1. NAME OF THE MEDICINAL PRODUCT

Diphtheria, Tetanus, Pertussis (Whole Cell) and Haemophilus Type b Conjugate Vaccine (Adsorbed) I.P.

Injectable, Suspension for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Diphtheria, Tetanus, Pertussis is a homogenous liquid containing purified diphtheria and tetanus toxoids, inactivated whooping cough (pertussis) organisms while Hib is bacterial subunit vaccine available in lyophilized form (freeze dried powder). It contains highly purified, non-infectious Haemophilus Influenzae type b (Hib) capsular polysaccharide chemically conjugated to a protein (Tetanus toxoid). The vaccine meets the requirements of WHO and BP when tested by the methods outlined in WHO, TRS (1990), 800, 897 (2000) and BP. The Hib polysachharide is prepared from capsular polysaccharide of H. Influenzae type B strain and after activation is coupled to Tetanus Toxoid.

On reconstitution, each dose of 0.5 ml contains:

Diphtheria Toxoid	≤ 25 Lf (≥ 30 IU)
Tetanus Toxoid	≥ 5 Lf (≥ 40 IU)
B. pertussis (whole cell)	≤ 16 OU (≥ 4 IU)
Purified Capsular Hib Polysaccharide (PRP)	10 mcg
Tetanus Toxoid (carrier protein)	19 to 33 mcg
Adsorbed on aluminium phosphate, Al^{+++}	≤ 1.25 mg
Preservative: Thiomersal	0.005%

For a full list of excipients, see section 6.1.

DTP+Hib lyophilized vaccine does not protect against disease due to other types of *H.influenzae* nor against meningitis caused by other organisms.

3. PHARMACEUTICAL FORM

Diphtheria, Tetanus, Pertussis is a homogenous liquid containing purified diphtheria and tetanus toxoids, inactivated whooping cough (pertussis) organisms and Haemophilus influenzae type b conjugate vaccine is available in lyophilized form.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DTP+Hib lyophilized vaccine is indicated for the active immunization of infants, at or above the age of 6 weeks against Diphtheria, tetanus, whooping cough and Haemophilus Influenzae type b infections.

In young children, the EPI recommends as many antigens as possible to be administered at a single visit.

The combined vaccine can be given safely and effectively at the same time as BCG, Measles and Polio vaccines (OPV and IPV), Yellow Fever vaccines and Vitamin A supplementation

4.2 Posology and method of administration

Posology:

For active immunization of infants and preschool children, it is recommended that three intramuscular injection of 0.5ml be administered with an interval of four weeks between doses starting at six weeks of age.

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). IAP (Indian Academy of Pediatrics) recommends that wherever combination vaccines are available they can be substituted for monovalent formulations in the national immunization schedule wherever indicated.

Administration:

Do not inject subcutaneously or intravenously

For a single dose presentation:

The vaccine is administered after Hib powder contained in the vial is reconstituted with one ampoule (0.5 ml) of DTP suspension. Shake until the powder has completely dissolved with ought producing too much foam. The whitish cloudy appearance after the reconstitution is normal.

For a multidose presentation:

Since the DTP vaccine is adsorbed, it is necessary to shake the vial gently to avoid foam formation, but sufficiently to ensure that the product is mixed homogeneously.

Reconstitute the vial of Hib vaccine (2, 5 and 10 doses) powder with the suspension contained in the ampoule/vial of DTP (1, 2.5 and 5ml) using a sterile syringe fitted with a sterile needle. The whitish cloudy appearance of the suspension after reconstitution is normal. This preparation is equivalent to 2, 5 and 10 doses.

Successful reconstitution and extraction of one or more doses of vaccine from a multidose vial essentially depends on the quality of the operation. The user must, using a sterile 1ml or 0.5ml syringe with a sterile needle extract, one dose (0.5 ml) from the multidose vial, on which the outer surface of the stopper has been disinfected with a disinfectant.

For each new dose extract 0.5 ml using a new sterile syringe fitted with a sterile needle. Between the different extractions the vial should be placed in a refrigerator to keep the product at its normal storage temperature i..e between +2ºC to +8ºC

The vaccine vial should be well shaken to get an opaque suspension. The vaccine should be administered by intramuscular injection. The anterolateral aspect of the thigh is the preferred injection site for infants and deltoid for children.

Another injection if co-administered with DTP+Hib vaccine should be made at a different site. Only sterile needles and syringes should be used for each injection.

The vaccine should be inspected visually for any foreign particulate matter and / or variation of physical aspects prior to administration. In the event of either being observed, discard the vaccine.

Once opened, multi-dose vials should be kept between +2º C and +8 º C. Multi-dose vials of DTP+Hib from which one or more doses of vaccine have been removed during an immunisation session may be used in subsequent immunisation sessions for upto a maximum of 6 hours, provided that all of the following conditions are met.

- The expiry date has not passed.
- The vaccines are stored under appropriate cold chain conditions;
- The vaccine vial septum has not been submerged in water;
- Aseptic technique has been used to withdraw all doses;

4.3 Contraindications

Hypersensitivity to any component of the vaccine.

It is a contraindication to use this or any other related vaccine after an immediate anaphylactic reaction associated with a previous dose.

It is a contraindication to administer the vaccine in the presence of any evolving neurological condition. Encephalopathy after a previous dose is a contraindication to further use.

Immunization should be deferred during the cause of an acute illness. Vaccination of infants and children with severe, febrile illness should generally be deferred until recovery. However, the presence of minor illnesses such as mild upper respiratory infections with or without low-grade fever is not contraindications to further use. Elective immunization procedures should be deferred during an outbreak of poliomyelitis.

4.4 Special warnings and precautions for use

Warnings:

If any of the following events occur in temporal relation to receipt of DTP, 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 40.5°C (105°F) or more within 48 hours of a dose unexplained by another cause.
- Collapse or shock-like state (hypotonic-hypo responsive 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.

Persons who experience Arthus-type hypersensitivity reactions or a temperature of 39.4°C (> 103 °F) following a prior dose of tetanus toxoid usually have high serum tetanus antitoxin levels and should not be given even emergency doses of TT more frequently than every 10 years even if they have a wound that is neither clean not minor.

DTP+Hib vaccine 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.

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 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+Hib vaccine to children with proven or suspected underlying neurologic disorders that are not actively evolving must be decided on an individual basis.

In the event of edematous reactions of the lower limbs occurring following an injection of a vaccine containing the Haemophilus influenzae type b component, the DTP and Hib vaccine should be administered at two separate injection sites on two different days

Precautions:

Prior to an injection of any vaccine, all known precautions 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 immunization history, current health status and a current knowledge of the literature concerning the use of the vaccine under consideration. Immuno-suppressed patients may not respond.

Prior to administration of DTP+Hib vaccine, health care personnel should inform the guardian of the child the benefits and risks of immunization and also inquire about the recent health status of the child to be injected. Parents of a child with a family history of seizures should be informed that their child has an increased risk of seizures following DTP administration and should be instructed regarding appropriate medical care in the unlikely event of a seizure. Special care should be taken to ensure that the injection does not enter a blood vessel.

ADRENALINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF THE VACCINE. For treatment of severe anaphylaxis, the initial dose of adrenaline is 0.1-0.5 mg (0.1-0.5 ml of 1:1000 injection) given s/c or i/m. Single dose should not exceed 1 mg (1 ml). For infants and children, the recommended dose of adrenaline is 0.01 mg/kg (0.01 ml/kg of 1:1000 injection). Single pediatric dose should not exceed 0.5 mg (0.5 ml). The mainstay in the treatment of severe anaphylaxis is the prompt use of adrenaline, which can be lifesaving.

As with the use of all vaccines, the vaccinee should remain under observation for not less than 30 minutes for possibility of occurrence of immediate or early allergic reactions. Hydrocortisone and anti-histaminics should also be available in addition to supportive measures such as oxygen inhalation.

IMMUNE DEFICIENCY

Individuals infected with human immuno-deficiency virus (HIV), both asymptomatic and symptomatic, should be immunized with combined vaccine according to standard schedules.

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

As a general rule, during pregnancy and breast feeding, it is recommended to always see your doctor for advice before taking medicinal product.

4.7 Effects on the ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Adverse reactions associated with the use of this vaccine include local redness, warmth, oedema, and induration with or without tenderness, as well as urticaria and rash. Systemic reactions such as fever, headache, nausea and weakness may appear in a few infants. Some data suggests that febrile reactions are more likely to occur in those who have experienced such responses after prior doses.

The type and rate of severe adverse reactions do not differ significantly from the DTP and Hib vaccine reactions describe separately.

For DTP, mild, local reactions are common. Some temporary swelling, tenderness and redness at the site of injection together with fever occur in large proportion of cases. Occasionally severe reactions of high fever, irritability and screaming develop within 24 hours of administration. Hypotonic-hypo responsive episodes have been reported. Febrile convulsions have been reported at a rate of one per 12500 doses administered. Administration of paracetamol at any time and 4-8 hours after immunization decreases the subsequent incidents of febrile reactions. The national childhood encephalopathy study in the United Kingdom showed a small increases 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 of Immunization Practices, and the pediatric association of Australia, Canada the United Kingdom, and the United States concluded that the data did not demonstrate the causal relationship between DTP and chronic nervous system dysfunction in children. Thus there is no scientific evidence that hypotonic-hypo responsive episode and febrile convulsions have any permanent consequences for the children.

Hib vaccine is also 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 resolved with 2 to 3 days and further medical attention is not required. Mild systematic 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.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines,

Hemophilus influenzae B, Combinations with pertussis and toxoids, ATC code J07AG52.

Immunological Data:

Various clinical trials performed to assess Immunogenicity and reactogenicity of the vaccine proved that the vaccine is immunogenic.

In a phase III multicentric study in India, the DTP+Hib (lyophilised) vaccine was administered in 156 children at 6, 10 and 14 weeks. Following vaccination, the seroprotection was 100% for diphtheria, tetanus, and Haemophilus influenzae B, and seropositivity was 96.79% for pertussis.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

The DTP+Hib vaccine of SIIL has been adequately tested in toxicology studies. The safety of the study vaccine was clearly proven. No mortality or abnormal clinical signs were seen in any group. No significant laboratory findings or gross pathological changes were observed with study vaccine in comparison with reference vaccine. Local reactions were the only findings and were similar to reference vaccine. In general, the test vaccine demonstrated similar safety profile as the licensed reference vaccine in all four studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

DTP

Aluminium Phosphate (Prepared from Aluminium chloride + Tri-sodium phosphate)

Thiomersal

Sodium chloride

Sodium Acetate

Water for Injection

Hib

TRIS (6%)

Sucrose (17.1%)

Water for Injection

6.2 Incompatibilities

This product must not be mixed with other medicinal products.

6.3 Shelf-life

Do not exceed the expiry date stated on the external packing.

6.4 Special precautions for storage

The components of the combination vaccine must be stored and transported between 2ºC to 8ºC. The DTP component must not be frozen.

6.5 Nature and contents of container

Single dose presentation : 1 dose (ampoule of 0.5 ml containing DTP liquid vaccine + vial containing lyophilized Hib vaccine)

Multi-dose presentation :

2 dose (vial of 1 ml containing DTP liquid vaccine + vial containing lyophilized Hib vaccine)

5 dose (vial of 2.5 ml containing DTP liquid vaccine + vial containing lyophilized Hib vaccine)

10 dose (vial of 5 ml containing DTP liquid vaccine + vial containing lyophilized Hib vaccine)

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER / PREQUALIFICATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

Permission No. - MF-7929/07 (Form 46).

Manufacturing License No. 10 in Form 28-D

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorization: 04.10.2007

Date: 31 December 2022