QUINVAXEM® in cPAD

DTwP – HepB – Hib fully liquid combination vaccine

DESCRIPTION

The vaccine is a homogeneous liquid containing purified diphtheria and tetanus toxoids, inactivated whooping cough (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 *Haemophilus influenzae* type b (Hib) capsular polysaccharide chemically conjugated to a protein CRM197 [Cross reacting material derived from Corynebacterium diphteriae strain C7(ß197)M8]. The HBsAg is produced by DNA recombinant technology in *H. polymorpha* yeast cells. The vaccine is adsorbed on to aluminium phosphate gel. The polysaccharide is derived from Hib bacteria grown in chemically defined media, and subsequently purified through a series of ultrafiltration steps. The quantity of the vaccine per single human paediatric 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.

COMPOSITION OF VACCINE per 1 ml:

Diphtheria toxoid	not less than 15 Lf/ml (not less than 60 IU/ml)
Tetanus toxoid	not less than 6.5 Lf/ml (not less than 120 IU/ml)
Pertussis antigen	not less than 30 OU/ml (not less than 8.0 IU/ml)
Hepatitis B surface antigen	20 µg/ml
Hib conjugate	70 µg/ml (20 µg Hib oligosacharide conjugated to 50 µg CRM197 protein)
Aluminium phosphate	0.6 mg/ml AL^{3+}
Sodium chloride	9 mg/ml

Thiomersal is present in traces as residue from the manufacturing process of wP vaccine.

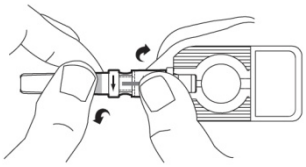
ADMINISTRATION

One paediatric dose is 0.5 mL. Before use, the cPAD injection system should be held by the port and should be shaken in order to homogenize 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 into the skin as this may give raise to local reactions. Quinvaxem® in cPAD should be administered as follows:

1

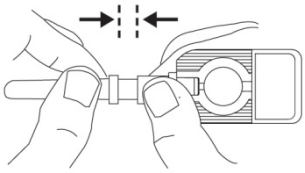
Hold the cPAD injection system by the port, shake vigorously, by flicking the wrist, until a homogeneous liquid suspension is obtained.

2



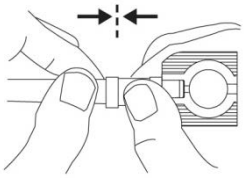
Hold the port and twist the tamper-evident seal to break it

3



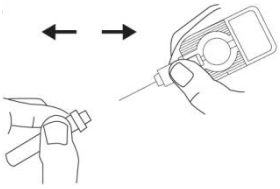
With a firm, rapid motion, push the needle shield into the port to activate the injection system.

4



Continue to push firmly until you close the gap between the needle shield and the port.

5



Hold the cPAD injection system by the port and remove the needle shield.

6

Holding the cPAD injection system by the port insert the needle into the anterolateral aspect of the upper thigh at a 90° downward angle*.

7

Squeeze the reservoir firmly to inject until the reservoir has completely collapsed. Remove the cPAD injection system. Do not recover the needle with the shield.

8

Discard the used cPAD injection system into a sharps disposal container and discard the needle shield.

* In preterm babies and/or children with little subcutaneous adipose tissue, bunch up the subcutaneous and muscle tissue (to minimize the chance of striking bone) and inject at a >60° - ≤90°

IMMUNIZATION SCHEDULE

Quinvaxem® should NOT be used for the birth dose of hepatitis B vaccination.

In countries where pertussis is of particular danger to young infants, primary vaccination with the combination vaccine should be started as soon as possible with the first dose given as early as 6 weeks, and two subsequent doses given in intervals of at least 4 weeks after the first dose. Quinvaxem® can be given to children who have received hepatitis B vaccine at birth. There is no evidence suggesting that the vaccine is not interchangeable with other DTP, HepB, Hib combined vaccines.

Reinforcing vaccination of toddlers (13–24 months after birth): one booster dose of 0.5 ml. Quinvaxem® booster dose can be given to toddlers initially vaccinated with DTwP – HepB – Hib. The 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, the different injections should be administered at a separate site. Vaccines should not be mixed with any other vaccine unless it is licensed for use as a combined product.

SIDE EFFECTS

The type and rate of adverse reactions of the DTwP – HepB – Hib fully liquid combination vaccine do not differ significantly from the DTwP, HepB and Hib vaccine reactions described separately. For DTwP, mild local or systemic 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 of high fever, irritability and screaming develop within 24 hours of administration. Hypotonic-hyporesponsive episodes have been reported. Febrile convulsions have been reported at a rate of one per 12500 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 DTP immunization. However, subsequent detailed reviews of all available 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 DTwP 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 transient fever 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-Barré-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. Hib 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 Hib 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. (DTwP – HepB – Hib fully liquid combination vaccine) 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 reported 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 (>1/10 000, ≤1/1000), Very rare (≤1/10 000, incl. isolated reports).

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:
Very common: Feeding disorders

NERVOUS SYSTEM DISORDERS:
Very common: Sleepiness

PSYCHIATRIC DISORDERS:
Very common: Irritability
Common: Crying
Uncommon: Persistent crying

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS:
Rare: Coughing

SKIN AND SUBCUTANEOUS TISSUE DISORDERS:
Common: Rash

Most solicited reactions showed similar frequencies after primary vaccination and after the booster dose. Higher incidence rates after the booster dose (difference vs. primary vaccination approximately more than 10%) were observed for change in eating habits and unusual crying.
The solicited systemic adverse reactions usually appeared within 48 hours after vaccination and in 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. DTwP – 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 DTwP – HepB – Hib fully liquid combination

vaccine 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 DTwP – HepB – Hib fully liquid combination vaccine. 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 DTP, 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 few contraindications to the **first** dose of DTwP – fits or abnormal cerebral signs in the newborn period or other serious neurological abnormality are contraindications to the pertussis component. In this case, the vaccines should not be given as a combination vaccine but DT should be given instead of DTwP 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. Minor illnesses such as common cold or other infections of the upper respiratory tract are not 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.

SPECIAL WARNINGS 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 reaction, following 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 recent 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 DTP vaccine, one or more of the following effects have been observed:
– 40.0 °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 during the 48 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 immunodeficiency disorder or receiving immunosuppressive therapy may have a reduced immunological response. Individuals infected with the human immuno-deficiency virus (HIV), both asymptomatic and symptomatic, should be immunized with combined vaccine according to standard schedules.
The vaccine must not be injected into a blood vessel.
Quinvaxem® (DTwP – HepB – Hib fully liquid combination vaccine) should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may

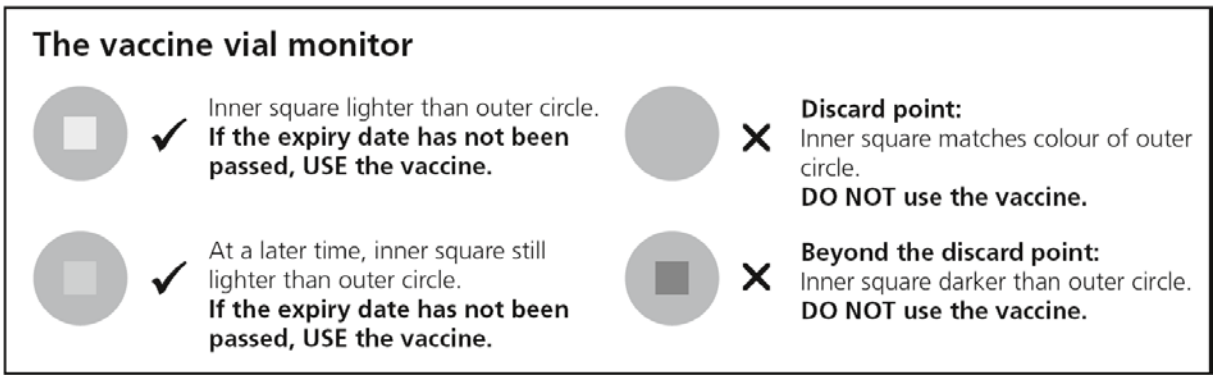
occur following an intramuscular administration to these subjects and firm pressure applied to the site (without rubbing) for at least two minutes following administration.

STORAGE

The combination vaccine must be stored and transported between +2 °C and +8 °C. **The DTwP – HepB – Hib vaccine MUST NOT BE FROZEN.**

PRESENTATION

Quinvaxem® in cPAD is supplied in a tray containing 20 single-dose injection systems



Vaccine Vial Monitors (VVMs) are part of the label on Quinvaxem® in cPAD supplied through Berna Biotech Korea Corporation; (Songdo-dong) 23, Harmony-ro 303 beon-gil, Yeonsu-gu, Incheon 406-840, Korea. The colour dot which appears on the label of the injection system is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the injection system has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level. The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the vaccine should be discarded.

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

Berna Biotech

NOVARTIS VACCINES