TYPHOID VI CONJUGATE VACCINE I.P.

ZyVac® TCV

Summary of product characteristics as per Annexure C

1. NAME OF THE MEDICINAL PRODUCT

- Typhoid Vi Conjugate Vaccine I.P

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 0.5 ml contains:

Purified Vi-capsular polysaccharide of *S.typhi*	25 µg
conjugated to Tetanus toxoid (Carrier protein)	16 to 50 µg
2-Phenoxyethanol (as preservative)	2.50 mg
Isotonic buffer solution	q.s.

3. PHARMACEUTICAL FORM

Drug Substance(s)

- Purified Typhoid Vi Polysaccharide conjugate bulk has been developed as per WHO TRS 987, Annexure 3, 2014 and Indian pharmacopoeia.

Drug Product

- Typhoid Vi Conjugate Vaccine I.P. has been developed as per WHO TRS 987, annexure 3, 2014 and Indian pharmacopoeia.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZyVac® TCV is indicated for the active immunization against *Salmonella typhi* infection in 6 months to 65 years age group.

4.2 Posology and method of administration

The immunizing dose of ZyVac® TCV for adults, children and infants of age ≥ 6 months is single dose of 0.5 ml. A booster dose may be given after 3 years of primary vaccination for those people who remain at risk of typhoid fever.

ZyVac® TCV should be given intramuscularly in the deltoid or the vastus lateralis of children below two years of age. ZyVac® TCV should not be injected into the gluteal area or areas where there may be a nerve trunk. Prevention becomes effective after 2-3 weeks after immunization.

4.3 Contraindications

ZyVac® TCV is contraindicated in the following conditions:

- Hypersensitivity to any constituent of the vaccine
- Pregnant and lactating women
- In the event of fever or severe infection.

4.4 Special warnings and precautions for use

The vaccine is for intramuscular injection only. Do not administer the vaccine intravenously, intradermally or subcutaneously.

ZyVac® TCV protects against typhoid fever caused by *Salmonella typhi*. It does not confer protection against *Salmonella paratyphi* or other non-typhoidal *Salmonellae*.

As with any vaccine, ZyVac® TCV may not protect 100% of individuals.

The vaccine should be visually inspected for the presence of any particulate matter.

Do not administer the vaccine if particulate matter is observed and discard it.

Adrenaline (epinephrine) injection, 1:1000 (1 mg/ml) must be immediately available in case of an acute anaphylactic reaction or any allergic reaction occurs due to any component of the vaccine.

Vaccinee should remain under medical supervision for not less than 30 minutes after vaccination. Like all other vaccines, supervision and appropriate medical treatment should always be readily available to treat any anaphylactic reactions following immunization.

Special care should be taken to ensure that the injection does not enter a blood vessel.

Intramuscular injection should be given with great care in patients suffering from thrombocytopenia or other coagulation disorders.

Product which has been exposed to freezing should not be used and it should be discarded.

4.5 Interaction with other medicinal products and other forms of interaction

For concomitant or co-administration, use different injection sites and separated syringes. ZyVac® TCV should not be mixed with any other vaccine or medicinal product, because interaction with other vaccines or medical products have not been established.

Immunosuppressive therapies may reduce the immune response to ZyVac® TCV. As with other intramuscular injections, use with caution in patients on anticoagulant therapy.

4.6 Special Population

The safety and effectiveness is not established in pregnant women and in lactating mothers. It is not known whether this vaccine is excreted in human milk. The safety and effectiveness is also not established in infants below 6 months of age and in geriatric subjects.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The safety of ZyVac® TCV was established in the clinical trials conducted in India.

***Phase II/III clinical trial*:** This was a randomized comparative study in which a total of 240 healthy subjects were enrolled into one of the two study groups; 119 subjects were administered ZyVaC® TCV and 121 subjects were administered a comparator Typhoid Vi Conjugate Vaccine (TCV). The local adverse events (AEs) reported in that study included injection-site pain (25.2%), injection-site swelling (4.2%) and injection-site redness (3.4%). The systemic AEs reported in that study included fever (5.9%), diarrhoea (2.5%), cold (1.7%), myalgia (1.7%), malaise (0.8%), headache (0.8%), arthralgia (0.8%), vomiting (0.8%), nausea (0.8%) and upper respiratory tract infection (0.8%). Incidence of AEs

reported in the subjects who had received Zyvac®TCV was comparable to the incidence of AEs reported in the subjects who had received comparator TCV. No serious adverse event (SAE) was reported in any subject in that clinical trial.

***Phase IV clinical trial*:** A total of 112 subjects who had participated in the previous phase II/III clinical trial were enrolled in this extension study and out of which, 17 subjects were administered booster vaccination with Zyvac®TCV. The local AEs reported in that study included injection-site pain (23.5%), injection-site swelling (11.8%) and injection-site redness (5.9%). The systemic AEs reported in that study included fever (5.9%) and headache (5.9%). No SAE was reported in any subject in that clinical trial.

***Phase III clinical trial*:** This was a randomized comparative study in which a total of 238 healthy adults aged 45 to 65 years were enrolled into one of the two study groups; 119 subjects each were administered ZyVac® TCV and comparator TCV. The AEs reported in that study included injection-site pain (7.6%), headache (0.8%) and fever (0.8%). Incidence of AEs reported in the subjects who had received ZyVac® TCV was comparable to the incidence of AEs reported in the subjects who had received comparator TCV. No SAE was reported in any subject in that clinical trial.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

ZyVac® TCV contains purified Vi capsular polysaccharide of Salmonella typhi conjugated to tetanus toxoid as carrier protein. The vaccine confers significant protection against typhoid fever based on the production of antibodies. Immunity appears within 2 to 3 weeks after injection.

5.1 PHARMACODYNAMICPROPERTIES

Typhoid fever is a very common and serious bacterial disease caused by *Salmonella typhi*. Typhoid conjugate vaccine studies have shown that the efficacy and immunogenicity are higher than the plain Vi polysaccharide vaccine. In the manufacturing of Zyvac®TCV, the Vi polysaccharide has been conjugated with nontoxic Tetanus Toxoid. This vaccine has a

higher immunogenicity response and is T-cell dependent which induces Vi antibodies that neutralize Vi antigen and hence prevents the infection.

Immune Response:

The immunogenicity of Zyvac®TCV has been evaluated in the clinical trials conducted in India.

***Phase II/III clinical trial*:** In this study, the seroconversion rate (proportion of subjects achieving ≥4-fold increase in anti-Vi IgG antibody titre) at 6 weeks post-vaccination in the subjects aged 6 months to 45 years (overall population), 6 months to < 18 years (pediatric cohort) and 18 to 45 years (adult cohort) was 94.8%, 93.1%, 96.6% respectively. The seroconversion rate reported with Zyvac®TCV was non-inferior to that reported with the comparator TCV. In the subjects who had received Zyvac®TCV, the pre-vaccination geometric mean titre (GMT) of anti-Vi IgG antibodies reported was 7.6 EU/ml, 5.7 EU/ml and 10.0 EU/ml in the overall population, pediatric cohort and adult cohort respectively, while the GMT of anti-Vi IgG antibodies reported at 6 weeks post-vaccination was 1121.0 EU/ml, 891.1 EU/ml and 1411.0 EU/ml in the overall population, pediatric cohort and adult cohort respectively. There was a significant increase in GMTs at 6 weeks post-vaccination as compared to pre-vaccination GMTs ($P<0.0001$). Both the pre-vaccination and post-vaccination GMTs reported in the subjects who had received Zyvac®TCV was comparable to the respective GMTs reported in the subjects who had received the comparator TCV in this study.

***Phase IV clinical trial*:** In this study, the subjects who had received primary vaccination with TCV in the previous phase II/III clinical trial were followed-up after 3 years of their vaccination. 77.2% of the subjects who had received Zyvac®TCV in the previous phase II/III clinical trial and enrolled in this study had anti-Vi IgG antibody titre above the protocol defined cut-off titre of 10 IU/ml when assessed using the first WHO International Standard for anti-typhoid capsular Vi polysaccharide IgG (human) (NIBSC code 16/138) [1] which is equivalent to the proposed seroprotective cut-off titre of 2 μg/ml [1] as derived from the studies of other TCV [2]. The baseline GMT of anti-Vi IgG antibodies (3 years after primary vaccination) reported in this study in the subjects who had received ZyVac® TCV as a part of previous phase II/III clinical trial was 140.8 EU/ml. This baseline GMT

was significantly higher as compared to pre-vaccination GMT reported for the same subjects in the previous phase II/III clinical trial (P<0.0001). A total of 17 subjects who had baseline anti-Vi IgG antibody below the proposed seroprotective cut-off titre were administered booster vaccination with ZyVac® TCV. All the subjects followed-up at 10 days and 28 days after booster vaccination achieved seroconversion (≥4-fold increase in anti-Vi IgG antibody titre). The GMTs of antibodies reported at 10 days and 28 days after booster vaccination were 2306.9 EU/ml and 1900.5 EU/ml respectively. The GMTs of antibodies after booster vaccination were higher than that reported after primary vaccination in the previous phase II/III clinical trial.

***Phase III clinical trial*:** In this study conducted in healthy adults aged 45 to 65 years, the seroconversion rate (proportion of subjects achieving ≥4-fold increase in anti-Vi IgG antibody titre) at 4 weeks post-vaccination was 94.1%. The seroconversion rate reported with ZyVac® TCV was non-inferior to that reported with the comparator TCV. In the subjects who had received ZyVac®TCV, the pre-vaccination GMT of anti-Vi IgG antibodies reported was 8.0 EU/ml while the GMT of anti-Vi IgG antibodies reported at 4 weeks post-vaccination was 1378.3 EU/ml. There was a significant increase in GMTs at 4 weeks post-vaccination as compared to pre-vaccination GMTs (P<0.0001). Both the pre-vaccination and post-vaccination GMTs reported in the subjects who had received ZyVac® TCV was comparable to the respective GMTs reported in the subjects who had received the comparator TCV in this study.

5.2 PHARMACOKINETIC PROPERTIES

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

5.3.1 Animal Toxicology & Pharmacology:

Non-clinical data reveal no special hazard for humans based on conventional single-dose and repeated-dose toxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Sodium Chloride
- 2-Phenoxyethanol
- Water for injection
- Sodium hydroxide
- Hydrochloric acid

6.2 Incompatibilities

This vaccine 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 at 2°C to 8°C.
Do not freeze. Discard if frozen.
Keep out of reach of children.
Shake gently before use.
Do not use the vaccine after the expiration date shown on the label

6.5 Nature and contents of container

Nature and contents of container for Vials

2R Clear tubular Glass Vial - USP Type I with 13 mm Grey Bromo Butyl Rubber Stopper and 13 mm Aluminium Flip Off Seals.

Nature and contents of container for PFS

1.0 ml PFS USP Type I Glass Barrels with Rubber plunger Bromo Butyl

6.6 Special precautions for disposal

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

7. Details of manufacturer

Zydus Lifesciences Limited
Plot Survey No. 23, 25/P, 37, 40/P, 42 to 47
Sarkhej- Bavla N.H. 8A, Opp. Ramdev Masala,
Village: Changodar, Taluka: Sanand,
Dist. Ahmedabad – 382 213

8. MARKETING AUTHORISATION NUMBER(S)

Permission No. MF-274/2017

9. DATE OF FIRST AUTHORISATION

15th December, 2017