PENTACEL™

Act-HIB® reconstituted with QUADRACEL™

Act-HIB®

Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate)

DESCRIPTION

Act-HIB®, Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate) (PRP-T), is a lyophilized vaccine of purified polyribose ribitol phosphate capsular polysaccharide (PRP) of *Haemophilus influenzae* type b, covalently bound to tetanus protein. Each single dose of 0.5 mL after reconstitution contains 10 µg of purified capsular polysaccharide covalently bound to 20 µg of tetanus protein.

Act-HIB® reconstituted with Diluent: The diluent for reconstitution is a 0.4% saline solution. After reconstitution, the vaccine appears clear and colourless and does not contain a preservative.

Act-HIB® reconstituted with Aventis Pasteur Limited's QUADRACEL™: After reconstitution, the vaccine appears cloudy and uniform. From the QUADRACEL™, Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine, the solution contains 0.6% ± 0.1% 2-phenoxyethanol as preservative and trace amounts of polymyxin B and neomycin may be present from the cell growth medium.

Act-HIB® reconstituted with Aventis Pasteur Limited's TRIPACEL™: After reconstitution, the vaccine appears cloudy and uniform. From the TRIPACEL™, Component Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids Adsorbed, the solution contains 0.6% ± 0.1% 2-phenoxyethanol as preservative.

CLINICAL PHARMACOLOGY

Clinical Data (PRP-T)

Act-HIB®, Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate) (PRP-T), 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,[1,2] and has been used widely in immunization programmes.

In clinical trials where 921 infants were given the vaccine at 2, 4 and 6 months, a titre of at least 0.15 µg/mL was achieved after dose 3 in 99% and a titre of at least 1.00 µg/mL in 93%. The weighted GMT achieved was 7.0 µg/mL (95% confidence limits are 3.4 - 14.2 µg/mL). Protective levels of anti-PRP developed after the second dose in 92.8% of these infants.[1]

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 Tables 1 and 2).[1,3] Aventis Pasteur Inc.'s whole-cell DPT vaccine was given concomitantly, at a separate site.[3]

TABLE 1:[1,3] ANTI-PRP ANTIBODY RESPONSES IN 2-MONTH OLD INFANTS NIH TRIAL IN TENNESSEE

		GEOMETRIC MEAN TITRE (GMT) (µG/ML)			
VACCINE	**n***	**Pre Immunization**	**Post Second Immunization**	**Post Third Immunization**	**Post Third Immunization % >1.0 µg/mL**
PRP-T†	65	0.10	0.30	3.64	83%
PRP-D§	62	0.07	0.08	0.28	29%
PRP-OMP¶	64	0.11	0.84	1.14	55%
HbOC‡	61	0.07	0.13	3.08	75%

TABLE 2:[1] ANTI-PRP ANTIBODY RESPONSES IN 2-MONTH OLD INFANTS NIH TRIAL IN MINNESOTA AND TEXAS

		GEOMETRIC MEAN TITRE (GMT) (µG/ML)			
VACCINE	**n***	**Pre Immunization**	**Post Second Immunization**	**Post Third Immunization**	**Post Third Immunization % >1.0 µg/mL**
PRP-T†	106	0.23	1.14**	6.64	98%
PRP-OMP¶	103	0.17	4.6***	6.48	88%
HbOC‡	99	0.16	0.46	6.83	93%

* n = Number of children
** p = 0.0001 for PRP-T vs HbOC
*** p = 0.0001 for PRP-OMP vs PRP-T, and for PRP-OMP vs HbOC
† Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate)
§ Haemophilus b Conjugate Vaccine (Diphtheria Toxoid - Conjugate)
¶ Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate
‡ Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)

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.[1]

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 µg/mL with a GMT of 4.17 µg/mL.[1]

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.[1]

Clinical Data - 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.

Clinical Data - 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 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 µg/mL, and 98% of recipients achieving anti-PRP antibody levels of >1.0 µg/mL. There were no significant interactions in the pertussis antibody responses PT, FHA, CHO, 69kDa, fimbriae, or agglutinins. Local and systemic reactions were similar in both study groups.

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 µg/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 3:[1] SUMMARY OF ANTI-PRP RESPONSES WITH VARIOUS DILUENTS

	Anti-PRP (Post 3rd Dose)			
	n	**≥0.15 µg/mL**	**≥1.0 µg/mL**	**GMT µg/mL**
Act-HIB® + DPT* combined[4]	209	97.6%	88.1%	4.44
Act-HIB® + DPT* separate[4]	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

INDICATIONS AND USAGE

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.

2. a) Infants starting their primary immunization series between the age of **3 and 6 months** should receive three doses at two month intervals with a booster dose at **18* months** of age. (While an interval of 2 months between doses is recommended, an interval as short as 1 month is acceptable.)

   b) 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.

   c) 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.

   d) 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.

3. Older children or adults with chronic conditions associated with increased risk of invasive Hib disease such as persons with splenic dysfunction (e.g., sickle cell disease, asplenia), antibody deficiency, HIV infection or certain malignancies may be immunized with a single dose of the vaccine.[5]

4. Aventis 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.

5. Aventis Pasteur Limited's TRIPACEL™ 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 and *Haemophilus influenzae* type b in a single injection at a single visit.

6. 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 OPV.

   Act-HIB® may also be given simultaneously with MMR at separate sites with separate syringes. This is based on data for MMR and Act-HIB® alone. 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 return of a vaccine recipient for further immunization is doubtful, simultaneous administration of all vaccines appropriate for age and previous vaccination status (including MMR, hepatitis B vaccine) at separate sites with separate syringes is indicated.[6,7]

7. Data on whether vaccination prevents acquisition and carriage of Hib are still limited. Thus, rifampin or other appropriate chemoprophylaxis should be used, in accordance with the usual recommendations,[6] for families and persons in day-care centres in which a case of invasive Hib disease has occurred and in which there are one or more contacts less than 48 months of age who have not been fully vaccinated against Hib.[5]

Currently, Haemophilus b conjugate vaccines are not recommended for infants younger than 2 months of age.

CONTRAINDICATIONS

General

Immunization with Act-HIB®, Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate), 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.[8]

Absolute Contraindications

Allergy to any component of Act-HIB® (see components listed in DESCRIPTION), 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 Aventis Pasteur Limited's TRIPACEL™ or QUADRACEL™ the contraindications for TRIPACEL™ or QUADRACEL™ must also be considered.

Elective immunization of individuals over 6 months of age should be deferred during an outbreak of poliomyelitis because of the risk of provocation paralysis.[9,10,11]

WARNINGS

Intramuscular injections should be given with care in persons suffering from coagulation disorders or on anticoagulant therapy because of the risk of hemorrhage.[8]

If Act-HIB®, Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate), is used in persons with malignancies, persons receiving immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, or persons who are otherwise immunocompromised (including HIV-infected individuals, transplant recipients, and persons suffering from autoimmune disorders), the expected immune response may not be obtained.

Corticosteroid therapy can result in immunosuppression although the exact dose and duration of therapy required to suppress the immune system is not well defined. Persons treated with high doses of systemic steroids, e.g., ≥2 mg/kg per day of prednisone orally for more than 2 weeks, should be considered to have a compromised immune system.[8]

As with any vaccine, immunization with Act-HIB® may not protect 100% of susceptible individuals.

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.[5]

PRECAUTIONS

General

The possibility of allergic reactions in individuals sensitive to components of the vaccine should be evaluated. Epinephrine Hydrochloride Solution (1:1,000) and other appropriate agents should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs.[8] When Act-HIB® is reconstituted with Aventis Pasteur Limited's TRIPACEL™ or QUADRACEL™, the possibility of allergic reactions to the components of these vaccines must also be evaluated. Health-care providers should be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings, including proper airway management.[6,12]

Before administration of any vaccine, all appropriate precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible hypersensitivity to the vaccine or similar vaccine, determination of previous immunization history, and the presence of any contraindications to immunization, current health status, and a current knowledge of the literature concerning the use of the vaccine under consideration.

Special care should be taken to ensure that the product is not injected into a blood vessel.

Caution

A separate sterile needle and syringe, or a sterile disposable unit, must be used for each individual patient to prevent the transmission of infectious agents.

There have been case reports of transmission of HIV and hepatitis by failure to observe scrupulously sterile technique.

Needles should not be recapped and should be disposed of properly.

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

Act-HIB® may be of benefit in preventing the occurrence of secondary cases. However, epidemiological studies have not been done and rifampin or other appropriate prophylaxis is still recommended. 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.

ALTHOUGH SOME IMMUNE RESPONSE TO THE TETANUS PROTEIN COMPONENT MAY OCCUR, IMMUNIZATION WITH THIS VACCINE DOES NOT SUBSTITUTE FOR ROUTINE TETANUS IMMUNIZATION. Individuals who have received multiple doses of products containing tetanus toxoid show no differences in reaction rates when immunized with this vaccine.

Pregnancy

Animal reproductive studies have not been conducted with Act-HIB®. It is also not known whether Act-HIB® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Act-HIB® is not recommended for use in pregnant women.

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

Human Immunodeficiency Virus (HIV) Infected Persons

HIV-infected individuals, both asymptomatic and symptomatic, should be immunized with DPT (Diphtheria, Pertussis and Tetanus) and Act-HIB® vaccine according to standard schedules.[8]

ADVERSE REACTIONS

Local reactions: Pain, redness, swelling or induration are seen in 5 - 30% of vaccinees. It is generally early, transient, and of moderate intensity. There have been rare cases of edematous reactions of the lower extremities reported. These consist of edema with cyanosis or transient purpura which appears soon after immunization and resolves rapidly and spontaneously.

There have been no reports of accompanying cardiorespiratory signs or symptoms. These reactions have been reported mainly when Act-HIB®, Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate), is administered concurrently with another vaccine.[1]

Systemic reactions including fever, irritability, drowsiness, prolonged or abnormal crying, anorexia and vomiting have occurred after immunization with Act-HIB® in conjunction with whole-cell DPT. The rates of reactions observed were generally comparable to those usually reported following whole-cell DPT with the exception that there were slightly more febrile reactions reported among PRP-T recipients within 6-24 hours of vaccination. Table 4 shows systemic reactions reported in a controlled clinical trial.[1]

TABLE 4: SYSTEMIC REACTIONS (%) WITHIN 24 HOURS OF VACCINATION

	First Dose		Second Dose		Third Dose	
GROUP	**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
>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

* $p > 0.001$

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

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. 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.

Rare cases of allergic reactions including urticaria, pruritus, and facial and laryngeal edema have been reported.

Physicians should be aware that 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.

Other adverse events reported with administration of other Haemophilus b conjugate vaccines include urticaria, seizures, rash, renal failure and Guillain-Barré Syndrome (GBS). A cause and effect relationship among any of these events and the vaccination has not been established.[1]

As with any vaccine, there is the possibility that broad use of the vaccine could reveal rare adverse reactions not observed in clinical trials. A temporal association of neurological disorders (including encephalopathy, with or without permanent brain damage and/or intellectual impairment) has been reported following the parenteral injection of other biological products and should always be carefully considered when an immunization is indicated.

Physicians should be familiar with the adverse reactions associated with whatever vaccine is used to reconstitute Act-HIB®, Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate), and read carefully the direction leaflet which accompanies each such vaccine.

Physicians, nurses and pharmacists should report any adverse occurrences temporally related to the administration of the product in accordance with local requirements and to the Medical Director, Aventis Pasteur Limited, 1755 Steeles Avenue West, Toronto, Ontario, Canada M2R 3T4.

DOSAGE AND ADMINISTRATION

Parenteral biological products should be inspected visually for extraneous particulate matter and/or discolouration before administration whenever solution and container permit. If these conditions exist, the product should not be administered.

This vaccine is indicated for routine immunization against invasive disease caused by *Haemophilus influenzae* type b in infants and children starting at 2 months of age. (See INDICATIONS.) Each dose is a single injection of 0.5 mL given intramuscularly.

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

Reconstitute the vaccine using only the diluent supplied, Aventis Pasteur Limited's TRIPACEL™ or QUADRACEL™. The use of any other vaccine to reconstitute Act-HIB®, Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate), 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 centre 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 PRECAUTIONS.)

When Aventis Pasteur Limited's TRIPACEL™ or QUADRACEL™ is used for the reconstitution of Act-HIB®, SHAKE THE SINGLE-DOSE AMPOULE OR VIAL WELL to distribute uniformly the suspension before withdrawing entire contents (about 0.5 mL). Before withdrawing the contents from an ampoule, tap the container first to ensure that all the vaccine is in the lower portion. Once the ampoule has been opened, any of its contents not used immediately should be discarded. Before withdrawing the contents from a stoppered vial, 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.

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide.

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 reports of limping due to muscle pain.[13]

After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

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.

STORAGE

Act-HIB®, Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate), should be stored 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.

Do not use after the expiration date.

HOW SUPPLIED

Act-HIB®, Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate), is supplied in packages containing five single-dose vials of Act-HIB® and five 0.5 mL (single-dose) ampoules of Aventis Pasteur Limited's DILUENT, 0.4% Saline for Reconstitution of Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate) Act-HIB®.

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

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

REFERENCES

1. Unpublished clinical data available from Aventis Pasteur Limited.
2. Fritzell B, Plotkin S. Efficacy and safety of a *Haemophilus influenzae* type b capsular polysaccharide-tetanus conjugate vaccine. J Pediatr 1992;121:355-362.
3. Decker MD, et al. Comparative trial in infants of four conjugate *Haemophilus influenzae* type b vaccines. J Pediatr 1992;120:184-189.
4. Scheifele D, et al. Can *Haemophilus influenzae* type b - tetanus toxoid conjugate vaccine be combined with diphtheria toxoid - pertussis vaccine - tetanus toxoid? Can Med Assoc J 1993;149(8):1105-1112.
5. National Advisory Committee on Immunization (NACI): Statement on *Haemophilus Influenzae* type b conjugate vaccines for use in infants and children. Can Dis Weekly Rep 1992;18-23: 169-176.
6. American Academy of Pediatrics. *Haemophilus Influenza* infections In: Peter G, ed. *1997 Red Book: Report of the Committee on Infectious Diseases. 24th ed.* Elk Grove Village, IL: American Academy of Pediatrics; 1997:21-22,220-231,394-407.
7. National Advisory Committee on Immunization (NACI). Supplementary statement on newly licenced *Haemophilus influenzae* type b (HIB) conjugate vaccines in combination with other vaccines recommended for infants. CCDR 1994;20-18:157-160.
8. National Advisory Committee on Immunization: Canadian Immunization Guide, Fourth Edition. Minister of Supply and Services Canada. 1993.
9. Expanded Programme on Immunization, Injections and Paralytic Poliomyelitis. Wkly Epidem Rec 1980;5:38-39.
10. Sutter RW, et al. Attributable Risk of DTP (Diphtheria and Tetanus Toxoids and Pertussis Vaccine) injection in provoking paralytic poliomyelitis during a large outbreak in Oman. J Infect Dis 1992;165:444-449.
11. Christie AB. *Infectious Diseases: Epidemiology and Clinical Practice. 4th Ed.* Edinburgh, Churchill Livingstone. 1987;2:817-825.
12. National Advisory Committee on Immunization (NACI). Anaphylaxis: statement on initial management in non-hospital settings. CCDR 1995;21-22:200-203.
13. Recommendations of the Advisory Committee on Immunization Practices (ACIP): General recommendations on immunization. MMWR 1994;43:1-38.

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Lyon, France

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QUADRACEL™

Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine

For Active Immunization against Diphtheria, Tetanus, Whooping Cough and Poliomyelitis

DESCRIPTION

QUADRACEL™, Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine, as supplied by Aventis Pasteur Limited, is a sterile, cloudy, uniform suspension of component pertussis vaccine, diphtheria and tetanus toxoids adsorbed on aluminum phosphate and suspended in water for injection and combined with inactivated poliomyelitis vaccine (Diploid Cell Origin - DCO). Component pertussis is an acellular pertussis vaccine composed of five purified pertussis antigens.

Each dose (0.5 mL) contains:	
pertussis toxoid (PT)	20 µg
filamentous haemagglutinin (FHA)	20 µg
fimbriae (agglutinogens 2 + 3)	5 µg
pertactin (69kDa membrane protein)	3 µg
diphtheria toxoid	15 Lf
tetanus toxoid	5 Lf
aluminum phosphate	1.5 mg
purified inactivated poliomyelitis vaccine:	Type 1 Mahoney
	Type 2 M.E.F.1
	Type 3 Saukett

0.6% ± 0.1% 2-phenoxyethanol added as preservative.

By calculation, the vaccine contains 10 ppm Tween 80 and less than 1 ppm of bovine serum. Trace amounts of polymyxin B and neomycin may be present from the cell growth medium.

CLINICAL PHARMACOLOGY

Immunization against diphtheria, tetanus, pertussis and polio has been associated with a striking decrease in the incidence of morbidity and mortality from these diseases. Simultaneous vaccination with a combination vaccine containing pertussis, diphtheria and tetanus toxoids and poliomyelitis vaccines has been a cornerstone of the Canadian immunization programme.

Diphtheria is a serious communicable disease caused by toxigenic strains of *Corynebacterium diphtheriae*. The organism may be harboured in the nasopharynx, skin or other sites of asymptomatic carriers, making eradication of the disease difficult. Routine immunization against diphtheria in infancy and childhood has been widely practised in Canada since 1930, resulting in a decline in morbidity and mortality. Fewer than 5 cases are now reported annually in Canada. The case-fatality rate remains 5 - 10%, with the highest death rates in the very young and elderly. The disease occurs most frequently in unimmunized or partially immunized individuals.[1] Diphtheria toxoid is a cell-free preparation of diphtheria toxin detoxified with formaldehyde. The immunity conferred is antitoxic, not antibacterial, and thus protects against the potentially lethal systemic effects of diphtheria toxin but not directly against local infection.[1]

Tetanus is an acute and often fatal disease caused by an extremely potent neurotoxin produced by *Clostridium tetani*. The organism is ubiquitous and its occurrence in nature cannot be controlled. Immunization is highly effective, provides long-lasting protection, and is recommended for the whole population. Only 2 to 3 cases of tetanus are now reported annually in Canada.[1] Tetanus toxoid is prepared by detoxification of tetanus toxin with formaldehyde.

Injection of bacterial proteins such as diphtheria and tetanus toxoids results in the production of protective antibodies. A primary series consisting of two or more injections is required to prime the immune system and produce a satisfactory protective antibody level. Tetanus antitoxin levels of >0.01 IU/mL are generally accepted as good evidence of immunity from tetanus. Diphtheria antitoxin levels of ≥0.01 IU/mL are thought to be the minimal level required for protection. Levels >0.05 IU/mL are considered optimal for protection.[2] After completion of a primary series, circulating antibodies to tetanus and diphtheria toxoids gradually decline but are thought to persist at protective levels for up to 10 years.[1] Tetanus and diphtheria toxoid boosters are recommended every 10 years.

Pertussis (whooping cough) is a highly communicable bacterial disease caused by *Bordetella pertussis*. Severity and mortality are greatest in infancy, and even infants born to apparently immune mothers are highly susceptible to infection, particularly if maternal immunity was induced by whole-cell pertussis vaccine. During the last 40 years, vaccination with whole-cell pertussis vaccine has been widely practised in Canada and the incidence of pertussis decreased by over 90% although outbreaks of pertussis continue to occur. Hospitalizations for pertussis are still common in Canada and several deaths from pertussis occur each year, particularly in unimmunized infants.[3] Controversy regarding the safety of whole-cell pertussis vaccine during the 1970s led to several studies of the benefits and risks of this vaccination during the 1980s. These epidemiologic analyses clearly indicate that the benefits of the pertussis immunization program outweigh the risks.[4,5] Acellular pertussis vaccines consisting of purified fractions of the *Bordetella pertussis* bacterium have been used effectively to control pertussis in children 2 years of age or older in Japan since 1981.[6]

In a randomized, double-blind controlled clinical trial conducted in Sweden with 82,892 infants comparing 3 acellular pertussis and one European whole-cell DPT vaccines, 20,746 infants received the formulation of TRIPACEL™ contained in QUADRACEL™, Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine, and Haemophilus b Conjugate Vaccine (Tetanus Protein Conjugate) at 2, 4 and 6 (2,552 infants) or 3, 5 and 12 (18,194 infants) months of age. TRIPACEL™ and the European whole-cell DPT vaccine had similar and high efficacy against culture-confirmed pertussis irrespective of duration. The other acellular pertussis combination vaccines were less effective.[7, 8] Rates of adverse events were less than or comparable to the rates in the other acellular pertussis and European whole-cell DPT groups in this study.[7, 8]

A randomized controlled efficacy study was conducted in Sweden using the formulation of TRIPACEL™, Component Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids Adsorbed, which contained lower concentrations of PT, FHA than the current formulation. In this study, 2,551 infants received TRIPACEL™ and 2,539 infants received a control vaccine containing diphtheria and tetanus toxoids at 2, 4 and 6 months of age. TRIPACEL™ demonstrated a clinical efficacy of 85.1% against pertussis disease (defined as 21 days of paroxysmal cough with culture or serologic confirmation of infection with *Bordetella pertussis*).[8,9]

Poliomyelitis is caused by infection with one of the three antigenic types of poliovirus. Following introduction of poliovirus vaccine in Canada in 1955, the indigenous disease has been virtually eliminated. The last significant outbreak of poliomyelitis occurred in 1978-79, when there were 11 cases of paralytic

disease among unimmunized contacts of imported cases. The last case of poliomyelitis attributed to imported, wild virus occurred in 1988.[1] However, circulation of wild viruses does occur in rare circumstances,[10] and it remains crucial that the highest possible level of vaccine-induced immunity be maintained in the population. Inactivated Poliomyelitis Vaccine (Diploid Cell Origin) - IPV, (sometimes referred to as e-IPV), is an enhanced formalin-inactivated product which has a higher potency than the original IPV. The three poliovirus types are propagated in human diploid cells. A primary series induces protective antibody levels in more than 99% of recipients.[8]

In clinical trials conducted in Canada, more than 3,000 children have received QUADRACEL™, Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine, alone or used to reconstitute Act-HIB®, Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate). Whether given at 2, 4, 6 months, at 18 - 19 months (fourth dose) or at the 4 - 6 year booster, QUADRACEL™ produced comparable anti-tetanus, diphtheria and polio responses to the DPT Polio Adsorbed control. Anti-PRP responses were comparable as well. Although QUADRACEL™ contains 15 Lf of diphtheria toxoid versus the 25 Lf of diphtheria toxoid in DPT Polio Adsorbed, no significant differences in diphtheria antitoxin responses were seen in any of the age groups. Responses to pertussis antigens PT, FHA and pertactin were significantly higher in QUADRACEL™ recipients than in recipients of DPT Polio Adsorbed.

TABLE 1[8]: COMPARISON OF QUADRACEL™ WITH WHOLE-CELL PERTUSSIS COMBINATIONS SEROLOGIC RESULTS

	GEOMETRIC MEAN TITRE (GMT)					
	7 months		19 - 20 months		4 - 6 years	
ANTIGEN	DPT Polio// PRP-T* (n = 105)	QUADRACEL™ (n = 108)	DPT Polio// PRP-T* (n = 94)	QUADRACEL™ (n = 92)	DPT Polio (n = 30)	QUADRACEL™ (n = 126)
Diphtheria	0.29	0.36	6.82	7.07	17.0	15.1
Tetanus	0.63	1.61	5.40	6.78	5.54	5.10
Agglutinins	438	444	642	848	1,315	1,939
PT	15.2	103	44.6	116	47.9	123.2
FHA	31.4	165	72.6	156	119.3	176.2
Pertactin	8.9	40.5	26.4	77	41.2	64.2
FIM	355	332	719	877	479	738
Polio 1	889	702	11,873	9,311	15,462	10,903
Polio 2	2,597	2,595	21,038	18,331	23,661	27,337
Polio 3	2,726	1,837	10,675	12,492	10,540	9,165

* Act-HIB® reconstituted with Aventis Pasteur Limited's DPT Polio Adsorbed.

With the exception of tetanus, no differences were found in immunogenicity when QUADRACEL™ was used to reconstitute Act-HIB® or the two vaccines were given at separate sites. Anti-PRP responses were comparable. All children were protected against polio. Pertussis responses were not affected by method of administration. 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.

QUADRACEL™ was significantly less reactogenic than DPT Polio Adsorbed.

INDICATIONS

QUADRACEL™, Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine, is indicated for the primary immunization of infants, at or above the age of two months and as a booster in children up to their 7th birthday against diphtheria, tetanus, whooping cough and poliomyelitis.

When both vaccines are indicated, QUADRACEL™ may be used to reconstitute Act-HIB®, Haemophilus b Conjugate Vaccine (Tetanus Protein - Conjugate), for simultaneous administration of all 5 antigens in a single injection. QUADRACEL™ must **not** be mixed in the same syringe with any other vaccines.

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 return of a vaccine recipient for further immunization is doubtful, simultaneous administration of all vaccines appropriate for age and previous vaccination status (including MMR, other *Haemophilus influenzae* type b conjugate vaccines, hepatitis B vaccine) at separate sites with separate syringes is indicated.[5]

Human Immunodeficiency Virus (HIV)-Infected Persons

HIV-infected individuals, both asymptomatic and symptomatic, should be immunized against diphtheria, pertussis, tetanus and poliomyelitis according to standard schedules.[1]

Children who have had tetanus or diphtheria should still be immunized since these clinical infections do not always confer immunity.[1] Children who have had natural pertussis can continue to receive pertussis-containing vaccines.[3]

Infants born prematurely whose clinical condition is satisfactory should be vaccinated according to their chronological age from birth.[5]

CONTRAINDICATIONS

General

Immunization with QUADRACEL™, Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine, 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]

Absolute Contraindications

Allergy to any component of QUADRACEL™ (see components listed in DESCRIPTION), or an allergic or anaphylactic reaction to a previous dose of DPT Polio Adsorbed are contraindications to vaccination.[1]

QUADRACEL™ should not be administered to children after their 7th birthday or to adults because of the quantity of diphtheria toxoid and because pertussis is less severe in these age groups than in infants and young children.

Relative Contraindications (Based on experience with whole-cell pertussis vaccine)

Hypotonic-hyporesponsive episodes (HHE): No long term sequelae have been associated with HHE; however, because there are no data on administration of component pertussis vaccine to infants and children who have experienced HHE it may be prudent in areas of low pertussis incidence to withhold the pertussis component and continue immunization with DT Polio Adsorbed in children who have experienced a HHE following a previous dose of pertussis-containing vaccine. Children can continue immunization with QUADRACEL™ if the incidence of disease is high in their area.[1]

Deferral

Deferral of the pertussis component of QUADRACEL™ should be considered in children with a progressive, evolving, or unstable neurologic condition (including seizures) because administration of the pertussis component may coincide with the onset of overt manifestations of such disorders and result in confusion about causation. It is prudent to delay initiation of immunization with pertussis vaccine until further observation and study have clarified the child's neurologic status. In addition, the effect of treatment, if any, can be assessed. Immunization with QUADRACEL™ should be reinstituted when the condition has resolved, been corrected or controlled.[1]

When immunization with pertussis vaccine is contraindicated or deferred, immunization with diphtheria and tetanus toxoids and poliomyelitis vaccine, when necessary, may be continued using DT Polio Adsorbed.

Elective immunization of individuals over 6 months of age should be deferred during an outbreak of poliomyelitis because of the risk of provocation paralysis.[11,12,13]

WARNINGS

Intramuscular injections should be given with care in patients suffering from coagulation disorders because of the risk of hemorrhage.[1]

If QUADRACEL™, Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine, is used in persons with malignancies, receiving immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, or who are otherwise immunocompromised (including HIV-infected individuals), the expected immune response may not be obtained.

Corticosteroid therapy can result in immunosuppression although the exact dose and duration of therapy required to suppress the immune system is not well defined. Persons treated with high doses of systemic steroids, e.g., ≥2 mg/kg per day of prednisone orally for more than 2 weeks, should be considered to have a compromised immune system.[1]

As with any vaccine, immunization with QUADRACEL™ may not protect 100% of susceptible individuals.

The use of fractional doses in an attempt to reduce the severity of adverse reactions cannot be recommended because there is insufficient evidence on the safety or efficacy of such smaller doses.[1]

PRECAUTIONS

General

The possibility of allergic reactions in individuals sensitive to components of the vaccine should be evaluated. Epinephrine Hydrochloride Solution (1:1,000) and other appropriate agents should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs.[1] Health-care providers should be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings, including proper airway management.[5,14]

Before administration of any vaccine, appropriate precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible hypersensitivity to the vaccine or similar vaccine, determination of previous immunization history, and the presence of any contraindications to immunization, current health status, and a current knowledge of the literature concerning the use of the vaccine under consideration.

Antipyretic Prophylaxis: Administration of acetaminophen (15 mg/kg per dose) or other appropriate antipyretic at the time of immunization and at 4 and 8 hours after immunization decreases the incidence of febrile and local reactions.[1] Since convulsions after whole-cell pertussis vaccine are almost always associated with fever, antipyretic prophylaxis may benefit children at increased risk of seizures. For such children, administration of an antipyretic every 4 to 6 hours for as long as 24 hours after vaccination should be considered. Caregivers should be aware that antipyretic therapy could also obscure fever caused by concomitant, unrelated infection.[5]

Special care should be taken to ensure that the product is not injected into a blood vessel. (See DOSAGE and ADMINISTRATION.)

A separate, sterile needle and syringe or a sterile disposable unit must be used for each individual patient to prevent the transmission of infectious agents. There have been case reports of transmission of HIV and hepatitis by failure to scrupulously observe sterile technique. In particular, the same needle and/or syringe must never be used to re-enter a multi-dose vial to withdraw vaccine even when it is to be used for inoculation of the same patient. This may lead to contamination of the vial contents and infection of patients who subsequently receive vaccine from the vial.[15]

Needles should not be recapped and should be disposed of properly.

A family history of convulsions in parents and siblings is not a contraindication to pertussis vaccination and children with such family histories should receive pertussis-containing vaccines according to the recommended schedule.[4] Parents of infants and children with family histories of convulsions should be informed of their children's increased risk of seizures following administration of any vaccine causing a febrile reaction.[16] Acetaminophen prophylaxis is particularly recommended for children with a personal or family history of convulsions.[1]

Frequent booster doses of tetanus or diphtheria toxoids in the presence of adequate or excessive serum levels of tetanus or diphtheria antitoxins have been associated with increased incidence and severity of reactions and should be avoided.

Before administration of QUADRACEL™, health-care personnel should inform the parent or guardian of the patient to be immunized of the benefits and risks of immunization, inquire about the recent health status of the patient and comply with any local requirements with respect to information to be provided before immunization.

ADVERSE REACTIONS

In clinical trials done in Canada, QUADRACEL™, Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine, had consistently lower rates of local and systemic reactions than DPT Polio Adsorbed, whether combined with Act-HIB® or given at separate sites. There was a trend towards increasing local reaction rates at the fourth and fifth doses, but these were still significantly lower than with whole-cell pertussis combination vaccines.[9]

TABLE 2:[8] LOCAL ADVERSE REACTIONS (%) WITHIN 24 HOURS OF VACCINATION WITH QUADRACEL™

REACTION	2 Months (n = 111)	4 Months* (n = 109)	6 Months* (n = 109)	18-19 Months** (n = 92)	4-6 Years*** (n = 163)
Redness	1	7	12	15	19
Swelling	5	4	7	8	19
Tenderness	19	17	10	22	75

* Received QUADRACEL™ for previous dose(s).
** Received whole-cell pertussis combination vaccine for first 3 doses.
*** Received whole-cell pertussis combination vaccine for first 4 doses.

TABLE 3:[8] SYSTEMIC ADVERSE REACTIONS (%) WITHIN 24 HOURS OF VACCINATION WITH QUADRACEL™

REACTION	2 Months (n = 111)	4 Months* (n =109)	6 Months* (n = 109)	18-19 Months** (n = 92)	4-6 Years*** (n = 163)
Fever	21	20	17	19	17
Fussiness	45	42	35	33	20
Crying	30	28	24	4	-
Decreased Activity	51	29	22	14	23
Decreased Eating	34	21	17	15	23
Vomiting	8	3	6	3	5
Diarrhea	8	8	10	8	2

* Received QUADRACEL™ for previous dose(s).
** Received whole-cell pertussis combination vaccine for first 3 doses.
*** Received whole-cell pertussis combination vaccine for first 4 doses.

In a clinical trial conducted in Sweden comparing 3 acellular pertussis vaccines and 1 whole-cell DPT vaccine, 20,745 infants received TRIPACEL™ at 2, 4 and 6 or 2, 5 and 12 months of age. Rates of adverse events were less than or comparable to the rates in the other acellular pertussis vaccine and whole-cell DPT groups in this study. The rates of reports of fever >40.5°C and seizures or suspected seizures were significantly higher following whole-cell DPT than following acellular pertussis vaccines.[7,8] Rates of hypotonic-hyporesponsive episodes were comparable, with 29 reports following administration of TRIPACEL™. No deaths or cases of encephalitis/acute encephalopathy, invasive bacterial infection, infantile spasms or anaphylactic reactions were reported within 48 hours of vaccination.[7,17,18]

Rare cases of allergic or anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) have been reported after receiving some preparations containing diphtheria, tetanus and/or pertussis antigens.[4] Death following vaccine-caused anaphylaxis has been reported.[19]

Localized reactions consisting of discomfort, pain, swelling and redness at the injection site may be associated with tetanus and diphtheria toxoids.[20,21] These are usually of low frequency and transient in duration. Following booster doses, local erythema and swelling are not uncommon and Arthus-type sensitivity may occur.[1] Severe local reactions are often associated with high levels of circulating antitoxin, usually resulting from over-immunization due to toxoid being given too frequently.

Systemic reactions, such as generalized urticaria, are uncommon. Influenza-like symptoms have been reported and usually occur within 12 hours of vaccination with diphtheria and tetanus toxoids.[21]

Neurological complications such as peripheral neuropathies[22,23] and demyelinating diseases of the central nervous system (CNS)[19] following some tetanus toxoids or diphtheria toxoids have been documented but are rare.[24] The U.S. Institute of Medicine has concluded that the evidence is inadequate to accept or reject a causal relation between tetanus toxoid, DT or Td and demyelinating diseases of the CNS (acute demyelinating encephalomyelitis, transverse myelitis, optic neuritis) or peripheral mononeuropathy (other than those caused by direct intraneural injection).[19]

The following neurologic illnesses have been reported as temporally associated with some vaccines containing tetanus toxoid: neurological complications[25] including cochlear lesion,[26] brachial plexus neuropathies,[24,26] paralysis of the radial nerve,[22] paralysis of the recurrent nerve,[26] accommodation paresis, and EEG disturbances with encephalopathy (with or without permanent intellectual and/or motor function impairment).[27] In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.[19,28] The Institute of Medicine concluded that the evidence favours acceptance of a causal relation between tetanus toxoid and brachial neuritis.[19]

On the basis of a case report and evidence that a vaccine-induced immunologic response can cause Guillain-Barré Syndrome (GBS), the Institute of Medicine concluded that tetanus toxoid-containing vaccines can trigger GBS in adults. No increased risk for GBS has been observed with the use of DPT in children.[24]

Persistent nodules at the site of injection have occurred following the use of an adsorbed product, but this complication is unusual,[29] and may be related to subcutaneous administration. Sterile abscess at the site of injection has been reported following use of adsorbed vaccines (6 - 10 per million doses).[5]

QUADRACEL™ does not contain a whole-cell pertussis vaccine, however, persistent, inconsolable crying lasting 3 or more hours (1%) and high-pitched, unusual screaming (0.1%) have been reported after whole-cell DPT vaccination. The incidence of both of these events is significantly lower with QUADRACEL™.[9] Convulsions and a hypotonic-hyporesponsive state have each been reported to occur at a frequency of about 1:1,750 doses of whole-cell DPT.[1,5,27] Most convulsions are brief, generalized and self-limited, and are usually associated with fever. Neither febrile nor afebrile convulsions have been shown to be associated with subsequent seizure disorder.[5] Complete recovery, without persistent sequelae, has been observed on follow-up of children with hypotonic-hyporesponsive episodes or convulsions.[1,3,5] (See CONTRAINDICATIONS and PRECAUTIONS.)

Although there has been a concern about the possible association of severe neurologic illness (including encephalopathy [with or without permanent intellectual and/or motor function impairment]) occurring within 72 hours of the administration of whole-cell pertussis-containing vaccines to previously healthy infants, the risk of an association is so small compared to the background rate for these types of events that the question of causation probably cannot be answered.[1,3]

Reanalysis of the National Childhood Encephalopathy Study (NCES) in the United Kingdom has failed to confirm that there was an increased risk of permanent brain damage following acute neurological illness occurring within 7 days of whole-cell pertussis vaccination. Additional studies have also failed to demonstrate an association between pertussis vaccine and permanent neurologic sequelae[1] (including permanent intellectual and/or motor function impairment).

Sudden infant death syndrome (SIDS) has been reported in temporal relationship to the administration of vaccines containing diphtheria and tetanus toxoids and pertussis vaccine (DPT). Review of the evidence does not indicate a causal relationship between whole-cell DPT vaccine and SIDS. Studies showing a temporal relation between these events are consistent with the expected occurrence of SIDS over the age range in which DPT immunization usually occurs.[29,30]

As with any vaccine, there is the possibility that broad use of the vaccine could reveal rare adverse reactions not observed in clinical trials.

Physicians, nurses, and pharmacists should report any adverse occurrences temporally related to the administration of the product in accordance with local requirements and report to the Medical Director at Aventis Pasteur Limited, 1755 Steeles Avenue West, Toronto, Ontario, Canada, M2R 3T4.

DOSAGE

For primary immunization of infants the following routine QUADRACEL™, Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine, immunization schedule is recommended: one 0.5 mL dose administered at 2, 4, 6 and 18 months of age.

If for any reason this schedule is delayed, it is recommended that three doses of 0.5 mL be administered with an interval of two months between doses, followed by a fourth dose of 0.5 mL administered approximately 6 - 12 months following the third dose.

A booster dose of 0.5 mL should be administered between four and six years of age (i.e., at the time of school entry). This booster dose is unnecessary if the fourth primary immunizing dose has been administered after the fourth birthday.[1]

Whenever feasible, QUADRACEL™ should be used for all doses in the vaccination series as there are no clinical data to support the use of QUADRACEL™ with any other licensed acellular pertussis combination vaccine in a mixed sequence. For situations where a different brand of DTaP or DTaP-IPV vaccine was originally used, or where the brand is unknown, please refer to the latest edition of Health Canada's *Canadian Immunization Guide*.

Thereafter, routine booster immunizations should be with Td or Td Polio, at intervals of 10 years. PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH QUADRACEL™.[1]

ADMINISTRATION

Parenteral biological products should be inspected visually for extraneous particulate matter and/or discolouration before administration. If these conditions exist, the product should not be administered.

SHAKE THE VIAL OR AMPOULE WELL to distribute uniformly the suspension before withdrawing each dose. Before withdrawing a dose from an ampoule, tap the container first to ensure that any vaccine in the ampoule neck falls to the lower portion of the ampoule. Once the ampoule has been opened, any of its contents not used immediately should be discarded. When administering a dose from a stoppered vial, do not remove either the stopper or the metal seal holding it in place. Aseptic technique must be used for withdrawal of each dose. (See PRECAUTIONS.)

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide.

Administer the vaccine **intramuscularly**. The preferred site is into the deltoid muscle or into the anterolateral aspect of the mid-thigh (vastus lateralis 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.[1,31]

After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

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.

STORAGE

QUADRACEL™, Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine, should be stored at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Product which has been exposed to freezing should not be used. Do not use vaccine after expiration date.

HOW SUPPLIED

Ampoule 5 x 0.5 mL (Single Dose)

QUADRACEL™ is also supplied in packages containing five single-dose vials of Act-HIB® and five 0.5 mL (single-dose) ampoules of QUADRACEL™ to be used for reconstitution in place of the diluent and sold under the name of PENTACEL™.

REFERENCES

1. National Advisory Committee on Immunization: *Canadian Immunization Guide, Fourth Edition.* Minister of Supply Services Canada. 1993.
2. Plotkin SA, Mortimer EA. *Vaccines. 2nd ed*. Philadelphia, W. B. Saunders Company. 1994:41-82.
3. National Advisory Committee on Immunization (NACI): Statement on pertussis vaccine. CCDR 1997;23:1-12.
4. Recommendations of the Immunization Practices Advisory Committee (ACIP). Diphtheria, tetanus, and pertussis: guidelines for vaccine prophylaxis and other preventive measures. MMWR 1991;40,RR-10:1-28.
5. American Academy of Pediatrics. In: Peter G, ed. *1997 Red Book: Report of the Committee on Infectious Diseases, 24th ed.* Elk Grove Village, IL: American Academy of Pediatrics 1997:21-22,394-407.
6. Kimura M. Japanese clinical experience with acellular pertussis vaccines. Symposium on pertussis: evaluation and research on acellular pertussis vaccines. Dev Biol Stand 1990;73:5-9.
7. Olin P, et al. A controlled trial of two-component, three-component, and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. Lancet 1997;350(9091):1569-1577.
8. Data on file at Aventis Pasteur Limited.
9. Gustafsson L, et al. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. N Engl J Med 1996;334:349-55.
10. National Advisory Committee on Immunization (NACI): Genomic analysis of type 3 wild poliovirus isolates in southern Alberta. CCDR 1993;19-13:96-99.
11. Expanded programme on immunization, injection and paralytic poliomyelitis. Wkly Epidem Rec 1980;5:38-39.
12. Sutter RW, et al. Attributable risk of DTP (Diphtheria and Tetanus Toxoids and Pertussis Vaccine) injection in provoking paralytic poliomyelitis during a large outbreak in Oman. J Infect Dis 1992;165:444-449.
13. Christie AB. *Infectious diseases: Epidemiology and clinical practice. 4th ed*. Edinburgh, Churchill Livingstone. 1987;2:817-825.
14. National Advisory Committee on Immunization (NACI). Anaphylaxis: statement on initial management in non-hospital settings. CCDR 1995:21-22:200-203.
15. Plott RT, et al. Iatrogenic contamination of multidose vials in simulated use. Arch Dermatol 1990;126:1441-1444.

16. Recommendations of the Immunization Practices Advisory Committee (ACIP). Pertussis immunization; family history of convulsions and use of antipyretics - supplementary ACIP statement. MMWR 1987;36:281-282.
17. Heijbel H, et al. Safety evaluation of one whole-cell and three acellular pertussis vaccines in Stockholm Trial II. Dev Biol Stand 1997;89:99-100.
18. Heijbel H, et al., Hypotonic hyporesponsive episodes in eight pertussis vaccine studies. Dev Biol Stand 1997;89:101-103.
19. Stratton KR, et al. *Adverse events associated with childhood vaccines; evidence bearing on causality.* National Academy Press 1994:67-117.
20. Eisen AH, et al. Reaction to tetanus toxoid; report of a case with immunologic studies. N Engl J Med 1963;269:1408-1411.
21. White WG, et al. Reactions to tetanus toxoid. J Hyg (Camb.) 1973;71:283-297.
22. Blumstein GI, Kreithen H. Peripheral neuropathy following tetanus toxoid administration. JAMA 1966;198:166-167.
23. Tsairis P, et al. Natural history of brachial plexus neuropathy; report on 99 patients. Arch Neurol 1972;27:109-117.
24. CDC. Update: vaccine side effects, adverse reactions, contraindications, and precautions-recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1996;45,RR-12:1-35.
25. Rutledge SL, et al. Neurological complications of immunizations. J Pediatr 1986;109:917-924.
26. Wilson GS. *The hazards of immunization.* Allergic manifestations: Post-vaccinal neuritis. 1967:153-156.
27. Cody CL, et al. Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. Pediatrics 1981;68:650-660.
28. Schlenska GK. Unusual neurological complications following tetanus toxoid administration. J Neurol 1977;215:299-302.
29. Report of the committee to review the adverse consequences of pertussis and rubella vaccines: Adverse effects of pertussis and rubella vaccines. Washington, Institute of Medicine. 1991;125-141.
30. Chen RT, et al. Investigation of sudden unexplained infant deaths following DTP, OPV and HBV vaccinations. Abstract of the 9th International Conference on Pharmacoepidemiology: Post Marketing Surveillance 1993;7(3):194.
31. Recommendations of the Advisory Committee on Immunization Practices (ACIP): General recommendations on immunization. MMWR 1994;43:1-38.

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