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Prescribing Information for a Registered Medical Practitioner

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

Comvac5® कॉमवैक५®

1. NAME AND DESCRIPTION OF THE MEDICINAL PRODUCT

Comvac5® is a sterile, whitish, cloudy, uniform suspension of *Corynebacterium diphtheria* and *Clostridium tetani* toxoids, *Bordetella pertussis* whole cell inactivated, *Hepatitis B* surface antigen and *Haemophilus influenzae type b* (Hib) PRP-TT conjugate adsorbed on a mineral carrier aluminium phosphate gel in isotonic saline solution.

The toxoids of *Corynebacterium diphtheria* and *Clostridium tetani* components are inactivated by formalin using established technology. The Pertussis component is whole cell culture of Bordetella pertussis inactivated by using standard methods.

The surface antigen of the Hepatitis B virus is manufactured by recombinant DNA technology in genetically engineered yeast cells of Pichia pastoris which carry the gene that codes for the major surface antigen of the Hepatitis B virus.

Purified Polyribosyl-Ribitol-Phosphate (PRP) is isolated from *Haemophilus influenzae type b* and conjugated to Tetanus Toxoid. This vaccine fulfills WHO requirements for Diphtheria, Tetanus, Pertussis (Whole Cell) and *Haemophilus influenzae type b* conjugate vaccine.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 0.5 mL contains:

Diphtheria Toxoid	≥ 20 Lf to ≤ 30 Lf (≥ 30 IU)
Tetanus Toxoid	≥ 5 Lf to ≤ 25 Lf (≥ 60 IU)
B. pertussis (Whole Cell Inactivated)	≥ 4 IU
Hepatitis B surface Antigen (HBsAg)	≥ 10µg
Hib PRP-TT Conjugate	≥ 10µg
Aluminium Phosphate Gel equivalent to Aluminium (Al^{+++})	0.3mg
Thiomersal IP	0.029mg

3. PHARMACEUTICAL FORM

Suspension for Injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Comvac5® is indicated for the primary immunization of infants from 6 weeks of age up to school going age of 6 years as a three-dose schedule at 6, 10 and 14 weeks against Diphtheria, Tetanus, Whooping Cough, Hepatitis caused by Hepatitis B virus and disease caused by *H. influenzae* Type b

4.2 Posology, Schedule and Method of Administration

Primary immunization consists of 3 doses of vaccine of 0.5 mL each with an interval of 4 weeks between each dose. The first dose is administered at six weeks of age. Each injection of the primary immunization series should be given at different injection sites.

As per UIP, the first booster dose is administered at the age of 15-18 months[1]. WHO recommends a second booster as a reinforcing dose of the vaccine at school entry, at the age of 4-6 years[2].

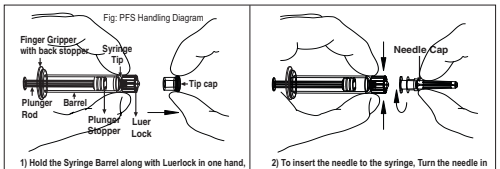
Shake the vial to obtain a homogenous, turbid, white suspension before each withdrawal of vaccine. The site of injection should be prepared with a suitable antiseptic 0.5 mL of vaccine should be given intramuscularly in the anterolateral aspect of the upper thigh in infants ≤ 12 months of age or into the deltoid muscles in older children. Another injection if co-administered with Diphtheria, Tetanus, Pertussis, Hepatitis B and *Haemophilus influenzae* type b Conjugate Vaccine Adsorbed, should be administered at a different site[3].

While using a multi-dose vial of **Comvac5®** care must be taken to use separate sterile syringes and needles for the administration of every dose. The used multi-dose vial that contains the remaining vaccine must be stored at the recommended storage temperature for up to a maximum of 4 weeks. Provided that following conditions are met. It can be reexamined carefully prior to reuse.

- 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

PFS Handling procedure: Prior to administration, ensure that the plunger rod is firmly attached to the rubber stopper by turning the plunger rod clockwise until slight resistance is felt. Do not over tighten. Remove rubber tip-cap from the syringe and fix the needle on syringe by turning in clock wise direction into Luer-lock until it is securely fixed to the syringe, remove the needle cap before injecting. Do not rotate Luer-lock. Finger grip with back stopper will prevent plunger rod coming out from the syringe barrel. Do not remove the back-stopper from the syringe.

Fig: PFS Handling Diagram



1) Hold the Syringe Barrel along with Luerlock in one hand, pull the Tip cap gently to dislodge cap from Syringe.

2) To insert the needle to the syringe, Turn the needle in the clockwise direction to Luerlock (See Illustration)

4.3 Contraindications

Comvac5® should not be administered or repeated to persons known to be hypersensitive to any of the components. **Comvac5®** should not be administered to infants or, children with fever or other evidence of acute illness or infection. The presence of an evolving or changing neurological disorder is a contraindication to receipt of the vaccine A personal or family history of central nervous system disease or convulsions is considered a contraindication to use of this vaccine.

The specific contraindications adopted by individual national health authorities should reflect a balance between the risk from the vaccine and the risk from the disease. The risk from the vaccine remains extremely low in comparison to the risk of the disease in many developing countries.

4.4 Special Warning/ Precautions

- **Comvac5®** should not be administered or repeated to persons known to be hypersensitive to any of the components.
- Epinephrine injection (1:1000) must be immediately available in case anaphylactic or other allergic reactions occur.

If any of the following events occur after the administration of the vaccine, the decision to give subsequent doses of vaccine containing Pertussis whole cell component should be carefully considered:

- Temperature of 40°C (104°F) within 48 hours, not attributed to any other known cause
- Collapse or shock-like state (hypotonic-hypo responsive episode) within 2 days
- Persistent, inconsolable crying lasting ≥3 hours, occurring within 2 days.
- Convulsions, with or without fever, occurring within 3 days.

Prior to Vaccination

- The healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an assessment of benefits and risks.
- As is the case with the use of any vaccine, the vaccine should remain under medical supervision for at least 30 minutes after vaccination.

4.5 Interactions with Other Medicinal Products

Comvac5® should not be mixed with any other vaccine or medicinal product, because the interactions with other vaccines or medical products have not been established.

4.6 Pregnancy and Lactation

Comvac5® is not intended for use in adults and hence information on its safety when used during pregnancy or lactation is unavailable.

4.7 Effects on ability to drive and use machines

Not Applicable

4.8 Undesirable effects

As with the use of injectable vaccine, mild local reactions consisting of Tenderness (3.3%), pain (4.1%), fever (5%), Vomiting (5.8%) Irritability (11.6%), Redness (3.5 %), Swelling (3.74%), and persistent crying (1%) induration at the site of injection are common, usually self-limited and subside without treatment. A small lump may occasionally be observed at the site of injection that disappears after a few days. If you develop side effects mentioned above or any other undesirable effects, please inform your doctor.

4.9 Overdose

No case of overdose has been reported

4.10 Clinical Trial Experience

Clinical Trials:

Phase 3 study was performed with PENTAVALENT (lyophilised-Hib) DTPw+HEP-B & Hib, a total of 100 healthy infants with 6-8 weeks of age were enrolled. Out of 100 subjects 50 were given Bharat Biotech International limited (BBIL) vaccine PENTAVALENT (lyophilised-Hib) DTPw+HEP-B & Hib and another 50 were given reference vaccine Panacea-EASY 5. The vaccines were given in three dose of 0.5 mL intra muscularly with an interval of four weeks between the doses. A total of 148 doses of BBIL vaccine and 144 doses of reference vaccine were administered. In BBIL vaccine group all 49 infants (100% subjects) became Sero positive for IgG antibodies to Pertussis, Diphtheria, Tetanus & Haemophilus influenzae B component, where as 87% (43 Infants) for Hepatitis-B component. These results are comparable to that of the results in terms of immunogenicity of reference vaccine and vaccines from earlier studies[4, 5]. Hence it can be concluded DTPw+HEP-B & Hib combination vaccine manufactured by Bharat Biotech is safe and immunogenic.

A prospective multi-centric randomized controlled double blind, comparative Phase 3 study to evaluate the safety and immunogenicity of BBIL's (Liquid Hib) DTP+HEP-B+Hib vaccine vs. a control vaccine (Panacea-Easy 5) in healthy volunteers. (non- inferiority trial) was conducted in 180 healthy infants of 6-8 weeks of age. Out of 180 subjects 90 were given BBIL'S vaccine and another 90 subjects were given control vaccine. A total of 263 doses of BBIL vaccine and 260 doses of control vaccine were administered. Fever was the most common symptom in both the study group, none of these subjects required physicians visit as they were treated symptomatically by paracetamol. The next common symptom was pain in both the groups; this can be attributed to whole cell pertussis component of the vaccine. Immunogenicity of BBIL- DTP+HEP-B+Hib vaccine: 98 % of the subjects were Seroprotected for Diphtheria, 98 % for Tetanus, 98 % for hepatitis-B, 76 % of subjects were Sero-protected for the Pertussis and 100 % were Sero-protected for Haemophilus influenzae B. The study demonstrates that the combination vaccine (DPT-HEP B& Hib) manufactured by Bharat Biotech International Limited is safe and immunogenic.

In Phase 3 study 140 subjects were enrolled and administered Bio-Hib vaccine produced by Bharat Biotech International Limited, in healthy infants of age 6 weeks to 6 months for assessment and confirmation of its reactogenicity and immunogenicity. The vaccine was given on day 0, 30th day and 60th day to all the enrolled study infants. Out of the 140 subjects, 106 subjects were evaluable for efficacy, as pre and post vaccination blood samples. The pre vaccination GMT in infants was 0.15 mg/L; there has been a significant increase in antibody titers to reach a level of 2.19 mg/L. Around 96 percentage of infants vaccinated with Bio-Hib had post vaccination antibody titers ≥ 0.15 mg/L (Seroprotection level).

A Phase 3, multicenter, randomized, safety and immunogenicity study of yeast derived recombinant hepatitis B vaccine in Pichia pastoris. A total of 226 subjects were enrolled into the study, out of 226, 105 females and 91 males. However only 142 subjects completed all the follow-ups and Anti-HBs titers, among these 142 subjects, 39 received Enivac-B, 69 received experimental vaccine and 34 received Revac-B vaccine respectively. Remaining 54 subjects dropped out from the study due to non-adherence to study protocol. The mean age group of subjects were 27.65. The schedule of vaccine is Day 0th, Day 30th and Day 60th. In overall trial subjects in all three groups there was 100% seroconversion at 60th and 90th time point. The data of the Geometric Mean titers at 30th, 60th and 90th day samples show an increase of titers from 310.5 mIU at 30th day to 10743.3 mIU at 90th day in the Revac-B vaccine group. The indigenously developed recombinant Hepatitis B vaccine is safe and well tolerated and highly immunogenic.

A phase 4, multicentric, controlled, open-label study to evaluate the safety and immunogenicity of **Comvac5®** (DTwP+Hep.B+Hib, Liquid Pentavalent Vaccine of BBIL) vs WHO prequalified control vaccine-EASY 5 of Panacea Biotec was conducted in 330 healthy infants, out of 330 subjects 247 were given BBIL'S vaccine and another 83 subjects were given control vaccine over aged 6-8 weeks. In BBIL vaccine group, all subjects 100% were seropositive for IgG antibodies to Diphtheria, Tetanus, PRP & Hepatitis B components, whereas 95.3% for Pertussis component. In all subjects of reference group 100% infants became seropositive for IgG antibodies to Diphtheria, Tetanus, PRP and Hepatitis B and 96.2% infants were seropositive for Pertussis component. The study demonstrated that the BBIL pentavalent vaccine was safe and immunogenic and comparable to commercially available combination vaccine.

Comvac5® vaccine was co-administered with Rotavac and oral Polio in a Phase 3 study of Rotavac non-interference with childhood vaccine. This study was conducted in infants between 42-55 days of age. 1356 infants were enrolled in this study, among them 1017 infants were administered with ROTAVAC® and 339 infants were given placebo along with childhood vaccines (OPV and **Comvac5®** vaccine) at 6-7, 10-<14 and 14-<18 weeks of age. Almost all infants, irrespective of the treatment group, developed protective antibody titer against diphtheria toxoid, tetanus toxoid and Hib (anti-PRP antibodies). Over 93% developed protective titer against HepB (anti-HBs antibodies). The difference in proportion of infants who developed protective antibody titers was 0.5% (95% CI −1.3%, 2.3%) for diphtheria toxoid, 0.9% (95% CI −0.3%, 2.4%) for tetanus toxoid, 2.2% (95% CI −1.7%, 6.0%) for anti-HBs antibodies and 0% (95% CI −1.3%, 1.1%) for anti-PRP antibodies. The ratio of GMCs between the placebo and ROTAVAC® groups for pertussis toxin was 1.0 (0.8, 1.1). This study demonstrated that three doses of **Comvac5®** can be safely co-administered with ROTAVAC® and OPV vaccine without interfering with infant's serum antibody response to each component of these vaccines[6].

This study was required to procure WHO pre-qualification to access regular use of the vaccine for children in lower income countries.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Not available

5.2 Pharmacokinetic Properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Pre-Clinical studies:

28-day subcutaneous toxicity in Swiss albino mice and 28-day intramuscular toxicity in New Zealand white rabbits were used to perform the pre-clinical studies with DTwP + Hep B + Hib vaccine. Two groups of mice each comprising of 10 males and 10 females, and similarly two groups of rabbits each comprising of 6 males and 6 females were injected with control and equivalent doses of DTwP+Hep.B+Hib vaccine on days 0, 7, 14, 21 and the animals were observed for clinical signs of toxicity due to the administration of vaccine for 28days. There were no significant changes or toxicity were observed. DTwP+Hep.B+Hib vaccine was found to be safe at the rate of 64.5 times of human equivalent dose in a swiss albino mice and white rabbit.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aluminium Phosphate Gel equivalent to Aluminium (Al^{+++})
Thiomersal IP

6.2 Shelf Life

The shelf life of **Comvac5®** is indicated on the label and carton of the product. Do not use the product after the expiry date shown on the label and carton.

6.3 Special precautions for Storage

Vaccine vial should be stored at +2C° and +8C° (35°F to 46°F)
Shake well before use. Do not freeze. DISCARD IF FROZEN. Keep out of reach of children.

7. PRESENTATION

Comvac5® is presented in USP type1 glass vial and PFS.

Single dose vial	0.5 mL
Single dose PFS	0.5 mL
Multi dose vial (5 dose)	2.5 mL
Multi dose vial (10 dose)	5.0 mL

Reference

[1] https://www.nhp.gov.in/sites/default/files/pdf/immunization_uip.pdf

[2] https://www.who.int/immunization/policy/Immunization_routine_table2.pdf

[3] Diphtheria, Tetanus, Pertussis, Hepatitis B and *Haemophilus influenzae* type b Conjugate Vaccine Adsorbed. Package inserts. Serum institute of india ltd. Hadapsar pune-411028, India.

[4] Chin- Yun Lee, John et al., an evaluation of the safety and immunogenicity of a five component a cellular pertussis, Diphtheria and tetanus toxoid vaccine (DTaP) when combined with a *Haemophilus influenzae* type B –Tetanus toxoid conjugate vaccine (PRP-T) in Taiwanese infants, Pediatrics ,1999, 103,25-30.

[5] Usonis A, Baskasenas V, Taylor D, and Vandepapelire P. The immunogenicity and reactogenecity of combined DTwP Hepatitis B vaccine in Lithuanian infants. Eur J Pediatr 1996; 155: 189-193.

[6] Temsunaro Rongsen Chandola, Sunita Taneja, Nidhi Goyal, Kalpana Antony, Kiran Bhatia, Deepak More, Nita Bhandari, Iksung Cho, Krishna Mohan, Sai Prasad, GVJA Harshvardhan, Tataji Surender Rao, Sudhanshu Vrati, Maharaj Kishan Bhan. ROTAVAC® does not interfere with the immune response to childhood vaccines in Indian infants: A randomized placebo-controlled trial. Heliyon 3 (2017) e00302. doi: 10.1016/j.heliyon.2017. e00302

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