SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT:

Name of the product: Diphtheria, Tetanus, Pertussis (Whole Cell) and Haemophilus infuenzae Type b Conjugate Vaccine (Adsorbed) IP

Strength:
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..... ≥ 4 IU
Hib PRP-TT Conjugate .....≥ 10 µg

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
Hib PRP-TT Conjugate ..... ≥ 10 µg
Aluminium Phosphate Gel equivalent to Aluminium (Al^{+++}) ..... 0.3 mg
Thiomersal ..... NMT 15 microgram

3. PHARMACEUTICAL FORM

Suspension for Injection.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Comvac4® is indicated for the primary immunization of infants aged 6 weeks and above as a three-dose schedule at 6, 10 and 14 weeks against diseases like Diphtheria, Tetanus, Whooping Cough and those caused by *Heamophilus influenzae* Type b.

4.2. Posology and Method of Administration

The vaccine should be given intramuscularly in the vastus lateralis (anterolateral aspect of thigh) in infants <12 months of age or in the deltoid (upper arm) muscle in children ≥12 months of age.

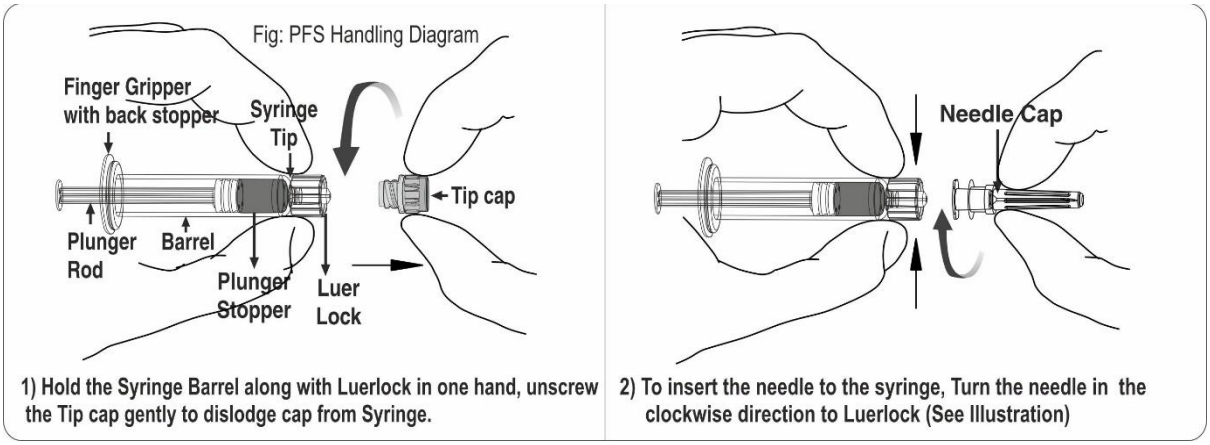
The site of injection should be prepared with a suitable antiseptic. Shake the vial to obtain a homogenous, turbid, white suspension. **Do not inject subcutaneously or intravenously, under any circumstances.**

If co-administered with **Comvac4®,** the other injection should be made at a different site.
If you forget to take one dose of **Comvac4®** injection, your doctor will decide when to give the missed dose.

Primary immunization consists of 3 doses of vaccine of 0.5 mL, each covered within the first 6 months of a child's age. The first dose should be given at 6 weeks of a child's age. Each dose is administered at an interval of 4 weeks.

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. Hold the Syringe Barrel along with Luer-lock in one hand, unscrew the Tip cap gently to dislodge cap from 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."



4.3 Contraindications

Comvac4® should be deferred during the course of an acute infection/illness. It must not be given to an infant with history of immediate anaphylactic reaction associated with a previous dose. Known hypersensitivity to any component of the vaccine is an absolute contraindication. The presence of an evolving or changing neurological disorder is a contraindication to receipt of the vaccine.

Comvac4® should not be administered to children over six years of age or to adults because of the danger of reactions to diphtheria toxoid or pertussis component.

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. Because the risk from the vaccine remains extremely low in comparison to the risk from the disease in many developing countries, the relevant authorities may choose to offer immunization to children who are mildly to moderately ill or malnourished.

4.4 Special Warnings and Precautions for use

There may be a possibility of allergic reactions in individuals sensitive to the components of the vaccine.

Epinephrine Hydrochloride Solution 1:1,000 dilution, 0.01 mg per kg in children, should be injected subcutaneously or intramuscularly, usually into the upper arm in case an anaphylactic or acute hypersensitivity reaction occurs.

4.5 Interaction with other medicinal products/active immunising agents and other forms of interaction

For concomitant or co-administration, use different injection sites and separate needles/syringes. **Comvac4®** 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

Comvac4®is not intended for use in adults and hence information on its safety when used during pregnancy or lactation is unavailable. It is not known whether this vaccine is excreted in human milk.

4.7 Effects on ability to drive and use machines

No studies on the effect of **Comvac4®** on the ability to drive and use machines have been performed.

4.8 Undesirable effects

As with the use of injectable vaccine, mild local reactions consisting of erythema, pain, tenderness, swelling and 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.

Mild to moderate systemic reactions may occur following injection of the vaccine; these include one or more of the following symptoms like temperature elevation, drowsiness, fretfulness, anorexia, vomiting, irritability and persistent crying. These symptoms occur during the first 24 hours of administration and may persist for one to two days.

Moderate to severe systemic reactions like high fever (>40.5° C), persistent and inconsolable crying for more than 3 hours, and encephalopathy may also occur. The incidence of these reactions is unknown and may occur in extremely rare cases.

The decision to give subsequent doses of **Comvac4®** should be carefully considered, if any of the following events occur, in temporal relation to its administration:

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

Prevention and treatment of common, minor vaccine reactions:

- Prior to administration, 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 vaccinee should remain under medical supervision for at least 30 minutes after vaccination.
- Paracetamol, at a dose of 15mg/kg every 6 to 8 hours with a maximum of 4 doses in 24 hours, is useful for the common minor reactions. It eases pain and reduces fever.
- A febrile child should be given a tepid sponge bath.
- Extra fluids should be given to a febrile child.
- For local reactions like pain, swelling and redness at the site of injection, a cold cloth applied to the site may ease the pain.

4.9. Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties:

Comvac4® is a sterile and uniform suspension of Diphtheria toxoid, Tetanus toxoid, *B pertussis* whole cell inactivated, and Hib PRP-TT Conjugate adsorbed on a mineral carrier Aluminum phosphate gel in isotonic saline solution and acts by inducing anti-diphtheria, anti-tetanus, anti-*B pertussis* and anti-Hib antibodies b

5.2. Pharmacokinetic Properties:

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3. Pre-clinical safety data:

Both DPT and Hib vaccines have been used extensively either separately or in combination with Hepatitis B vaccine. It is also known that the use of combined DPT-Hib vaccine does not result in reduced efficacy when compared to DPT and Hib vaccine given separately. Clinical studies conducted with combination vaccine have shown that 100% of subjects developed protective antibody titers against diphtheria, tetanus, and Hib and 95.3% of subjects developed protective antibody titers against pertussis.

Safety data in the Clinical Trial:
The infants who received **Comvac4®** had adverse events like Fever (seen in 60.34% of the vaccine recipients), solicited local adverse events like Pain at injection site (seen in 36.21% of vaccinees), followed by Swelling at injection site (seen in 28.45% of vaccinees) and Redness at injection site (seen in 15.52% of vaccinees) being most common AEs. The Adverse event profile of **Comvac4®** is similar to that of Comvac3™+BioHib and is clinically acceptable. No Serious Adverse events were observed in either groups.

Immune response:
A Phase 3, multicentric, randomized, open-label, active-controlled study was conducted to evaluate the immunogenicity and safety of DTwP-Hib (**Comvac4®)** vaccine in comparison with reference vaccine Comvac3™+BioHib in healthy infants of 6 to 7 weeks age. 240 healthy infants participated in this study, of which 232 infants were evaluable for immunogenicity and safety. Three doses of both **Comvac4®** or Comvac3™+BioHib vaccines were given to infants at 6, 10 and 14 weeks of age. A baseline blood sample was collected prior to administration of 1st dose of vaccine (Pre-vaccination sample) and another blood sample was collected 28 days after the 3rd dose of vaccination. The immunogenicity in terms of seroprotection rates were evaluated for non-inferiority against the reference vaccine.

The seroprotection rates of **Comvac4®** against diphtheria, tetanus and Hib were 99.14%, 100% and 93% respectively whereas seroprotection rates of Comvac3™+BioHib against diphtheria, tetanus and Hib were 99.14%, 100% and 94% respectively. The seroprotection rate against pertussis was 61.2% and 47.4% in **Comvac4®** and Comvac3™+BioHib groups, respectively based on the seroprotection limits against each antigen of Diphtheria, Tetanus, Pertussis and *Hemophilus influenzae* as shown in the table below:

Name of component	**Seroprotection limits**
Diphtheria anti-D	NLT 0.1 IU/mL
Tetanus anti-T	NLT 0.1 IU/mL
Pertussis anti-PT	NLT 15.0 IU/mL
HiB-anti-PRP	NLT 0.15 µg/mL

In summary, the seroprotection rates of **Comvac4®** were proved to be non-inferior to that of the reference vaccine.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Aluminium Phosphate Gel equivalent to Aluminium (Al^{+++})
Thiomersal IP

6.2. Incompatibilities
This medicinal product must not be mixed with other medicinal products.

6.3. Shelf Life
The expiry date of the vaccine is indicated on the label and carton of the product.

6.4. Special Precautions for Storage

Store in a refrigerator at +2°C to +8°C. Do not freeze. Discard if frozen. Shake well before use. Protect from light. Keep out of reach of children. Do not use **Comvac4®** vaccine after the expiry date which is stated on the carton and the label.

6.5 Nature and contents of container

Comvac 4® is presented in USP type 1 glass PFS
Single dose PFS - 0.5 mL

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

BHARAT BIOTECH Lead Innovation

Bharat Biotech International Limited situated
Sy. No. 230, 231 & 235, Genome Valley,
Turkapally, Shamirpet Mandal,
Medchal, Malkajgiri District, Telangana State, India, Pin: 500078.

8. MARKETING AUTHORISATION NUMBER

MF/BIO/21/000107

9. DATE OF FIRST MARKETING AUTHORISATION

20-SEP-2021

10. DATE OF REVISION

January 2023