Size : 95 x 300 mm

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

Rx

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

Easyfive-TT®

Fully Liquid Pentavalent Vaccine

NAME OF THE MEDICINAL PRODUCT

Trade/ Brand Name: Easyfive-TT® (Fully Liquid Pentavalent Vaccine)
Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) IP

QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose of 0.5 ml contains:

Diphtheria Toxoid*	20 Lf (30 IU)
Tetanus Toxoid*	7.5 Lf (60 IU)
Inactivated w-*B. pertussis**	12 OU (4 IU)
HBsAg	10 mcg
H. influenzae type b (PRP) conjugated to Tetanus Toxoid	10 mcg
Aluminium content (Al^{3+}) (As Aluminium Phosphate Gel)	0.25 mg
Thiomersal	0.025 mg
Physiological saline	q.s.

*Bulk source : PT. BioFarma, Indonesia

DOSAGE FORM AND STRENGTH

Liquid suspension for injection.
Single Pediatric dose vial containing 0.5 ml vaccine
Multidose vial containing 5 ml (10 Pediatric doses) vaccine
Single dose pre-filled syringe containing 0.5 ml vaccine .

CLINICAL PARTICULARS

Therapeutic indication

For active immunization of infants against Diphtheria, Tetanus, Pertussis (Whooping Cough), Hepatitis B & infections caused by *Haemophilus influenzae* (Type b).

Posology

Primary immunization
Easyfive-TT® is indicated for active immunization of infants, the primary vaccination schedule consists of three doses of 0.5ml each administered with an interval of four weeks between doses, starting at 6 weeks of age. The customary age for the first dose of primary immunization is recommended to be 6 weeks of age.
Specifically, WHO recommends 6, 10, and 14 weeks primary series schedule for Diphtheria, Tetanus, Whole-cell pertussis (DTwP), Hepatitis B (Hep B) and *Haemophilus influenza* type b conjugate (Hib)
The interval can vary from 4-to 8 weeks.
A booster dose of DTwP is recommended at the age of 12-23 months.

Booster immunization

The booster dose of Hep B and Hib can be given ⩾ 6 months after the last primary dose.
Accordingly booster dose of Easyfive-TT® Vaccine can be administered at 12-15 months.

Method of administration

The liquid vaccine vial should be shaken before use to homogenize the suspension. The vaccine should be injected intramuscularly. The anterolateral aspect of the upper thigh is the preferred site of injection, or into the deltoid muscles of older children. An injection into a child's buttocks may cause injury to the sciatic nerve and is not recommended. It must not be injected into the skin as this may give rise to a local reaction. One pediatric dose is 0.5 ml. A sterile syringe and sterile needle must be used for each injection.

Contraindications

Known hypersensitivity to any component 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, fits or abnormal cerebral signs or other serious neurological abnormalities are contraindications to the pertussis component. In this case, the vaccines should not be given as a combination vaccine but DT should be given instead of DTwP and HepB and Hib vaccines given separately. The vaccine will not harm individuals currently or previously infected with the hepatitis B virus.

Immune deficiency

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

Special warnings and precautions for use

The administration of Easyfive- TT® should be postponed in subjects suffering from acute severe febrile illness.
If any of the following events occur in relation to the administration of Easyfive- TT® the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered:

- The temperature of >40.0 °C within 48 hours, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hypo responsive episode) within 48 hours.
- Persistent crying lasting >3 hours, occurring within 48 hours.
- Convulsions with or without fever, occur within 3 days.

Easyfive- TT® should be administered with caution to subjects with a bleeding disorder.
Medical treatment should always be available in case of anaphylactic reactions. The patient should remain under medical supervision for 30 minutes after vaccination. Easyfive- TT® should under no circumstances be administered intravenously or subcutaneously.

IMMUNIZATION SCHEDULE

Easyfive- TT® vaccine should NOT be used for the birth dose.
In countries where pertussis is of particular danger to young infants, the combination vaccine should be started as soon as possible with the first dose given as early as 6 weeks, and two subsequent doses given at 4-week intervals.

Drugs Interactions

Co-administration with other vaccines

Co-administration of Easyfive- TT® with other vaccine is not recommended

Use in special populations (such as pregnant women, lactating women, pediatric patients, geriatric patients, etc.)

Pregnancy and Lactation

As Easyfive-TT® Vaccine is not intended for use in adults, information on the safety of the vaccine when used during pregnancy or lactation is not available.

Pediatric Use

Premature infants

Easyfive-TT® Vaccine can be given to preterm infants, however, as expected in this population, a lower immune response can be observed for some antigens and the level of clinical protection is unknown. Also, the potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunization series to very preterm infants (born ⩽ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in these infants, vaccination should not be withheld or delayed.

Effects on ability to drive and use machines

Although no such studies have been performed, it is expected that Easyfive-TT® Vaccine would have no or negligible influence on the ability to use bicycles and other such machines.

Side Effects

Side Effects 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 12500 doses administered. Administration of acetaminophen at the time and 4-8 hours after immunization decreases the subsequent incidence of febrile reaction.
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.
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 the administration of the Hib vaccine. More serious reactions are very rare.
In a randomized clinical study of Easyfive Vaccine in healthy infants following adverse events was reported.
Very common: ≥ 1/10, Common: ≥ 1/100 to <1/10, Uncommon: ≥1/1000 to <1/100, Rare: ≥1/10000 to <1/1000, Very rare: <1/10000.

System Organ Class	Frequency	Adverse events
General disorders and administration site conditions	Very common	Pain/ tenderness, Fever, Swelling, Redness, warm to touch
Psychiatric disorders	Common	Lot fussier/Crying, Restless
Gastrointestinal disorders	Common	Vomiting, Diarrhoea
Nervous system disorders	Common	Sleepier
Metabolism and nutrition disorder	Common	Poor eating
Congenital Familial Genetic disorder	Rare	Microcephaly

Most of these symptoms were resolved within 48 hours after vaccination.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to pvg@panaceabiotec.com **OR** Mobile No. +91-9650138282

Overdose

Experience of overdose is limited.
There is no specific treatment for an overdose with Easyfive-TT® Vaccine. In the event of an overdose, the infant should be monitored and provided with symptomatic treatment as appropriate.

PHARMACOLOGICAL PROPERTIES

Mechanism of Action

Diphtheria

Diphtheria is an acute toxin-mediated disease caused by toxigenic strains of *C. diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection. Antitoxin levels of ⩾ 0.1 IU/mL are generally regarded as protective. Levels of 1.0 IU/mL have been associated with long-term protection. **Tetanus**

Tetanus is an acute disease caused by an extremely potent neurotoxin produced by *C. tetani*. Protection against disease is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxin level of ⩾ 0.01 IU/mL, measured by neutralization assay is considered the minimum protective level. A tetanus antitoxoid level ⩾ 0.1 IU/mL as measured by the ELISA used in clinical studies of VAXELIS is considered protective.

Pertussis

Pertussis (whooping cough) is a respiratory disease caused by *B. pertussis*. This Gram-negative coccobacillus produces a variety of biologically active components, though their role in either the pathogenesis of, or immunity to, pertussis has not been clearly defined.

Hepatitis B

Hepatitis B virus is one of several hepatitis viruses that cause systemic infection, with major pathology in the liver. Antibody concentrations of ⩾ 10 mIU/mL against HBsAg correlate with protection against hepatitis B virus infection.

***Haemophilus influenzae* type b**

H. influenzae type b can cause invasive diseases such as meningitis and sepsis. The anti-PRP antibody has been shown to correlate with protection against invasive disease due to *H. influenzae* type b. Based on data from passive antibody studies and an efficacy study with *H. influenzae* type b polysaccharide vaccine in Finland, a post-vaccination anti-PRP level of ⩾ 0.15 mcg/mL is considered a minimal protective level. Data from an efficacy study with *H. influenzae* type b polysaccharide vaccine in Finland indicate that an anti-PRP level of ⩾ 1.0 mcg/mL 3 weeks after vaccination predicts protection through a subsequent 1-year period. These levels have been used to evaluate the effectiveness of *H. influenzae* type b conjugate vaccines.

Pharmacodynamic properties

Pharmaco-therapeutic group: Bacterial and viral vaccines combined.

Immunogenicity

In a randomized Phase 3 trial, Easyfive-TT® (DTwP-HepB-Hib) Vaccine of Panacea Biotec Ltd. was found to be non-inferior to DTwP-HepB/Hib Tritanrix-HB™ reconstituted with Hiberix™ by GSK Biologicals. The vaccine was safe and immunogenic. The immunogenicity of the Easyfive-TT® vaccine was evaluated in 6, 10, 14 weeks schedule (3-doses given at 4 weekly intervals). The seroprotection rates/ immune responses for all components of the vaccine after 1-month completion of the 3-dose primary vaccination schedule were as follows: The anti-HBsAg seroprotection rate was 97.3%, anti-PRP seroprotection rate was 89.55%, anti-diphtheria seroprotection rate was 97.7% and anti-tetanus seroprotection rate was 99.0%. The response rate of pertussis IgG and anti-PT was 30.7% and 35.0% respectively.

Differences in Seroprotection / Immune Response rates between Groups, with 95% Cis:

Antigen	Easyfive-TT®		DTwP-HepB/Hib		Difference in Seroprotection Rate		
					Difference in%	95% CI	
	N	n%	N	n%		LL	UL
Anti HBsAg (⩾10 mIU/ml)	292	284(97.3%)	284	266 (93.7 %)	-3.6	-7.0	-0.2
Anti PRP (⩾ 1.0 µg/ml)	256	229 (89.5 %)	262	248 (94.7%)	5.2	0.6	9.8
Diphtheria (⩾ 0.1 IU/ml)	299	292 (97.7%)	296	281 (94.9%)	-2.7	-5.8	0.3
Tetanus (⩾ 0.1 IU/ml)	299	296 (99.0 5)	295	293 (99.3%)	0.3	-1.1	1.8
Pertussis IgG (⩾ 4-fold rise)	277	85 (30.7 %)	92	92 (35.2%)	4.6	-3.4	12.5
Anti-PT (⩾ 4-fold rise)	300	105 (35.0%)	95	95 (32.1%)	-2.9	-10.5	4.8

Pharmacokinetic properties

Not applicable

NON CLINICAL PROPERTIES

Animal toxicology

Toxicological studies carried out by PanEra Biotec Pvt. Ltd. Lalru, Punjab, India for Hepatitis B component

Toxicological studies on recombinant Hepatitis B vaccine (Enivac HB) were carried out in Swiss mice, guinea pigs, and rabbits in three parts viz; acute toxicity, single dose toxicity, and local tolerance.
The data from the three studies were analyzed and the following results were obtained.

1. No Pre terminal deaths.
2. No toxic signs or tissue reaction at the site of injection.
3. No significant dose-related effects on body weight and organ weight.
4. No treatment or dose-related changes in the hematological and the clinical parameters, except some incidental findings.
5. On Histopathological examination, no effects of toxicity were seen in the organ studied.

Toxicological studies carried out for the HIB-TT component and Easyfive vaccine

The single dose with local tolerance and repeated dose toxicity studies for *Haemophilus Influenzae* Type b conjugate Vaccine (HIB-TT Conjugate Vaccine) and Easyfive vaccine were performed
Based on the data from pre-clinical toxicity studies it is concluded that the HIB-TT conjugate vaccine and Easyfive vaccine did not produce any adverse effect in mice and rabbits with single-dose and repeated dose administration (following N+1=4 schedule) by intramuscular route.

DESCRIPTION

Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA) & *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) IP (DTwP-Hep-B-Hib) (Easyfive- TT®) is a sterile and uniform suspension of Diphtheria toxoid, Tetanus toxoid, whole cell Pertussis vaccine, Hepatitis B surface antigen and conjugated *Haemophilus influenzae* type b (PRP-TT) vaccine adsorbed on aluminium phosphate gel and suspended in isotonic sodium chloride solution. Thiomersal is added as a preservative. Diphtheria and tetanus toxoids are obtained by detoxification of respective toxins by formalin. Pertussis vaccine is a suspension of heat-killed Bordetella pertussis of all the three major agglutinogens viz. 1, 2 and 3. Surface antigen of Hepatitis B virus is obtained from cultures of transformed yeast by insertion in its genome of the gene coding for the surface antigen (HBsAg) using recombinant DNA procedures. *Haemophilus influenzae* type b (PRP-TT) vaccine is derived from highly purified capsular polysaccharide isolated from *Haemophilus influenzae* type b coupled with Tetanus toxoid.
The production process of Diphtheria, Tetanus, whole cell Pertussis, recombinant HBsAg and Hib vaccine complies with WHO recommendations.
The potency of the vaccine per single human dose is at least 30 IU for diphtheria, 60 IU for tetanus (determined in mice), 4 IU for whole cell pertussis, 10 mcg for Hepatitis B surface antigen and 10 mcg for conjugated *Haemophilus influenzae* type b (PRP-TT).
The final product has an appearance of a white or almost white material which sediments at the bottom of the container defining two phases: a clear supernatant essentially protein-free composed of physiological saline with the preservative substance dissolved, plus aluminum phosphate gel with the antigen adsorbed on it. When shaken, a white or almost white suspension is formed, lasting for some minutes, which is the form in which the product is to be administered.

PHARMACEUTICAL PARTICULARS

Incompatibilities

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

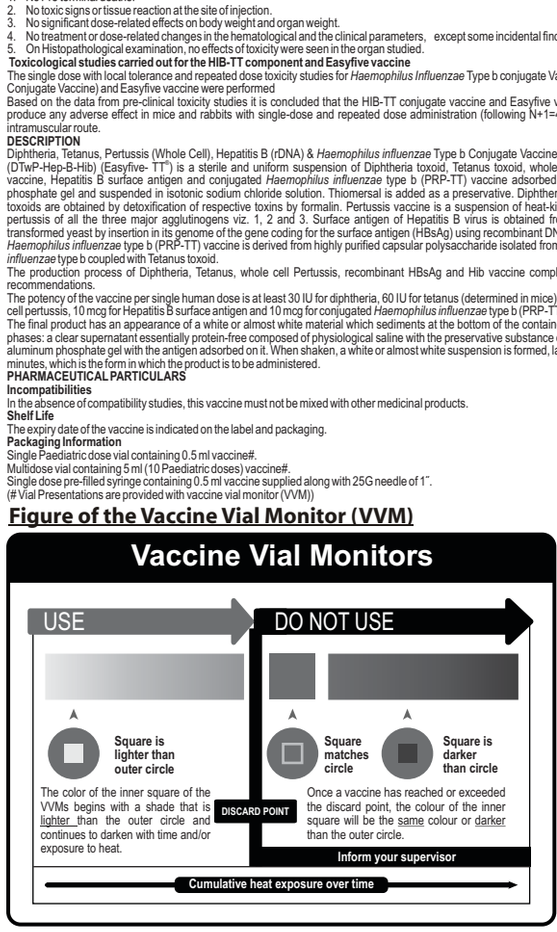
Shelf Life

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

Packaging Information

Single Paediatric dose vial containing 0.5 ml vaccine#.
Multidose vial containing 5 ml (10 Paediatric doses) vaccine#.
Single dose pre-filled syringe containing 0.5 ml vaccine supplied along with 25G needle of 1".
(# Vial Presentations are provided with vaccine vial monitor (VVM))

Figure of the Vaccine Vial Monitor (VVM)



Vaccine Vial Monitors (VVMs) supplied by TEMPTIME Corporation, U.S.A are put on Flip of seal of all Easyfive- TT® vaccine vials. 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". If the color of this square is lighter than the color of the circle, the vaccine can be used. If the color of the central square is the same as that of the circle or of darker than the circle, the vaccine vial should be discarded.

Storage and Handling Instructions

The combination vaccine must be stored and transported at 5°C ± 3°C. The DTwP-Hep B-Hib vaccine MUST NOT BE FROZEN. The vaccine which has been exposed to freezing should not be used. Protect from light. Do not use after the expiration date shown on the label. Discard unused portions.
Multi-dose vials of Easyfive-TT® 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 28 days provided that all of the following conditions are met (as described in the WHO policy statement: Handling of multi dose vaccine vials after opening, WHO/IVB/14.07):

- The vaccine is currently prequalified by WHO;
- The vaccine is approved for use for up to 28 days after opening the vial, as determined by WHO;
- The expiry date of the vaccine has not passed;
- The vaccine vial has been, and will continue to be, stored at WHO - or manufacturer recommended temperatures; furthermore, the vaccine vial monitor, if one is attached, is visible on the vaccine label and is not past its discard point, and the vaccine has not been damaged by freezing.

Withdrawing the vaccine from a vial

Shake the vial to disperse the contents thoroughly immediately before each withdrawal of the vaccine. Remove the flip of the seal and a small circular portion of the rubber stopper is seen.
DO NOT REMOVE THE RUBBER STOPPER FROM THE VIAL.
Apply a sterile piece of cotton moistened with a suitable antiseptic to the surface of the rubber stopper and allow it to dry. Draw into the sterile syringe a volume of air equal to the amount of vaccine to be withdrawn from the vial. Pierce the center of the rubber stopper with the sterile needle of the syringe, invert the vial, slowly inject into it, the air contained in the syringe, and keeping the point of the needle immersed, withdraw into the syringe the required amount of vaccine. Then hold the syringe plunger steady and withdraw the needle from the vial.
Carefully insert the needle intramuscularly at the prepared injection site.

PREPARATION FOR INJECTION (PFS)

Remove the prefilled syringe from the blister pack. Holding the syringe barrel, remove the Plastic rigid cap (PRTC) from the tip of the syringe. The PRTC design makes the tip cap easy to open and promote aseptic technique by reducing risk of syringe tip contamination during cap removal. Attach the needle to the Luer Lok syringe.
In the unusual event of the piston rod becoming loose off, screw it clockwise in to the plunger in order to secure it. The peel-off label on the barrel of the prefilled syringe is to be pasted on the vaccine's vaccination card for future reference.
Each prefilled syringe should be used only once.

PATIENT COUNSELLING INFORMATION (PCI)

Advise the patient to read the approved patient labeling (Patient Information).
Inform the parent or guardian of the following:
The potential benefits and risks of immunization with Easyfive-TT® Vaccine.
The common adverse reactions that have occurred following the administration of Easyfive-TT® Vaccine.
Other adverse reactions can occur. Call your doctor with any adverse reactions of concerns.

DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Market Authorization No. : MB/07/632
Date of First Authorization: 09 August, 2012

Manufactured by:
Panacea Biotec Ltd.
Malpur, Baddi,
Distt. Solan (H.P.) - 173 205, India.

Panacea Biotec
Innovation in support of life

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