For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

QUINVAXEM®

Diptheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA) and *Haemophilus Influenzae* Type b Conjugate Vaccine (Adsorbed) IP

1. NAME OF THE MEDICINAL PRODUCT

Diptheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA) and *Haemophilus Influenzae* Type b Conjugate Vaccine (Adsorbed) IP.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose (0.5 ml) vial contains:

Purified Diphtheria toxoid	7.5Lf (≥30 IU)
Purified Tetanus toxoid	3.25 Lf (≥60 IU)
Inactivated B. pertussis	15 OU (≥4 IU)
Purified Hepatitis B surface antigen	10 µg
Hib oligosaccharide	10 µg, conjugated to approx. 25µg of CRM 197
Aluminium Phosphate	0.3 mg Al^{3+}
Sodium Chloride	4.5 mg
Water for Injections	Ad 0.5 mL

3. PHARMACEUTICAL FORM

Liquid suspension for intramuscular injection.

The vaccine has a milky appearance after shaking.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paediatric combination vaccine against diphtheria, tetanus, pertussis, hepatitis B and disease caused by *Haemophilus influenzae* type b.

4.2 Posology and Method of Administration

Posology

Primary vaccination of infants (first year of life): 3 doses of 0.5 mL each, at least one month apart, starting as early as 6 weeks of age.

QUINVAXEM can be given to children who have received hepatitis B vaccine at birth but should not be used for hepatitis B vaccination at birth.

Booster vaccination of toddlers (13–24 months after birth): one dose of 0.5 mL. A booster dose might be given to toddlers to reinforce the primary vaccination.

In the comparative clinical trial, one dose of *TRITANRIX HB+Hib* followed by *QUINVAXEM* as the second and third doses was non-inferior to three doses of *QUINVAXEM* alone with respect to immunogenicity. The safety profile was similar between the two groups.

Method of Administration

Intramuscular injection in the anterolateral part of the upper thigh. Alternatively, the vaccine could be administered in the deltoid region of the arm in toddlers (children 13–24 months after birth).

4.3 Contraindications

Known hypersensitivity to any component of the vaccine, or a serious reaction to a previous dose of this or a similar 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-containing vaccines – fits or abnormal cerebral signs in the newborn period or other serious neurological abnormality are contraindications to the pertussis component. Also children who have experienced encephalopathy after a previous vaccination with a pertussis-containing vaccine should not be vaccinated with *QUINVAXEM*. In these cases, 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.

4.4 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.

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.

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 in a given population, 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.

DO NOT INJECT INTRAVENOUSLY.

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. 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.

4.5 Interaction with other medicinal products and other forms of interaction

QUINVAXEM can be given safely and effectively at the same time with oral polio vaccine (OPV) and vitamin A supplementation. Clinical data showed that measles vaccine can be safely co-administered with the booster dose of *QUINVAXEM*. The co-administration of other vaccines has not been studied in clinical trials. If *QUINVAXEM* is given at the same time as other vaccines, it should be administered at a separate site.

QUINVAXEM should not be mixed in the vial or syringe with any other vaccine unless it is licensed for use as a combined product.

4.6 Pregnancy and Lactation

Not applicable as *QUINVAXEM* is administered to infants and toddlers only.

4.7 Effects on Ability to Drive and Use Machines

Not applicable as *QUINVAXEM* is administered to infants and toddlers only.

4.8 Undesirable 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 12,500 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, this has not been confirmed in follow-up studies or in subsequent investigations.

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.

Clinical trial data

In the five major clinical trials performed, 3495 doses *QUINVAXEM* were administered in 1278 healthy infants from six weeks of age. Of these, 3120 doses were administered as part of a primary vaccination regimen and 375 as a booster dose. 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 events attributable to the vaccine have been reported during the course of clinical trials.

The frequencies, based on the number of doses administered, are provided according to the following convention:

Very common	$\geq 1/10$
Common	$\geq 1/100$ and $< 1/10$
Uncommon	$\geq 1/1000$ and $< 1/100$
Rare	$\geq 1/10000$ and $< 1/1000$
Very rare	$< 1/10000$, including isolated reports

Gastrointestinal disorders:
Common: diarrhoea; vomiting

General disorders and administration site conditions:
Very common: injection site pain; injection site swelling; injection site redness; fever, crying
Common: persistent crying
Uncommon: fever ≥39.5 °C; influenza-like illness

Metabolism and nutrition disorders:
Very common: feeding disorders

Nervous system disorders:
Very common: sleepiness

Psychiatric disorders
Very common: irritability

Skin and subcutaneous tissue disorders:
Common: rash

Postmarketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience.

In the post-authorisation period rare cases of hypotonic-hyporesponsive episodes have been reported with *QUINVAXEM.* In all cases the symptoms disappeared spontaneously with no sequelae. Allergic reactions, including urticaria and rarely severe anaphylactic reactions have been reported.

4.9 Overdose

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Bacterial and viral vaccines, combined, ATC code: J07CA.

Clinical studies

Results are available from five core clinical studies,carried out to assess the immunogenicity and safety of *QUINVAXEM* in which a total of 3495 doses were administered to 1278 healthy infants and toddlers. In total, 375 out of these 1278 infants received *QUINVAXEM* as a booster dose. The immunizations were carried out according to the local immunization program schedules. Immunogenicity results showed that between 91% to 100% of children were protected against diphtheria, tetanus, pertussis and invasive illnesses caused by *H. influenzae* type b after *QUINVAXEM*, either as a three dose primary vaccination course or as booster.

More than 91% of children were protected against hepatitis B when the vaccine was administered using the most immunologically demanding vaccination schedule (6–10–14 weeks), including in children without hepatitis B vaccination at birth.

Based on a study to assess the interchangeability of *QUINVAXEM* with another pentavalent vaccine (DTwP-HepB/Hib) during the primary vaccination course, non inferiority was demonstrated for DTwP-Hep/Hib when administered interchangeably with *QUINVAXEM* compared to a full vaccination course of *QUINVAXEM.* The differences in seroprotection/serconversion between the two groups were not significant for any antigen; these data support the literature evidence that pentavalent vaccines are interchangeable in primary and/or booster vaccination.

5.2 Pharmacokinetic Properties

Not available.

5.3 Preclinical Safety Data

Not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Aluminium phosphate (adjuvant), sodium chloride, water for injections.

6.2 Incompatibilities

The vaccine must not be mixed with other medicinal products.

6.3 Shelf Life

36 months.

The expiry date of the vaccine is indicated on the label and packaging.

6.4 Special Precautions for Storage

Store at a temperature between +2°C and +8°C.

Do not freeze. Discard if vaccine has been frozen.

Keep out of reach of children

6.5 Nature and contents of container

Neutral glass vial, type I, containing 0.5 mL of vaccine (1 dose) with a rubber stopper (chlorobutyl).

Presentations: 0.5ml/vial.

6.6 Special precautions for disposal and other handling

Shake well to homogenize the liquid suspension before use. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever the solution and container permit. The vial should be inspected visually for cracks or any abnormalities, such as evidence of tampering prior to administration.

Dispose the used vial and used syringe into designated vials disposal bin and sharps disposal container, respectively.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Pharmaceuticals Limited.
Registered Office
Dr Annie Besant Road,
Worli,
Mumbai 400030, India.

8. MARKETING AUTHORISATION NUMBER(S)

Import Permission No.:

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization (Form 45):

Manufactured by:
Janssen Vaccines Corporation,
(Songdo-dong) 23,
Harmony-ro303 beon-gil,
Yeonsu-gu, Incheon,
22014 Korea.
Imported and Marketed by:
GlaxoSmithKline Pharmaceuticals Limited,
S.No.14/04, Godown No. 01 & 02,
Village Yavai, Near Water Filtration Plant,
Bhiwandi Dist. Thane 421302.
Registered Office:
Dr. Annie Besant Road, Worli, Mumbai 400 030, India.

TRITANRIX is a trademark & *QUINVAXEM* is a registered trademark.

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