Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA) and Haemophilus Type b Conjugate Vaccine IP

DESCRIPTION:
The vaccine is a homogenous liquid containing purified diphtheria and tetanus toxoids, inactivated whole cell (pertussis) organisms, highly purified, non-infectious particles of hepatitis B surface antigen (HBsAg) and Hib components as a bacterial subunit vaccine containing highly purified, non-infectious particles of Haemophilus influenzae type b (Hib) capsular polysaccharide chemically conjugated to a protein CRM197 [Cras reaction material derived from Corynebacterium diphtheriae strain C8(197)] M8]. The HBsAg is produced by DNA recombinant technology in P. polymorpha yeast cells. The vaccine is not adsorbed on to aluminium phosphate gel. The Hib polysaccharide is derived from Hib bacteria grown in chemically defined media, and subsequently purified through a series of ultrafiltration steps. The purity of the vaccine per single human palmar dose is at least 4.0 IU for whole cell pertussis (wp), 30 IU for diphtheria, 60 IU for tetanus (determined in mice), 10 µg HBsAg and 10 µg Hib oligosaccharide conjugated to 25 µg CRM197 protein.

One 0.5 mL dose of vaccine contains:

- Diphtheria toxoid: not less than 30 IU
- Tetanus toxoid: not less than 60 IU
- Pertussis antigen: not less than 4.0 IU
- Hb conjugate: 10 µg, conjugated to approx. 25 µg of CRM 197
- Hepatitis B surface antigen, purified: 10 µg
- Aluminium hydroxide (adjuvant): 0.3 mg
- Sodium chloride: 4.5 mg

Quinvaxem inj. is free of preservative with no thiomersal added*. *There may be a present of traces in residue of the manufacturing process.

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS
Active primary and booster immunisation of infants and toddlers for protection against diphtheria, tetanus, pertussis, hepatitis B, and invasive illness caused by H. influenzae type b. Quinvaxem provides flexibility within the WHO-recommended Expanded Programme on Immunisation (EPI) vaccination schedule (three doses each of diphtheria, tetanus, pertussis, DTIP, HepB, and Hib vaccines) and can fit around a country's existing vaccination calendar.

ADMINISTRATION:
Before use, the vial with a vaccine should be shaken in order to homogenise the liquid suspension. The vaccine should be injected intramuscularly. The anterolateral part of the upper thigh is the preferred site of injection. An injection into a child's buttocks may cause injury to the sciatic nerve and is not recommended. The vaccine must not be injected subcutaneously as this may give rise to local reactions. A sterile syringe and sterile needle must be used for each injection.

IMMUNIZATION SCHEDULE:
Primary vaccination of Infants: 3 doses of 0.5 mL each, based on vaccination schedule.

- Primary vaccination of Infants: 3 doses of 0.5 mL each, based on vaccination schedule.
- Primary vaccination of Toddlers (15–18 months after birth): one booster dose of 0.5 mL. Quinvaxem booster dose can be given to toddlers initially vaccinated with DTwP – HepB – Hib.
- Reinforcing vaccination: DTwP – HepB – Hib vaccine can be given safely and effectively at the same time as BCG, measles, polio (OPV or IPV) and yellow fever vaccines, and vitamin A supplementation. If DTwP – HepB – Hib vaccine is given at the same time as other vaccines, it should be administered at a separate site.

SIDE EFFECTS:
The incidence and type of adverse reactions of the Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA) and Haemophilus Type b Conjugate Vaccine IP do not differ significantly from the DTIP, HepB and Hib vaccine reactions described separately. For DTIP, mild or local reactions are common. Some temporary swelling, tenderness and redness at the site of injection together with fever occur in a large proportion of cases. Occasionally severe reactions such as partial or total high fever, irritability and somnolence within 24 hours of vaccination. Hypotonic-hyporesponsive episodes have been reported. Febrile convulsions have been reported at a rate of 1/5000 doses administered. Administration of paracetamol at the time and 4–8 hours after immunization decreases the subsequent incidence of febrile reactions. The national childhood encephalopathy study in the United Kingdom showed a small increased risk of acute encephalopathy (primarily seizures) following DTIP immunization. However, subsequent detailed receiving no evidence from studies by a number of groups, including the United States Institute of Medicine, the Advisory Committee on Immunization Practices, and the paediatric associations of Australia, Canada, the United Kingdom and the United States, concluded that the data did not demonstrate a causal relationship between DTIP and chronic nervous system dysfunction in children. Thus there is no scientific evidence that these reactions have any permanent consequences for the children*.

Hepatitis B vaccine is very well tolerated in placebo-controlled studies, with the exception of local pain, reported events such as myalgia and fatigue have not been more frequent than in the placebo group. Reports of severe anaphylactic reactions are very rare. Available data do not indicate a causal association between hepatitis B vaccine and Guillain-Barre syndrome, or demyelinating disorders including multiple sclerosis, nor is there any epidemiological data to support a causal association between hepatitis B vaccination and chronic fatigue syndrome, arthritis, autoimmune disorders, asthma, sudden infant death syndrome, or diabetes. HBV vaccine is very well tolerated. Localized reactions may occur within 24 hours of vaccination, when recipients may experience pain and tenderness at the injection site. These reactions are generally mild and transient. In most cases, they spontaneously resolve within two to three days and further medical attention is not required. Mild systemic reactions, including fever, rarely occur following administration of HBV vaccines. More serious reactions are very rare; a causal relationship between more serious reactions and the vaccine has not been established.

DATA FROM CLINICAL STUDIES:
In the four clinical trials performed 2115 doses of Quinvaxem inj. Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA) and Haemophilus Type b Conjugate Vaccine IP have been administered as a primary vaccination in 730 healthy infants from six weeks of age. In these clinical studies, signs and symptoms were actively monitored in all subjects for five to seven days following the administration of the vaccine. No serious adverse reactions attributable to the vaccine have been reported during the course of clinical trials.

Solicited reactions are listed below. Frequencies, based on number of doses, are reported as:

- Very common (>1/10), Common (>1/100, ≤1/10), Uncommon (>1/1000, ≤1/100), Rare (>1/10000)

- Very rare (<1/10000), Incl. isolated reports.

A clinical study in 175 Indian infants administered 6, 10, and 14 weeks of age demonstrated that Quinvaxem is highly immunogenic and has an acceptable safety profile. Percentages of infants achieving predefined protective antibody levels were 99% diphtheria, 100% tetanus, 98% Hepatitis B, 95% Hib short-term (<0.15 µg/mL); 95% Hib long-term (≥0.1 µg/mL) protection, and 99% for...
pertussis. The vaccine was well tolerated, with no vaccine-related serious AEs. Most frequently reported reactions were mild to moderate tenderness and erythema. Frequencies of all AEs declined with subsequent vaccinations.

**GASTROINTESTINAL DISORDERS:**

- Common: Diarrhoea, Vomiting

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS:**

- Very common: Injection site pain, injection site swelling, fever
- Common: Injection site redness
- Uncommon: Fever ≥39.5 °C
- Uncommon: Influenza-like illness

**METABOLISM AND NUTRITION DISORDERS:**

- Nervous System Disorders:
  - Common: Seizures
  - Very common: Convulsions

**PSYCHIATRIC DISORDERS:**

- Very common: Irritability
- Common: Crying

**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS:**

- Rare: Coughing

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS:**

- Most cases disappeared spontaneously. All local and systemic reactions resolved without sequelae.

**Data from post-marketing experience**

As with any vaccine, there is the possibility that broad use of the vaccine in post-authorisation could reveal adverse reactions not observed in clinical trials. DTaP – HepB – Hib fully liquid combination vaccine is based on the combination of known and registered vaccine components. Safety and efficacy of these vaccines has been demonstrated for many years, and the differences in safety and tolerability of the Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA) and Haemophilus Type b Conjugate Vaccine IP compared to the formulation for the established vaccines are not considered to be clinically significant.

In the post-authorisation period rare cases of hypotonic-hyporesponsive episodes have been reported with Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA) and Haemophilus Type b Conjugate Vaccine IP. In all cases the symptoms disappeared spontaneously with no sequelae.

Allergic reactions, including anaphylactic reactions and urticaria, have been reported very rarely following vaccination with DT, Hepatitis B and Hib containing vaccines.

**CONTRAINdications:**

Known hypersensitivity to any component of the vaccine, or a serious reaction to a previous dose of the combination vaccine or any of its constituents is an absolute contraindication to subsequent doses of the combination vaccine or the specific vaccine known to have provoked an adverse reaction. There are no free contradictions to the first dose of DTaP – fits or abdominal cramps in the newborn period or other serious neurological abnormalities are contradictions to the pertussis component. In this case, the vaccines should not be given as a combination vaccine but DT1 should be given instead of DTaP and Hep B and Hib vaccines given separately. The vaccine will not harm individuals currently or previously infected with the hepatitis B virus.

As with other vaccines, vaccination should be postponed in children suffering from acute febrile illness, Mumps or measles such as common cold or other infections of the upper respiratory tract considered contraindications to the vaccination.

Equally, it is not necessary to postpone vaccination in the case of treatment with topical corticosteroids or systemic use at low dosage (i.e. ≤0.5 mg/kg prednisone or equivalent), or in case of skin diseases like dermatitis, eczema, or other localised skin disorders.

**Warances and Precautions for Use**

As with any injectable vaccine, appropriate medical supervision and treatment should always be readily available in case of immediate allergic reactions, such as anaphylactic shock or anaphylactic reactions resulting from administration of the vaccine.

Before administering the vaccine, precautions should be taken to avoid undesirable reactions. These precautions include: review of the individual's medical history, particularly regarding hypersensitivity reactions to previous administration of any type of vaccine, as well as the individual's history of other health disorders and any previous vaccinations.

The administration of any subsequent dose of a vaccine containing the whole-cell pertussis component should be carefully considered if, in connection with the administration of DTaP vaccine, one or more of the following effects have been observed:

- ≥40 °C temperature within 48 hours following vaccination (not due to other identifiable causes);
- collapse or shock (hypotonic hyporesponsive episodes) within 48 hours following vaccination;
- persistent crying lasting more than 3 hours following vaccination;
- convulsions, with or without fever, within 3 days following vaccination.

There may be circumstances, such as high incidence of pertussis, when potential benefits outweigh possible risks.

**HIV seropositivity does not represent a contraindication to vaccination. Patients with an immunode- ficiency disorder or receiving immunosuppressive therapy may have a reduced immunological re- sponse. Individuals infected with the human immuno-deficiency virus (HIV), both asymptomatic and symptomatic, should be immunised with combined vaccine according to standard schedules.**

The vaccine must not be injected into a blood vessel.

Quinwaxen inj. Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA) and Haemophilus Type b Conjugate Vaccine IP should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following the intramuscular administration to these subjects. A fine needle should be used for the vaccination and firm pressure applied to the site (without rubbing) for at least two minutes following administration.

**STORAGE:**

The combination vaccine must be stored and transported between +2 °C and +8 °C.

**PRESENTATION:**

- The vaccine is supplied in single dose vials.

* In Weekly Epidemiological Record, No. 18, 7 May 1999. Page 139

**Manufacturing**

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**Marketing by:**