

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diphtheria, Tetanus, Pertussis (Whole cell), Hepatitis B (rDNA) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed), Liquid vaccine suspension for intramuscular injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis-B (rDNA) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) is a sterile suspension for injection which contains diphtheria (D), tetanus (T) toxoids, whole cell inactivated pertussis bacteria (wP), purified major surface antigen of the hepatitis B virus (HBV), adsorbed on aluminium salts and conjugated *Haemophilus influenzae* type b polysaccharide.

The Diphtheria and Tetanus toxoids are prepared from the toxins of cultures of *Corynebacterium diphtheriae* and *Clostridium tetani* by formalin inactivation using established technology. The Pw component is obtained by heat inactivation of phase I culture of *Bordetella pertussis* bacteria.

The surface antigen of HBV (HBsAg) is produced from genetically-engineered yeast cells (*Pichia pastoris*) which carry the gene coding for the major surface antigen of the HBV. This HBsAg expressed in yeast cells is purified by several physico-chemical steps.

The capsular polysaccharide is produced from cultures of *Haemophilus influenzae* type b and purified. Purified polysaccharide (PRP) is covalently bound to tetanus toxoid (T) to produce PRP-T conjugate.

1 dose (0.5 mL) contains:

Diphtheria Toxoid	25 Lf (not less than 30 IU)
Tetanus Toxoid	5.5 Lf (not less than 60 IU*)
B. Pertussis (Whole cell)	16 IOU (not less than 4 IU**)
r-HBsAg	12.5 micrograms
Purified capsular polysaccharide of Hib (PRP) covalently linked to 20 - 36.7 micrograms of tetanus toxoid	11 micrograms
Al ⁺⁺⁺ (as AlPO ₄)	Not more than 1.25 mg
Preservative: Thiomersal BP/Ph. Eur	0.01 % w/v

* Not less than 40 IU when tested in guinea pigs and not less than 60 IU when tested in mice.

** The lower fiducial limit (p=0.95) of the estimated potency is not less than 2.0 IU.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Suspension for intramuscular injection.

The product is a whitish turbid liquid in which the mineral carriers, tends to settle down slowly on keeping and disperse uniformly upon shaking.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DTwP-rHepB-Hib liquid vaccine is indicated for active immunization against diphtheria, tetanus, pertussis, hepatitis B (HB) and *Haemophilus influenzae* type b disease in infants from 6 weeks of age.

4.2 Posology and method of administration

Posology

The primary vaccination schedule consists of three doses of 0.5 mL each given intramuscularly within the first six months of life. Three vaccine doses at 6-10-14 weeks of age must be administered at intervals of at least 4 weeks.

Where HBV vaccine is not given at birth, the combined vaccine must be administered beginning as early as 6 weeks of age. Where there is a high endemicity of HBV, the practice to administer HBV vaccine at birth may be continued.

In the case of children born to known HBV carrier mothers, the immuno-prophylactic measures for hepatitis B should not to be modified. This may require separate vaccination with HBV and DTwP vaccines and also include the administration of HBIg at birth.

Method of administration

The DTwP-rHepB-Hib liquid vaccine vial should be shaken well to get a uniform suspension. This pentavalent vaccine is for deep intramuscular injection, preferably in the anterolateral aspect of the thigh. As with all parenteral drug products, aseptic procedures should be followed during the administration of this vaccine.

Parenteral drug products should be inspected visually for extraneous particulate matter and or discoloration prior to administration whenever solution and container permit. If these conditions exist, the vaccine should not be administered.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Severe 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.

Convulsions/seizures or abnormal cerebral signs in the newborn period or other serious neurological abnormalities are contraindications to the pertussis component. In these cases, the vaccine should not be given as a combination vaccine but DT should be given instead of DTwP and Hep B and Hib vaccine 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

Vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination by a qualified physician.

If any of the following events occur in temporal relation to receipt of this vaccine, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered.

- Temperature $\geq 40^{\circ}\text{C}$ within 48 hours, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
- Persistent crying lasting ≥ 3 hours, occurring within 48 hours.
- Convulsions with or without fever, occurring within 3 days.

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

A history of febrile convulsions, a family history of convulsions, a family history of SIDS (Sudden Infant Death Syndrome) and a family history of an adverse event following DTwP-rHepB-Hib vaccination do not constitute contraindications.

HIV infection is not considered as a contraindication for diphtheria, tetanus, pertussis, Hepatitis-B and Hib vaccination. The expected immunological response may not be obtained after vaccination of immunosuppressed patients, e.g. patient on immunosuppressive therapy.

DTwP-rHepB-Hib liquid vaccine should be administered with caution to subjects with thrombocytopenia, a bleeding disorder since bleeding may occur following intramuscular administration of vaccine to these subjects.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine, 1:1000 adrenaline should be available for immediate treatment if such reaction occurs. For this reason the vaccinee should remain under medical supervision for at least 30 minutes after immunization.

As with other vaccines, the administration of DTwP-rHepB-Hib liquid vaccine should be postponed in subjects suffering from acute severe febrile illness. The presence of minor infection, however, is not a contraindication for vaccination.

DTwP-rHepB-Hib liquid vaccine should under no circumstances be administered intravenously.

The vaccine is NOT to be used for the treatment of Diphtheria, Tetanus, Pertussis, Hepatitis-B or *Haemophilus influenzae* type b infection.

4.5 Interaction with other medicinal products and other forms of interaction

As with other intramuscular injections, use with caution in patients on anticoagulant therapy.

Immunosuppressive therapies, including irradiations, anti-metabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiological doses), may reduce the immune response to vaccines. Short-term (< 2 weeks) corticosteroids therapy or intra-articular, bursa, or tendon injections with corticosteroids would not be immunosuppressive. (See section 4.4)

4.6 Fertility, pregnancy and lactation

Not applicable.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Summary of the safety profile

The type and rate of severe adverse reactions do not differ significantly from the DTwP, rHepB and Hib vaccine reactions described separately.

In an earlier phase 3 clinical trial, 35% of the subjects reported at least one adverse event, out of which commonly reported local adverse events were pain (13%) and swelling (4%) and systemic adverse event was fever (28%).

Description of selected adverse reactions

For this vaccine, mild local or systemic reactions are common. Some temporary swelling, tenderness and redness at the site of injection together with fever may occur in a small number of cases. With similar pentavalent vaccines occasional severe reactions of high fever, irritability and screaming may 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 acetaminophen at the time and 4-8 hours after vaccination decreases the subsequent incidence of febrile reactions.

Paediatric population

The national childhood encephalopathy study in the United Kingdom showed a small increased risk of acute encephalopathy (primary seizures) following DTwP 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 association 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.

4.9 Overdose

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bacterial and viral vaccines, combined, ATC code: J07CA11

In a phase-III clinical trial involving 6-8 week old healthy infants the combined liquid pentavalent DTwP-rHepB-Hib vaccine manufactured by Biological E. Limited has demonstrated a comparable safety and immunogenicity in comparison with a licensed, WHO prequalified vaccine marketed in India. The primary immunogenicity analysis showed seroprotection rates of 98.25%, 100%, 96.49%, 94.74% and 89.47% against Diphtheria, Tetanus, Pertussis, Hepatitis-B and *Haemophilus influenzae* type b antigen components respectively.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Al⁺⁺⁺ (as AlPO₄) (Adjuvant)
Thiomersal BP/Ph. Eur (Preservative)
Sodium Chloride (Isotonic agent)
Sodium Hydroxide (For pH adjustment)
Hydrochloric Acid (For pH adjustment)
Water for Injection (q.s.)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

30 months from the date of manufacture.

6.4 Special precautions for storage

DTwP-rHepB-Hib Vaccine should be stored between 2°C - 8°C throughout their use.

Do not freeze. Discard if the vaccine has been frozen.

Once opened, multi dose vials of Liquid Pentavalent Vaccine from which one or more doses of vaccine have been removed during an immunization session may be used in subsequent immunization sessions for up to a maximum of 4 weeks, provided that all of the following conditions are met:

1. The expiry date has not passed.
2. The vaccines are stored under appropriate cold chain conditions.
3. The vaccine vial septum has not been submerged in water.
4. Aseptic technique has been used to withdraw all doses.
5. The vaccine vial monitor (VVM) has not reached the discard point.

6.5 Nature and contents of container





DTwP-rHepB-Hib vaccine is filled in USP type I glass vials stoppered with bromobutyl rubber stoppers and sealed using Aluminium flip-off seals.

- 0.5 mL of suspension in a vial containing single dose
- 1 mL of suspension in a vial containing two doses
- 2.5 mL of suspension in a vial containing five doses
- 5 mL of suspension in a vial containing ten doses

6.6 Special precautions for disposal and other handling

DTwP-rHepB-Hib liquid vaccine is available as a suspension. Upon storage, a white deposit and clear supernatant may be observed. The vaccine should be shaken well in order to obtain a homogenous turbid white suspension and visually inspected for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either of the above being observed, discard the vaccine.

Presentation available with or without vaccine vial monitor.

The vaccine vial monitor...(Optional)	
 ✓	<p>-----</p> <p>Inner square lighter than outer circle. If the expiry date has not been passed, USE the vaccine.</p>
 ✓	<p>At a later time, inner square still lighter than outer circle. If the expiry date has not been passed, USE the vaccine.</p>
 ✗	<p>Discard point, Inner square matches colour of outer circle. DO NOT use the vaccine.</p>
 ✗	<p>Beyond the discard point: Inner square darker than outer ring. DO NOT use the vaccine.</p>

Vaccine Vial Monitor (VVM) is part of the label. The colour dot that appears on the label of the vial, is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial 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 vial should be discarded.

Any unused medicinal product or waste material should be discarded as Biomedical waste.

7. MARKETING AUTHORISATION HOLDER

Marketing authorization holder in India:

Biological E. Limited – 18/1 & 3, Azamabad, Hyderabad, Telangana - 500 020, INDIA

Marketing authorization holder in Thailand:

Biogenetech Co., Ltd. – 18 Soi Udomsuk 37, Sukhumvit 103 Rd., Bangjak, Prakanong, Bangkok 10260, Thailand. Tel. 02-748-9333 Fax. 02-748-9393

Manufacturer:

Biological E. Limited. – Plot No. 1, S.P. Biotechnology Park, Phase-II, Kolthur Village, Shameerpet Mandal, Ranga Reddy District – 500 078, Telangana, INDIA

8. MARKETING AUTHORISATION NUMBER(S)

2C 15082/61 (NBC)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 December 2018

10. DATE OF REVISION OF THE TEXT

2019