For the use of a Registered Medical Practitioner only

Typhoid Vi Conjugate Vaccine
ZyVac®TCV

1. NAME AND DESCRIPTION OF THE MEDICINAL PRODUCT

ZyVac®TCV is a sterile, clear and colorless liquid containing purified Vi capsular polysaccharide of *Salmonella typhi* which is conjugated to tetanus toxoid as carrier protein. The typhoid conjugate vaccines induce immunogenicity response which is T-cell dependent unlike plain Vi polysaccharide vaccines which induce T-cell independent response.

The vaccine confers significant protection against typhoid fever based on the production of antibodies. Immunity appears within 2 to 3 weeks after injection.

ZyVac®TCV is administered in a single 0.5 ml intramuscular dose to infants, children, adolescents and adults aged 6 months to 65 years. The vaccine meets the requirements of WHO.

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

Liquid for intramuscular injection

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

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.

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 Dosage and Schedule

Single dose of 0.5 ml to be given intramuscularly to adults, children and infants of age ≥ 6 months.

4.4 Contraindications

ZyVac®TCV is contraindicated in the following conditions:

- Hypersensitivity to any constituent of the vaccine
- In the event of fever or severe infection

4.5 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.

The safety and effectiveness of the vaccine is not established in infants below 6 months of age and in geriatric subjects more than 65 years of age.

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

4.6 Interaction with other medicinal products/other forms of interaction

For concomitant or co-administration, use different injection sites and separate syringes.

The concomitant administration of ZyVac®TCV with Measles & Rubella (MR) vaccine and Yellow fever (YF) vaccine has been evaluated in separate clinical trials. There was no immunological interference reported when ZyVac®TCV was administered concomitantly with MR vaccine or YF vaccine (refer section 4.11). There was also no significant safety concern reported when ZyVac®TCV was administered concomitantly with MR vaccine or YF vaccine (refer section 4.9). Therefore, ZyVac®TCV can be concomitantly administered with MR vaccine and YF vaccine. 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.

4.7 Pregnancy and Lactation

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.

4.8 Effect 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.

4.9 Undesirable effects

Clinical Trial Experience

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 (Extension of Phase II/III *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.

Phase IV clinical trial (non-interference study with MR vaccine) : This was a randomized, three-arm, comparative study in which a total of 900 subjects were enrolled; 297 subjects in the test group (TCV+MR), 303 subjects in the reference group 1 (MR/TCV) and 300 subjects in the reference group 2 (TCV/MR). The subjects in test group (TCV+MR) were administered both ZyVac®TCV and MR vaccine concomitantly while the subjects in the reference group were administered study vaccines at an interval of 4 weeks; MR vaccine followed by ZyVac®TCV in the reference group 1 (MR/TCV), and ZyVac®TCV followed by MR vaccine in the reference group 2 (TCV/MR). Overall, the proportion of subjects for whom AEs were reported and total number of AEs reported was lower in the test group as compared to the reference group. The local / injection site AEs have been reported more frequently than systemic AEs in all the 3 study groups. Amongst the solicited local AEs (local AEs reported within 7 days of vaccination) reported after ZyVac®TCV administration, injection site pain (13.1-16.0%) was the most common AE followed by injection site swelling (2.4-4.7%), injection site erythema (2.0-6.0%) and injection site induration (0.0-1.3%). Likewise, amongst the solicited local AEs reported after MR vaccine administration, injection site pain (3.0-8.9%) was the most common AE followed by injection site swelling (0.7-2.3%), injection site erythema (0.7-2.3%) and injection site induration (0.0-0.7%). Amongst the solicited systemic AEs (systemic AEs reported within 14 days of vaccination) reported after concomitant administration of ZyVac®TCV and MR vaccine in the test group (TCV+MR), pyrexia (6.1%) was the most common AE followed by irritability (1.7%) and rhinorrhoea (1.3%). Amongst the solicited systemic AEs reported after ZyVac®TCV administration in the reference groups, pyrexia (4.0-6.7%) was the most common AE followed by irritability (2.0-3.7%). Likewise, amongst the solicited systemic AEs reported after MR vaccine administration in the reference groups, pyrexia (3.7-4.0%) was the most common AE followed by irritability (0.0-2.6%), rhinorrhoea (1.0-1.7%) and cough (0.7-1.0%). The other solicited systemic AEs were reported with <1% incidence in all the study groups. The unsolicited AEs (AEs reported 28 days after vaccination) were reported infrequently as compared to solicited AEs. The most common unsolicited AE was pyrexia (1.3-2.3%) followed by cough (0.7-2.3%), rhinorrhoea (0.7-1.7%) and diarrhoea (0.3-1.0%). The other unsolicited AEs were reported with <1% incidence in all the study groups. One SAE, Febrile convulsion was reported in a subject in the reference group 2 (TCV/MR). The SAE resolved without any sequelae and was considered related to ZyVac®TCV.

Phase IV clinical trial (non-interference study with YF vaccine): This was a randomized, three-arm, comparative study in which a total of 715 healthy subjects were enrolled; 241 subjects in the test group (TCV+YF), 244 subjects in the reference group 1 (TCV) and 230 subjects in the reference group 2 (YF). The subjects in test group (TCV+YF) were administered both ZyVac®TCV and YF vaccine concomitantly; subjects in the reference group 1 (TCV) received only ZyVac®TCV while subjects in the reference group 2 (YF) received only YF vaccine. The subjects were followed up for 4 weeks post-vaccination. A total of 83, 53 and 33 AEs were reported in 24.1%, 17.6% and 12.6% subjects in the test group (TCV+YF), reference group 1 (TCV) and reference group 2 (YF) respectively. The local / injection site AEs were reported more frequently than systemic AEs in all the 3 study groups. The most common AE was injection site pain reported in 16.6%, 13.1% and 7.8% subjects in the test group (TCV+YF), reference group 1 (TCV) and reference group 2 (YF) respectively. Other common AEs included pyrexia reported in 8.7%, 4.9% and 3.0% subjects; injection site erythema reported in 2.1%, 0.8% and 1.7% subjects and injection site swelling reported in 1.2%, 0.8% and 0.4% subjects in the test group (TCV+YF), reference group 1 (TCV) and reference group 2 (YF) respectively. The other local & systemic AEs such as injection site induration, arthralgia, myalgia, asthenia, dizziness, headache, upper respiratory tract infection and bacterial conjunctivitis were less common, reported with an incidence rate of <1%. No SAE was reported in any subject in that clinical trial.

Post-marketing Surveillance (PMS) Study Experience

A total of 3037 subjects of 6 months to 45 years age group were enrolled in the PMS study. Amongst the enrolled subjects, a total of 1537, 499, 502 and 499 subjects were enrolled in the age cohort of 6 months to < 2 years, 2 to < 5 years, 5 to < 18 years and 18 to 45 years respectively. The subjects were followed up till 6 months after administration of ZyVac®TCV. The local AEs reported in that study included injection-site pain (11.7%), injection-site redness (1.9%), injection-site swelling (1.2%) and injection-site induration (0.3%). The systemic AEs reported in that study included fever (5.1%), abnormal crying (0.5%), drowsiness (0.4%), headache (0.3%), irritability (0.2%), malaise (0.2%), myalgia (0.2%), upper respiratory tract infection (0.1%), vomiting (0.1%), cough (0.1%), diarrhoea (0.1%) and loss of appetite (<0.1%). No SAE was reported in any subject in that PMS study.

4.10 Overdose

No case of overdose has been reported.

4.11 Immune Response

The immunogenicity of ZyVac®TCV has been evaluated in the clinical trials and PMS study 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 (Extension of Phase II/III *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 study protocol defined cut-off titre. 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 study protocol defined 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 postvaccination 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 (non-interference study with MR vaccine): In this study, the seroconversion rate for anti-Vi IgG antibodies (proportion of subjects achieving ≥4-fold increase in anti-Vi IgG antibody titre) at 4 weeks after administration of ZyVac®TCV was 90.2%, 75.3% and 89.5% in the test group (TCV+MR), reference group 1 (MR/TCV) and reference group 2 (TCV/MR) respectively; the seroconversion rate for anti-measles IgG antibodies (proportion of subjects with pre-vaccination titre < 9 NTU and post-vaccination titre ≥ 9 NTU) at 4 weeks administration of MR vaccine was 80.4%, 75.2% and 77.7% in the test group (TCV+MR), reference group 1 (MR/TCV) and reference group 2 (TCV/MR) respectively; and the seroconversion rate for anti-rubella IgG antibodies (proportion of subjects with pre-vaccination titre < 10 IU/ml and post-vaccination titre ≥ 10 IU/ml) at 4 weeks administration of MR vaccine was 87.7%, 84.0% and 85.2% in the test group (TCV+MR), reference group 1 (MR/TCV) and reference group 2 (TCV/MR) respectively. Likewise,the seroconversion rate for anti-Vi IgG antibodies at the end of the study was 87.1%, 71.6% and 83.0% in the test group (TCV+MR), reference group 1 (MR/TCV) and reference group 2 (TCV/MR) respectively; the seroconversion rate for anti-measles IgG antibodies at the end of the study was 90.1%, 90.0% and 90.4% in the test group (TCV+MR), reference group 1 (MR/TCV) and reference group 2 (TCV/MR) respectively; and the seroconversion rate for anti-rubella IgG antibodies at the end of the study was 99.2% in both test group (TCV+MR) & reference group 1 (MR/TCV) and it was 98.6% in the reference group 2 (TCV/MR). The seroconversion rate for all 3 antibodies in the test group (TCV+MR) was non-inferior to that reported in the reference groups (MR/TCV and TCV/MR) at 4 weeks after respective vaccination as well as at the end of the study. The anti-Vi IgG antibody titre at 4 weeks after vaccination in the test group (TCV+MR) was higher than that reported in the reference group 1 (MR/TCV) while it was comparable to that reported in the reference group 2 (TCV/MR). The anti-measles and anti-rubella IgG antibody titres at 4 weeks after vaccination in the test group (TCV+MR) were comparable to that reported in the reference groups (MR/TCV and TCV/MR). The anti-Vi and anti-measles IgG antibody titres at the end of the study in the test group (TCV+MR) were comparable to that reported in the reference groups (MR/TCV and TCV/MR) while anti-rubella IgG antibody titre at the end of the study in the test group (TCV+MR) was higher than that reported in the reference groups (MR/TCV and TCV/MR).

Phase IV clinical trial (non-interference study with YF vaccine): In this study, the seroconversion rate for anti-Vi IgG antibodies (proportion of subjects achieving ≥4-fold increase in anti-Vi IgG antibody titre) at 4 weeks after administration of ZyVac®TCV was 94.4% in the test group (TCV+YF) and 95.9% in the reference group 1 (TCV). The seroconversion rate for anti-YF antibodies (proportion of subjects with pre-vaccination PRNT50 titre < 1:10 and post-vaccination PRNT50 titre ≥ 1:10) at 4 weeks after administration of YF vaccine was 79.8% in the test group (TCV+YF) and 81.6% in the reference group 2 (YF). The seroconversion rates for both antibodies in the test group were non-inferior to those observed in the respective reference groups. Likewise, GMTs of anti-Vi IgG and anti-YF antibodies at 4 weeks post-vaccination in the test group were comparable to those reported in the corresponding reference groups.

PMS study: In the PMS study, 300 out of total 3037 enrolled subjects were considered in the immunogenicity subset. Amongst these 300 subjects; 150, 49, 51 and 50 subjects were enrolled from the age cohort of 6 months to < 2 years, 2 to < 5 years, 5 to < 18 years and 18 to 45 years respectively. The seroconversion rate (proportion of subjects achieving ≥4-fold increase in anti-Vi IgG antibody titre) at 4 weeks post-vaccination in the overall immunogenicity subset was 94.7% and the same was 96.0%, 98.0%, 94.1% and 88.0% in the age cohorts of 6 months to < 2 years, 2 to < 5 years, 5 to < 18 years and 18 to 45 years respectively. In the overall immunogenicity subset, the pre-vaccination GMT of anti-Vi IgG antibodies reported was 4.5 EU/ml while the GMT of anti-Vi IgG antibodies reported at 4 weeks post-vaccination was 1787.8 EU/ml. Likewise, the pre-vaccination GMTs of anti-Vi IgG antibodies were 3.6 EU/ml, 3.7 EU/ml, 3.9 EU/ml and 12.4 EU/ml, while the GMTs of anti-Vi IgG antibodies reported at 4 weeks post-vaccination were 1745.7, 1997.4, 1766.7 and 1743.5 in the age cohorts of 6 months to < 2 years, 2 to < 5 years, 5 to < 18 years and 18 to 45 years respectively. There was a significant increase in GMTs at 4 weeks post-vaccination as compared to pre-vaccination GMTs (P<0.0001) in the overall immunogenicity subset as well as in the individual age cohorts.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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.

5.2 Pharmacokinetic Properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical Safety Data

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

2-Phenoxyethanol (Preservative).
Sodium Chloride.

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 expiry date shown on the label.

7. PRESENTATIONS

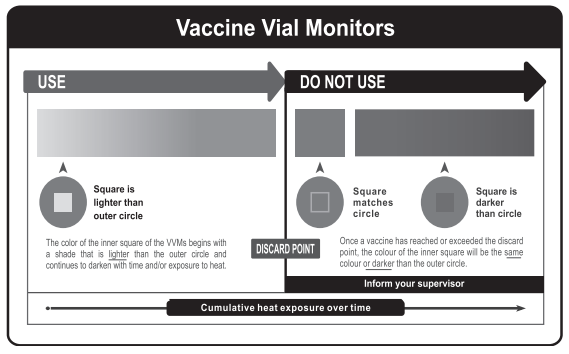
ZyVac®TCV is offered in the 2.5ml Multi dose Vial presentation.

7.1 Handling of Multidose vial

For multidose vials use different syringes each time. Once opened, multi dose vials of ZyVac®TCV 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:

- 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.
- The vaccine vial monitor (VVM) (if attached) has not reached the discard point.

8. The Vaccine Vial Monitor



Vaccine Vial Monitor (VVM30) dot is a part of the label on ZyVac®TCV vials supplied through Zydus Lifesciences Limited. 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. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the vial should be discarded.

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Manufactured & Marketed by:

Zydus Lifesciences Limited

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