طبقا للنشره المنشوره بموقع WHO فى ٢٦/ ١٢/ ٢٠١٧ وطبقا لموافقات الشبات بتاريخ ١٧/ ٣/ ٢٠١٥

٢٨/ ٤/ ٢٠١٥ و ١٤/ ١١/ ٢٠١٧ و ١٥/ ١٢/ ٢٠١٧ د/ فاطمة محمد محمود

Diphtheria, Tetanus, Pertussis (Whole cell), Hepatitis-B (r-DNA) and Haemophilus Type b Conjugate Vaccine (Adsorbed)

Liquid Pentavalent Combination Vaccine

ComBE Five®

(Liquid)

وزارة الصحة والسكان
الادارة المركزية للشئون الصيدلية
ادارة التسجيل والمستحضرات الحيوية
نشرة معتمده تاريخ ٢٦/ ١٢/ ٢٠١٧ د/ فاطمة محمد محمود

1. Description:

Diphtheria, Tetanus, Pertussis, Hepatitis-B (r-DNA) and Haemophilus 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. It is a whitish turbid liquid wherein the mineral carriers, upon keeping, may settle down to deposit at bottom and disperse uniformly upon shaking. The vaccine meets WHO requirements.

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 the 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.

2. Composition

Each dose of 0.5 mL 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) of Hib covalently linked to 20 to 36.7 µg of tetanus toxoid	11 µg
Al*** (as $AlPO_4$)	≤ 1.25 mg
Thiomersal	0.01% w/v

* ≥40 IU when tested in guinea pigs and ≥60 IU when tested in mice

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

3. Pharmaceutical Form:

DTwP-rHepB-Hib liquid vaccine suspension for injection.

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.

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.

4.2 Posology and method of administration:

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.

8. Presentation

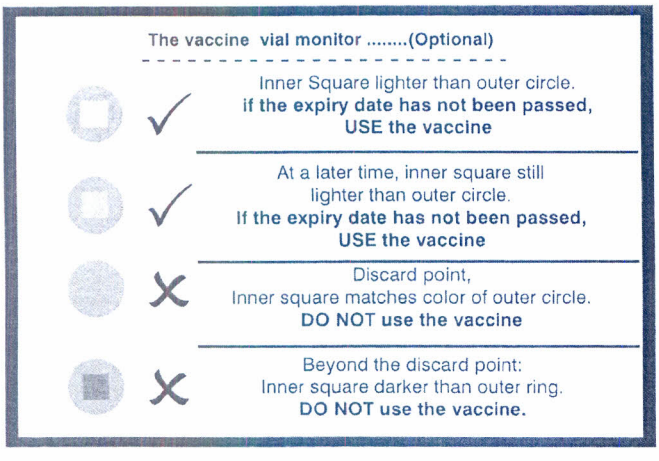
DTwP-rHepB-Hib liquid vaccine is available 0.5 ml single dose vial

DTwP-rHepB-Hib liquid vaccine is avalilable 1 ml two dose vial

DTwP-rHepB-Hib liquid vaccine is avalilable 2.5 ml five dose vial

DTwP-rHepB-Hib liquid vaccine is available 5 ml ten doses vial

Presentation available with or without vaccine vial monitor.



Vaccine Vial Monitor (VVMs) is part of the label. The colour dot 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.

For use only by a Registered Medical Practitioner or a Hospital or a Laboratory.

References

1. WHO model pack insert
2. Data on Biological E Limited's file

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

Manufactured by :

Biological E. Limited

Corporate Address:18/1 & 3, Azamabad, Hyderabad-500 020, Andhra Pradesh, INDIA.

Web: www.biologicale.com

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 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 Contraindication:

Known hypersensitivity to any components of the vaccine, or a 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. There are few contraindications to the first dose of DTwP Vaccine. Conditions like 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 of ≥ 40°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, eg. patients on immunosuppressive therapy.

As with all injectable vaccines, appropriate medical treatment should always be readily available in case of anaphylactic reactions following the administration of the vaccine. For this reason the vaccinees should remain under medical supervision for atleast 30 minutes after vaccination.

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 atleast 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.

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

4.5 Interactions 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 physiologic doses), may reduce the immune response to vaccines. Short-term (<2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids would not be immunosuppressive.

4.6 Pregnancy and lactation

Not applicable

4.7 Undesirable effects1 :

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 atleast one adverse event, out of which commonly reported local adverse events were pain (13%) and swelling (4%) and systemic adverse event was fever (28%).

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 12500 doses administered. Administration of acetaminophen 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.

5. Shelf life

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

6. Storage

Multi-Dose vials: use within 28 days after first opening.

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

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

7. Instruction for use/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 homogeneous 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.