all vaccines appropriate for age and previous vaccination status at separate sites with separate syringes is indicated. (1) (5)

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. (See 7 WARNINGS AND PRECAUTIONS, Immune).

9.3 Drug-behavioural Interactions

Interactions with behaviour have not been established.

9.4 Drug-Drug Interactions

Interactions with drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Capsular polysaccharide antigen can be detected in the urine of vaccinees for up to 2 weeks following immunization with conjugate vaccines. This phenomenon should not be confused with invasive Hib infections.

10 CLINICAL PHARMACOLOGY

10.2 Pharmacodynamics

Hib conjugate vaccines are the second generation of vaccines against Hib disease, having replaced earlier polysaccharide vaccines. Polysaccharide-protein conjugate antigens have the advantage of producing greater immune response in infants and young children than purified polysaccharide vaccine. The latter stimulates only B-cells, whereas the former activates macrophages, T-helper cells

and B-cells, resulting in greatly enhanced antibody responses and establishment of immunologic memory.

Immunogenicity studies in infants ≥2 months of age given a primary series demonstrated that almost all developed anti-PRP antibody titre ≥0.15 mcg/mL, and approximately 90% had a titre ≥1 mcg/mL after the 3rd dose. A booster dose administered 8 to 12 months later induced a very significant increase in the mean titre of the PRP antibodies. A serum level of 0.15 mcg/mL is considered to indicate a positive response to conjugated vaccine. A level of >1.0 mcg/mL indicates long-term protection.

10.3 Pharmacokinetics

No pharmacokinetic studies have been performed.

Duration of Effect

In children who received four doses of Act-HIB® (at 2, 4, 6 and 18 months), anti-PRP antibodies remained above 0.15 mcg/mL at 4-5 years of age in 99%, and all responded vigorously to restimulation, consistent with persistent immune memory.

11 STORAGE, STABILITY AND DISPOSAL

Store at 2° to 8°C (35° to 46°F). **Do not freeze.**

Product which has been exposed to freezing should not be used.

The vaccine should be used immediately after reconstitution.

12 SPECIAL HANDLING INSTRUCTIONS

Do not use after the expiration date.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate)

Product Characteristics:

Act-HIB® [Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate)], produced by Sanofi Pasteur SA, is a sterile, lyophilized powder which is reconstituted at the time of use with saline diluent (0.4% Sodium Chloride) for intramuscular use only.

The vaccine consists of the Haemophilus b capsular polysaccharide (polyribosyl-ribitol-phosphate, PRP), a high molecular weight polymer prepared from the *Haemophilus influenzae* type b strain 1482 grown in a semi-synthetic medium, covalently bound to tetanus toxoid. The tetanus toxoid is prepared by extraction, ammonium sulfate purification, and formalin inactivation of the toxin from cultures of *Clostridium tetani* (Harvard strain) grown in a modified Mueller and Miller medium. The toxoid is filter sterilized prior to the conjugation process. Potency of Act-HIB® is specified on each lot by limits on the content of PRP polysaccharide and protein in each dose and the proportion of polysaccharide and protein in the vaccine which is characterized as high molecular weight conjugate.

When Act-HIB® is reconstituted with saline diluent, each single dose of 0.5 mL is formulated to contain 10 µg of purified capsular polysaccharide conjugated to 18-30 µg of inactivated tetanus toxoid, and 8.5% of sucrose. The lyophilized Act-HIB® powder and saline diluent contain no preservative.

The vaccine reconstituted, using the saline diluent provided, appears clear and colourless.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Immunization Against Invasive Disease Caused By *H. influenzae* type b In Infants And Children Starting At 2 Months Of Age.

Act-HIB® [Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate)] has been administered during clinical trials to over 110,000 infants and children in Canada, the United States, Finland, France, Chile, Israel, and the United Kingdom using local immunization schedules, and has been used widely in immunization programs.

Study Results- Act-HIB®

In clinical trials where 921 infants were given the vaccine at 2, 4 and 6 months, a titre of at least 0.15 mcg/mL was achieved after dose 3 in 99% and a titre of at least 1.00 mcg/mL in 93%. The weighted GMT achieved was 7.0 mcg/mL (95% confidence limits are 3.4 - 14.2 mcg/mL). Protective levels of anti-PRP developed after the second dose in 92.8% of these infants.

Two clinical trials supported by the U.S. National Institutes of Health (NIH) compared the anti-PRP response of four Hib conjugate vaccines in a racially mixed population of infants. In these studies, infants were immunized with Hib conjugate vaccines at 2, 4 and 6 months of age (see Table 3). Sanofi Pasteur Inc.'s whole-cell DPT vaccine was given concomitantly, at a separate site.

Table 3: Anti-PRP Antibody Responses in 2-month-old Infants NIH Trial in Tennessee, Minnesota and Texas

Vaccine	N*	Geometric Mean Titre (GMT) (mcg/mL)			Post Third Immunization % >1.0 mcg/mL
		Pre Immunization	Post Second Immunization	Post Third Immunization	
Tennessee					
PRPT[a]	65	0.10	0.30	3.64	83%
PRP-D[b]	62	0.07	0.08	0.28	29%
PRP-OMP[c]	64	0.11	0.84	1.14	55%
HbOC[d]	61	0.07	0.13	3.08	75%
Minnesota and Texas					
PRP-D[b]	106	0.23	1.14[e]	6.64	98%
PRP-OMP[c]	103	0.17	4.6[f]	6.48	88%
HbOC[d]	99	0.16	0.46	6.83	93%

* Number of children

[a] *Haemophilus* b Conjugate Vaccine (Tetanus Protein – Conjugate)

[b] *Haemophilus* b Conjugate Vaccine (Diphtheria Toxoid – Conjugate)

[c] *Haemophilus* b Conjugate Vaccine (Meningococcal Protein Conjugate)

[d] *Haemophilus* b conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)

[e] P = 0.0001 for PRT-T vs HbOC

[f] P = 0.0001 for PRP-OMP vs PRP-T, and for PRP-OMP vs HbOC

Multi-centre trials in the United States have evaluated a single dose of Act-HIB® in 12-15, 18 and 17-24 month-old children. In this age group, a single dose of Act-HIB® produced an anti-PRP response which was comparable to that seen after three doses were administered in infants.

Following three doses of Act-HIB® at 6 weeks, four and six months of age, 81% of native Alaskan infants showed an anti-PRP titre of ≥1.0 mcg/mL with a GMT of 4.17 mcg/mL.

In clinical trials conducted in England and France, infants received 3 doses of Act-HIB® at one month intervals. Anti-PRP responses were comparable to those trials where 2-month intervals were used.

Study Results — Act-HIB® Reconstituted with QUADRACEL®

In clinical trials conducted in Canada, 215 infants received 3 doses of either Act-HIB® reconstituted with QUADRACEL® or the same vaccines administered simultaneously at separate sites at 2, 4 and 6 months of age. An additional 186 18-month old children received a single dose of either Act-HIB® reconstituted with QUADRACEL® or the same vaccines administered simultaneously at separate sites. With the exception of tetanus, no differences were found in immunogenicity between the two methods of immunization. Tetanus antitoxin levels were lower in the combined vaccine groups, but all children had protective levels (≥0.01 EU/mL). Following the 18-month dose, all children had tetanus antitoxin levels ≥0.10 EU/mL and all but one had diphtheria antitoxin levels ≥0.10 EU/mL. Anti-PRP responses were comparable. All children were protected against polio. Pertussis responses were not affected by method of administration.

Study Results — Act-HIB® Reconstituted with TRIPACEL®

In a clinical trial conducted in Canada, 17-19 month old children previously immunized with TRIPACEL® [Component Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids Adsorbed] ($CP_{10/5/5/3}DT$) at 2, 4 and 6 months of age received either a single injection of TRIPACEL® used to reconstitute Act-HIB® (n = 33), or separate injections of TRIPACEL® and Act-HIB® reconstituted with diluent at the same visit (n = 33). All subjects received OPV at the same visit. There were no differences between the study groups for tetanus and diphtheria antitoxin levels or anti-PRP antibody, with all participants achieving tetanus and diphtheria antitoxin levels of >1.0 IU/mL, and anti-PRP antibody levels of >0.15 mcg/mL, and 98% of recipients achieving anti-PRP antibody levels of >1.0 mcg/mL. There were no significant interactions in the pertussis antibody responses PT, FHA, CHO, 69kDa, fimbriae, or agglutinins.

In a clinical trial conducted in Taiwan, 68 infants received a different formulation of TRIPACEL® ($CP_{20/20/5/3}DT$) used to reconstitute Act-HIB® and a control group of 67 received the same vaccines administered at separate sites at 2, 4 and 6 months of age. All subjects received OPV at 2, 4, 6 and 18 months. The method of administration did not affect overall serologic responses. All subjects in both groups achieved protective levels for anti-PRP, diphtheria, tetanus and polio. A fourth dose of the same vaccines was given at 18 months of age to 62 children who had received the combined vaccines and 66 who had received separate injections. One hundred percent of participants achieved protective levels for anti-PRP (≥1.0 mcg/mL), diphtheria (≥0.1 IU/mL) and tetanus (≥0.1 EU/mL) antitoxin. There was no difference in pertussis serology between the groups. Polio antibody levels were not measured.

Table 4: Summary of anti-PRP Responses with Various Diluents

Anti-PRP (Post 3rd Dose)				
	n	**≥0.15 mcg/mL**	**≥1.0 mcg/mL**	**GMT mcg/mL**
Act-HIB® + DPT combined**	209	97.6%	88.1%	4.44
Act-HIB® + DPT separate**	213	98.6%	87.9%	4.06
Act-HIB® + DPT Polio@@ combined	211	93.8%	71.6%	2.04
Act-HIB® + DPT Polio@@ separate	211	98.1%	78.7%	2.76
Act-HIB® + Diluent (saline)	65	99.0%	83.0%	3.64
Act-HIB® + QUADRACEL® combined	107	99.1%	84.9%	5.04
Act-HIB® + QUADRACEL® separate	108	100.0%	88.9%	3.83
Act-HIB® + TRIPACEL® ($CP_{20/20/5/3}$DT) combined	64	100.0%	96.3%	11.80
Act-HIB® + TRIPACEL® ($CP_{20/20/5/3}$DT) separate	67	100.0%	98.5%	13.00

** whole-cell DPT

@@ whole-cell DPT-Polio

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Data in animals including single dose, repeated dose and local tolerance studies revealed no unexpected findings and no target organ toxicity.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Act-HIB®

Haemophilus b Conjugate Vaccine (Tetanus Protein – Conjugate)

Read this carefully before Act-HIB® is given to you or your child. This leaflet is a summary and will not tell you everything about this vaccine. Talk to your healthcare professional about your (or your child's) medical condition and treatment and ask if there is any new information about Act-HIB®.

What is Act-HIB® used for?

Act-HIB® is a vaccine that protects against infection with *Haemophilus influenzae* type b (Hib). Hib causes bacterial meningitis and other serious infections. All children 2 months to 5 years of age should receive Hib vaccine, usually combined with QUADRACEL®. Children over 5 years old usually do not need Hib vaccine, but some older children or adults with special health conditions should get it. These conditions include removal of the spleen, sickle cell disease, HIV/AIDS, certain cancers, or other conditions. Persons who have or are going to have cochlear implants also should get Hib vaccine. Ask your doctor or nurse for details.

How does Act-HIB® work?

Act-HIB® causes your (or your child's) body to produce its own protection against Hib bacteria. After receiving a Hib vaccine, your (or your child's) immune system produces antibodies. Antibodies help the body to fight disease. When you are exposed to the Hib bacteria, the antibodies will help to keep you (or your child) from getting sick. As with all vaccines, Act-HIB® does not protect 100% of people immunized.

What are the ingredients in Act-HIB®?

Medicinal Ingredients: polyribose ribitol phosphate capsular polysaccharide (PRP) of *Haemophilus influenzae* type b, covalently bound to tetanus protein.

Non-medicinal ingredients: Sodium chloride solution, Sucrose, Tris (hydroxymethyl) aminomethane.

Act-HIB® comes in the following dosage forms:

- Each single dose of Act-HIB® is a freeze-dried vaccine to be dissolved in 0.5 mL of the diluent for Act-HIB®.
- Freeze-dried Act-HIB® may also be dissolved in a single dose of QUADRACEL® or TRIPACEL® if both vaccines are needed.

Do not use Act-HIB® if:

- You (or your child) have had an allergic reaction to a previous dose of Act-HIB® or to any component of Act-HIB® or its container.
- You (or your child) have a fever or serious illness. Wait until you are better before taking the vaccine. A person who has had a mild illness (such as a mild cold) may have the vaccine. Ask your doctor, nurse or pharmacist for advice.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you or your child take Act-HIB®. Talk about any health conditions or problems you may have, including if you or your child:

- **Have a weakened immune system.** The vaccine may provide you (or your child) with a lower level of protection than it does for people with healthy immune systems.
- **Have a coagulation disorder or are on anticoagulant therapy.** Tell the person giving the injection about your/your child's condition. There is a risk of excessive bleeding at the site of injection if it is not done carefully.
- **Are pregnant or breast-feeding.** It is important that you understand the risks and benefits of vaccination. Act-HIB® should be given to a pregnant or nursing woman only if it is clearly needed. Tell the person giving the injection if you (or your child) are pregnant or breast-feeding.
- **Have an allergy to any component of the vaccine or the container.**
- **Fainting can occur following, or even before, any needle injection. Therefore, tell your doctor or nurse if your child fainted with a previous injection.**

Tell your healthcare professional about all the medicines you (or your child) take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Act-HIB®:

- Act-HIB® may be mixed with its own diluent, with TRIPACEL®, or with QUADRACEL®. Act-HIB® must not be mixed with other vaccines or medicinal products in the same syringe.

How to take Act-HIB®:

Usual dose:

Each dose is a single injection of 0.5 mL given intramuscularly.

Infants receive one injection at 2, 4, and 6 months of age, followed by a booster at 18 months of age.

If your infant does not start his/her series at 2 months of age, ask your doctor or nurse when the doses of Hib vaccine are needed.

Older children or adults usually receive one injection.

Overdose:

If you think you, or a person you are caring for, have taken too much Act-HIB® , contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If a dose is missed, it can be given at any time.

What are possible side effects from using Act-HIB® ?

These are not all the possible side effects you may feel when taking Act-HIB®. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warning and Precautions.

A vaccine, like any medicine, may cause serious problems, such as severe allergic reactions. The risk of Act-HIB® causing serious harm is extremely small. The small risks associated with Act-HIB® are much less than the risks associated with getting the diseases against which it protects.

Some children may have mild pain, swelling and redness for a few days at the spot where the needle was given. A very few children may get a mild fever, rash or hives.

Serious side effects are extremely rare.

If you have a troublesome side symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Suspected Side Effects for Vaccines

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and Sanofi Pasteur Limited cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and send it to your local Health Unit.

Storage:

Store the vaccine in a refrigerator at 2° to 8°C (35° to 46°F). Do not freeze. Discard product if it has been exposed to freezing.

Do not use after the expiration date.

Keep out of reach and sight of children.

If you want more information about Act-HIB®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the Sanofi Canada website (www.sanofi.ca) or by contacting the vaccine producer, Sanofi Pasteur Limited at 1-888-621-1146 (no charge).

This leaflet was prepared by Sanofi Pasteur Limited.

Last Revised: April 4, 2023

R15 0123 Canada