Summary of Product Characteristics (SPC)

Drug Substance: DTwP-rHepB-Hib Vaccine (Adsorbed)
(Liquid Pentavalent Vaccine)

Trade Name : ComBE Five® (Liquid)

BIOLOGICAL E. LIMITED
18/1&3, AZAMABAD
HYDERABAD – 500020, A.P., INDIA.

1. NAME OF THE MEDICINAL PRODUCT

Name of Medicinal Product:	DTwP-rHepB-Hib Vaccine (Adsorbed)
Trade Name:	ComBE Five® (Liquid) Injection for IM use
Presentation:	Single dose vial of 0.5 ml Two dose vial of 1 ml Five dose vial of 2.5 ml Ten dose vial of 5 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ComBE Five® (Liquid) injection (combined penatavalent DTwP-rHepB-Hib vaccine) is a ready-to-use, fully liquid combined vaccine containing diphtheria and tetanus toxoids, whole cell Bordetella pertussis inactivated suspension, hepatitis B surface antigen (HBsAg), and Haemophilus influenza type b PRP-T conjugate.

The diphtheria and tetanus toxoids are obtained from Corynebacterium diphtheriae and Clostridium tetani cultures, respectively, by formaldehyde inactivation and purification. The pertussis suspension component is obtained from B. pertussis cultures after inactivation and purification.

The hepatitis B surface antigen is produced in genetically engineered unicellular methylotropic yeast cells (Pichia pastoris) carrying the relevant gene of the HBsAg.

The polyribosyl ribitol phosphate (PRP) component of Haemophilus Influenzae type B, is made of purified capsular polysaccharide conjugated to tetanus toxoid as protein carrier.

2.1 Liquid Pentavalent DTwP-rHepB-Hib Vaccine (Adsorbed)

Each dose of 0.5ml contains:

Diphtheria toxoid	25 Lf (≥ 30 IU)
Tetanus toxoid	5.5 Lf (≥ 60 IU)
B. Pertussis (whole cell)	16 IOU (≥ 4 IU)
r-HBsAg	12.5 µg
Purified capsular polysaccharide (PRP) Tetanus toxoid (carrier protein) 20 to 36.7 µg of tetanus formal toxoid	11 µg
Al^{+++} (as AlPO4)	≤ 1.25 mg
Preservative: Thiomersal	0.01% w/v

Note: The label claim is as recommended by WHO

3. PHARMACEUTICAL FORM

DTwP-rHepB-Hib – Vaccine suspension for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

ComBE Five® (Liquid) vaccine is indicated for active primary immunization against diphtheria, tetanus, pertussis, haemophilus influenzae type b and hepatitis B diseases in infants from 6 weeks of age.

In a phase-III clinical trial involving healthy 6-8 week old infants the combined liquid pentavalent DTwP-rHepB-Hib vaccine manufactured by Biological E. Limited has demonstrated a comparable safety and immunogenicity 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.

4.2 Posology and method of administration:

The recommended dose (0.5 ml) of the vaccine must be administered deep intramuscularly in anterolateral aspect of thigh for infants 6-8 weeks of age at the 1st vaccination. An injection into a child's buttocks may cause injury to the sciatic nerve and is not recommended. A total of 3 doses at predefined interval of 4 weeks between each dose viz., 6, 10 and 14 weeks (EPI schedule of $1^{1/2}$, $2^{1/2}$ and $3^{1/2}$ months) respectively must be administered.

The vaccine should be inspected visually for any foreign particulate matter prior to use. In the event of it being observed, discard the vaccine.

The vaccine should be administered immediately or within 6 hours. The vaccine should not be mixed with any other vaccines in the same vial or syringe unless it is manufactured as combined product.

EPI recommendation in young children is to administer as many antigens as possible at a single visit. This vaccine can be given safely and effectively at the same time as BCG, measles and polio vaccines (OPV and IPV), however no separate studies were available in support of the same.

A booster dose of DTP and Hib can be given at the age of 15-18 months. A reinforcing injection of DTP should be administered at 5 years of age (i.e. at the time of school entry). Indian Academy of Pediatrics (IAP) recommends that wherever combination vaccines are available, they can be used as substitute for monovalent formulations in the national immunization schedule wherever indicated. The whole cell pertussis containing vaccines are not recommended for use in adolescents and adults.

4.3 Contraindications:

ComBE Five® (Liquid) should not be administered to infants/children with known hypersensitivity to any component of the vaccine, or to infants/children having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, Hepatitis-B and HIB containing vaccines.

As with other vaccines, ComBE Five® (Liquid) administration should be postponed in infants/children suffering from acute illness and acute severe febrile illness until recovery.

ComBE Five® (Liquid) is contra-indicated if the child has experienced convulsions / seizures, encephalopathy or abnormal cerebral signs in the newborn or other serious neurological abnormalities of unknown aetiology following previous vaccination with pertussis containing vaccine. In these situations the vaccination course should be continued separately with DT, HB and Hib vaccines.

4.4 Special Warnings and Precautions for use:

Warnings: Vaccination should be preceded by a review of the medical history with regard to previous vaccination and possible occurrence of undesirable events and a clinical examination. If any of the following events occur in temporal relation to receipt of DTP or its combinations, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered. There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks, particularly since these events are not associated with permanent sequelae.

- Temperature 104 °F (≥40°C) or more within 48 hours of a dose unexplained by another cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
- Persistent, inconsolable crying lasting 3 hours or more occurring within 48 hours.
- Convulsions with or without fever occurring within three days.

DTP should not be given to children with any coagulation disorder, including thrombocytopenia that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.

A history of febrile convulsions, a family history of convulsions, 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 haemophilus type B vaccinations. The expected immunological response may not be obtained after vaccination of immunosuppressed patients, e.g. patients on immunosuppressive therapy.

ComBE Five® (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.

Recent studies suggest that infants and children with a history of convulsions in first-degree family members (i.e. siblings and parents) have a 3:2 fold increased risk for neurologic events compared to DTP vaccine and permanent neurologic damage.

Infants and children with recognized possible or potential underlying neurologic conditions seem to be at enhanced risk for the appearance of manifestation of the underlying neurologic disorder within two or three days following vaccination.

The administration of DTP to children with proven or suspected underlying neurologic disorders that are not actively evolving must be decided on an individual basis.

Special care should be taken to prevent administration of vaccine into blood vessel.

Precautions:

Prior to administration of the vaccine, health care personnel should inform the vaccinee or guardian of the vaccinee about the benefits and risks of immunization. Health care professional must be aware of all known precautions and same should be taken to prevent adverse reactions. This includes a review of the parent's history with respect to possible sensitivity and any previous adverse reactions to the vaccine or similar vaccines. Previous history of immunization, current health status of the vaccinee and current knowledge of the literature concerning the use of the vaccine to be administered should be considered. Immunosuppressed patients may not respond.

Parents of a child with a family history of seizures should be informed that their child has an increased risk of seizures following DTwP administration and should be instructed regarding appropriate medical care in the unlikely event of a seizure.

In case of an acute anaphylactic reaction that might be due to any of the components of vaccine, Injection Adrenaline (1:1000) must be readily available to be injected.

For treatment of severe anaphylaxis the initial dose of adrenaline is 0.1-0.5 mg (0.1- 0.5ml of 1:1000 injection) given subcutaneously (SC) or Intramuscularly (IM). Single dose should not exceed 1 mg (1ml). For infants and children the recommended dose of adrenaline is 0.01mg/kg (0.01ml/kg of 1:1000 injection).

Single pediatric dose should not exceed 0.5mg (0.5ml). The mainstay in the treatment of severe anaphylaxis is the prompt use of adrenaline, which can be lifesaving.

The vaccinee should remain under observation for not less than 30 minutes post vaccination for possibility of occurrence of immediate or early allergic reactions. Hydrocortisone and antihistamines should also be available in addition to supportive measures such as oxygen inhalation.

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 irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses) may reduce the immune response to vaccines. Short-term (< 2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive.

4.6 Pregnancy and Lactation:

Not applicable as ComBE Five® (Liquid) inj. (Liquid Pentavalent DTwP-rHepB-Hib vaccine) is a paediatric vaccine.

4.7 Effects on ability to drive and use machines:

Not relevant.

4.8 Undesirable Effects:

In a phase-III pentavalent DTwP-rHepB-HIB vaccine study, the total number of infants with atleast one adverse event were 35.0%. The type and rate of severe adverse reactions do not differ significantly from the DTwP, rHepB and Hib vaccine reactions described separately. These reactions are generally mild and transient.

Few mild to moderate local reactions like injection site pain, swelling, and redness and mild to moderate systemic reactions like fever, feeding problem, unusual crying and irritability are commonly reported. Some temporary swelling, redness and tenderness at the site of injection together with fever occur in some proportion of cases. Occasionally, severe reactions of high fever, irritability and unusual crying develop within 24 hours of administration of vaccine. Instances of feeding and sleep disturbances were also reported in small proportion of children. All these adverse reactions may occur within one week of vaccination. In most cases, they spontaneously resolve within two to three days and further medical attention is usually not required.

Though hypotonic hypo responsive episodes have not occurred with this vaccine, they were reported with other similar DTP containing vaccines. Reports of severe anaphylaxis or anaphylactic shock were also recorded with DTP containing vaccines but are very rare. Rare instances of febrile convulsions were also reported in susceptible individuals. 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. If an association of DTP and chronic encephalopathy exists, the risk is primarily in the first 3 days after DTP vaccination.

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 pediatric associations of Australia, Canada, the United Kingdom and 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 concluding scientific evidence that these reactions have any permanent consequences for the children. Current data available globally was found to be insufficient to determine whether DTP containing vaccines increase the overall risk for chronic nervous system dysfunction in children.

Global Advisory Committee on Vaccine Safety (GACVS) considered the possible association between hepatitis B vaccination and chronic fatigue syndrome and concluded that, based on the evidence available, there are no grounds to support the association.

Available published 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmaco-therapeutic group: Bacterial and viral vaccines combined, ATC code J07CA11.

This liquid pentavalent DTwP-rHepB-HIB vaccine is a paediatric vaccine for intramuscular administration in infants ≥6 weeks of age. The pharmacodynamics of any preventive vaccine is usually gauged by its immunogenicity (appearance and increase of antibody titers). Immune mechanisms conferring protection following receipt of any pentavalent vaccine are not fully understood, though it is well-established that all the five antigenic components of this vaccine provide clinical protection against all five diseases in vaccines.

5.1.1 Site and Mechanism of Action

Evaluation of pharmacokinetic properties is not required for vaccines

5.1.2 Clinical Trials

In a phase-III non inferiority study, a 0.5mL dose of liquid pentavalent DTwP-rHepB-HIB vaccine was administered intramuscularly to infants between 6-8 weeks of age as per 6-10-14 week 3-dose EPI schedule. Immunogenicity was documented one month after the primary vaccination series. A total of 98.25%, 100%, 96.49%, 94.74% and 89.47% of infants were seroprotected with anti-Diphtheria, anti-Tetanus, anti-Pertussis, anti-HBs and anti-PRP-T antibody titres respectively. A total of 35% of infants reported atleast one adverse event out of which 21.67% were medically attended, all of which were non-serious and mild to moderate in their intensity.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines

6. Pharmaceutical Particulars:

List of Excipients:

Aluminium Phosphate ($ALPO_4$)

Thiomersal (Preservative)

6.2 Incompatibilities

In the absence of specific compatibility studies, the DTwP-rHepB-Hib vaccine [ComBE Five® (Liquid)] should not be mixed with other vaccines in the same syringe.

6.3 Shelf Life:

Two years (24 Months).

6.4 Special precaution for storage:

Both single and multi-dose ComBE Five® (Liquid) vials should be stored between +2°C to +8°C throughout their use.

- Do not freeze.
- Do not use the vaccine if frozen.
- Keep out of reach of children.

6.5 Nature and contents of the container

Single dose vial of 0.5 mL

Two dose vial of 1 mL

Five doses vial of 2.5 mL

Ten doses vial of 5 mL

7. MARKETING AUTHORISATION HOLDER

Biological E. Limited
18/1&3, Azamabad,
Hyderabad – 500020 A.P., INDIA.

8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

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10. DATE OF REVISION OF THE TEXT
