2. All prescription medicines should be accompanied by SmPC presented in both pdf and Microsoft word formats.

Please find the SmPC of Adsorbed Tetanus Vaccine BP [BEtt®] (1 & 20 Doses) enclosed in the following pages.

Summary of Product Characteristics (SPC)

Product Name: Adsorbed Tetanus Vaccine BP

**Trade Name : ** BEtt®

Marketing Authorization Holder:
Plot No. 1, Biotech Park, Phase-II, Kolthur Village, Shameerpet,
Medchal-Malkajgiri District, Telangana State, INDIA – 500078

Registered Office:
18/1&3, Azamabad, Hyderabad – 500020, Telangana, India.

1. NAME OF THE MEDICINAL PRODUCT

Name of Medicinal Product: Tetanus Vaccine (Adsorbed) BP

Presentation: 1 dose ampoule and vial of 0.5 ml
10 dose vial of 5 ml
20 dose vial of 10 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 0.5 ml contains:

Tetanus Toxoid	≥ 40 IU
Adsorbed on Aluminium Phosphate ($AlPO_4$)	≥ 1.5 mg
Preservative: Thiomersal B.P	0.01% w/v

3. PHARMACEUTICAL FORM

Suspension for Intramuscular Injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

Tetanus prophylaxis: Tetanus vaccine Adsorbed is indicated for active immunization against tetanus in adults, children and in infants 6 weeks of age or older.
Monovalent Adsorbed Tetanus vaccine should not be used in children less than 7 years of age. In children less than 7 years of age, the use of diphtheria, tetanus and pertussis (DTwP) vaccine combination is recommended unless pertussis vaccine is contraindicated. If pertussis is contraindicated then the use of diphtheria and tetanus toxoids (DT) is recommended.

Post exposure prophylaxis of tetanus: Tetanus infection may not confer immunity; therefore initiation or completion of active immunization is indicated at the time of recovery from this infection.

Neonatal tetanus prevention: If vaccination is required, tetanus toxoid can be used during pregnancy. Teratogenic effects have not been reported with tetanus toxoid in humans. Waiting until the second trimester to administer tetanus vaccine is a reasonable precaution for minimizing any concern regarding the theoretical possibility of adverse reactions.

Tetanus prophylaxis in wound Management: Tetanus toxoid can also be used prophylactically for wound management in persons 7 years of age and older; tetanus and diphtheria toxoid (Td) is preferred, to maintain adequate levels of diphtheria immunity.

4.2 Posology and method of administration:

The vaccine vial should be shaken before use to homogenize the suspension. A sterile needle and a sterile syringe should be used for each injection.

Immunization schedule: The primary immunizing course for unimmunised individuals 7 years of age or older consists of two doses or 0.5ml each 4 to 8 weeks apart followed by a third (reinforcing) dose of 0.5 ml, 6 to 12 months after the second dose. The reinforcing dose is an integral part of primary immunizing course. Individuals who have not completed primary immunization against tetanus, or whose immunization history is unknown or uncertain, should be immunized with a tetanus toxoid-containing product.

TT may be given at the same time as BCG, measles, rubella, mumps, polio (OPV and IPV), hepatitis B, *Haemophilus influenzae* type b, and yellow fever vaccines and vitamin A supplementation.

For neonatal tetanus prevention: Antenatal immunization is recommended for the prevention of neonatal tetanus in the previously unimmunized mother. A previously unimmunized pregnant woman who may deliver her child under non hygienic circumstances and/or surroundings should receive two doses of a tetanus toxoid-containing preparation before delivery (4 to 8 weeks apart), preferably during the last 2 trimesters. Incompletely immunized pregnant women should complete the 3 dose series. Those immunized more than 10 years previously should have a booster dose.

Table - Tetanus toxoid immunization schedule for pregnant women and women of child bearing age

Recommended Schedule	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5
Pregnant women with no previous immunization (or unreliable immunization)	**TT or Td**	**TT or Td**	**TT or Td**	**TT or Td**	**TT or Td**
	As early as possible in first pregnancy	At least 4 weeks later	At least 6 months later	At least 1 year later	At least 1 year later
Pregnant women with 3 childhood DTP doses	**TT or Td**	**TT or Td**	**TT or Td**	**TT or Td**	**TT or Td**
	As early as possible in first pregnancy	At least 4 weeks later	At least 1 year later, or on next pregnancy		
Pregnant women with 4 childhood DTP doses	**TT or Td**	**TT or Td**	**TT or Td**	**TT or Td**	**TT or Td**
	As early as possible in first pregnancy	At least 1 year later, or on next pregnancy			
Supplementary immunization activities in high risk areas (women of childbearing age)	**TT or Td**	**TT or Td**	**TT or Td**	**TT or Td**	**TT or Td**
	During round 1	During round 2, at least 4 weeks after round 1	During round 3, at least 6 months after round 2	At least 1 year later (in next pregnancy)	At least 1 year later (in next pregnancy)

Source: WHO EPI 2006

In tetanus prophylaxis in wound management: The need for active immunization with a tetanus toxoid-containing preparation, with or without passive immunization with TIG (Human) depends on both the condition of the wound and the patient's vaccination history. Tetanus toxoid vaccine in conjunction with tetanus immune globulin is recommended for prophylactic contaminated wound management in un-immunized, uncertain, or incomplete immunization status patients.

A thorough attempt must be made to determine whether a patient has completed primary immunization. Individuals who have completed primary immunization against tetanus, and who sustain wounds which are minor and uncontaminated, should receive a booster dose of a tetanus toxoid-containing preparation only if they have not received tetanus toxoid within the preceding 10 years.

For tetanus prone wounds (e.g. wounds contaminated with dirt, faeces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite), a booster is appropriate if the patient has not received a tetanus toxoid-containing preparation within the preceding 5 years. If a booster dose is given sooner than 10 years as part of wound management, the next routine booster should not be given for 10 years thereafter.

Human Immunodeficiency Virus (HIV) infected persons: HIV-infected persons, both asymptomatic and symptomatic, should be immunized with Adsorbed Tetanus vaccine according to standard schedules.

4.3 Contraindications:

Hypersensitivity to any component of the vaccine, including thiomersal, a mercury derivative, is a contraindication.

The occurrence of any type of neurological symptoms or signs, following administration of this product is a contraindication to further use. Immunization should be deferred during the course of any febrile illness or acute infection. A minor afebrile illness such as a mild upper respiratory infection is not usually reason to defer immunization.

The attending physician should consider risk/benefit ratio at all times. Routine immunization should be deferred during an outbreak of poliomyelitis provided the patient has not sustained an injury that increases the risk of tetanus.

4.4 Special Warnings and Precautions for use:

Warnings: The occurrence of a neurologic or severe hypersensitivity reaction following a previous dose is a contraindication to further use of this product. The administration of booster doses more frequently than recommended may be associated with increased incidence and severity of reactions. Persons who experience Arthus-type hypersensitivity reactions or temperature greater than 39°C after a previous dose of tetanus toxoid usually have very high serum tetanus antitoxin levels and should not be given even emergency doses of tetanus toxoid more frequently than every 10 years, even if they have a wound that is neither clean nor minor.

Adsorbed Tetanus Vaccine should not be given to individuals with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection, unless the potential benefit clearly outweighs the risk of administration.

Patients with impaired immune responsiveness may have a reduced antibody response to active immunization procedures.

Special care should be taken to prevent injection into blood vessel.

PRECAUTIONS

General:

- Prior to administration of any dose of vaccine, the parent, guardian, or adult patient should be asked about the recent health status and immunization history of the patient to be immunized in order to determine the existence of any contraindication to immunization.

- When the patient returns for the next dose in a series, the parent, guardian, or adult patient should be questioned concerning occurrence of any symptom and/or sign of an adverse reaction after the previous dose.

- Before the injection of any biological the physician should take all precautions known for prevention of allergic or any other side reactions. This should include: a review of the patient's history regarding possible sensitivity, the ready availability of epinephrine 1:1000 and other appropriate agents used for control of immediate allergic reactions.

- A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

- Shake vigorously before withdrawing each dose to re-suspend the contents of the vial.

4.5 Interaction with other medicinal products and other forms of interaction:

It is current practice in pediatric vaccination to co-administer different vaccines during the same session with injectable vaccines being administered at separate injection sites.

TT Vaccine can be administered simultaneously at separate sites or in any temporal relationship with other pediatric vaccines if this fits conveniently in the immunization scheme.

As a general rule live attenuated viral or bacterial vaccines should not be administered to patients who are immunosuppressed as a result of large amounts of corticosteroids (more than 10 mg of prednisone or equivalent for more than two weeks).

4.6 Pregnancy and Lactation:

Animal reproductive studies have not been conducted with this product. There is no evidence that Adsorbed Tetanus Vaccine is teratogenic. Adsorbed Tetanus Vaccine should be given to inadequately immunize pregnant women because it affords protection against neonatal tetanus. Waiting until the second trimester is a reasonable precaution to minimize any theoretical concern.

4.7 Effects on ability to drive and use machines:

Not relevant

4.8 Undesirable Effects:

Local reactions, such as erythema, induration, and tenderness, are common after the administration of Tetanus Toxoid. Such local reactions are usually self limited and require no therapy. Nodule, sterile abscess formation, or subcutaneous atrophy may occur at the site of injection. Systemic reactions, such as fever, chills, myalgias, and headaches, also may occur. Arthus type hypersensitivity reactions, or high fever, may occur in persons who have very high serum antitoxin antibodies due to frequent injections of toxoid.

Neurological complications such as convulsions, encephalopathy, and various mono and polyneuropathies, including guillain-barre syndrome, have been reported following administration of preparations containing tetanus antigen.

Urticaria, erythema multiforme or other rash, arthralgias, and more rarely, a severe anaphylactic reaction (i.e., urticaria with swelling of the mouth, difficulty in breathing, hypotension, or shock) have been reported following administration of preparations containing tetanus antigen.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

5.1.1 Site and Mechanism of Action

Tetanus toxoid preparations contain the toxin produced by virulent tetanus bacilli (detoxified growth products of Clostridium tetani). The toxin has been modified by treatment with formaldehyde so that it has lost toxicity but still retains ability to act as antigen and produce active immunity.

5.1.2 Clinical Trials

In a prospective, open-label phase-IV bridging study to elucidate the efficacy and safety profile of monovalent tetanus vaccine adsorbed manufactured by BE LTD (TT), 72 healthy children and adults (excluding pregnant women) between 10-50 years of age were enrolled.

A 0.5mL single dose sterile suspension of BE Tetanus vaccine Adsorbed vaccine was given deep intramuscular injection in deltoid muscle. A total of 3 dose schedule, at a predefined interval of one month between 1st and 2nd dose and 6 months between 2nd and 3rd dose was administered.

All subjects, who completed the study, showed >8 fold rise (a minimum of 4 fold required) in the Geometric Mean Titre values from the baseline values. This shows the study vaccine is highly immunogenic. All volunteers who received the TT Vaccine and completed the protocol did not show any serious adverse reactions. The majority of the volunteers immunized with TT Vaccine reported no or few minor symptoms. The solicited adverse events were transient mild pain (6.9%) and redness (4.2%) at the injection site and mild fever (4.2%) and malaise (4.2%) systemically. No unsolicited adverse events were reported at any time during the study. The vaccine was found to be very safe with a low reactogenicity profile.

In another prospective, open label, phase-IV bridging study to elucidate the efficacy and safety profile of monovalent tetanus toxoid vaccine, 60 pregnant women in the age groups of 18-44 years and between 13-20 weeks of gestation were enrolled.

All subjects, who completed the study, showed >8 fold rise (a minimum of 4 fold required) in the Geometric Mean Titre values from the baseline values. This shows the study vaccine is highly immunogenic. All volunteers who received the TT Vaccine and completed the protocol did not show any serious adverse reactions. The majority of the volunteers immunized with TT Vaccine reported no or few minor symptoms. The solicited adverse events were transient mild pain (6.7%), redness (3.3%) at the injection site and mild fever (1.7%). No unsolicited adverse events were reported at any time during the study. The vaccine was found to be very safe with a low reactogenicity profile.

The Tetanus Vaccine adsorbed, manufactured by BE LTD, was found to be highly immunogenic and safe at the given dose and immunisation schedule studied in both these studies. As expected it generated significant neutralizing antibody responses typically associated with protection against tetanus. The vaccine continues to be safe and highly immunogenic in spite of change over in the manufacturing process.

5.2 Pharmacokinetic properties

- Onset and Duration
- Drug Concentration Levels

5.2.1 Onset and Duration

- Initial Response
  - ➢ Immunization, intramuscular: 10 days after second dose (Menon et al, 1976).
- After the first dose of tetanus toxoid adsorbed, little or no antibody response is observed. Antibody levels increased to effective levels following the second dose (Harrison & Fulginiti, 1980b).
- Duration
  - Multiple Dose
    - ➢ Immunization, intramuscular: 12 years (Peebles et al, 1969).

It is recommended, however, that immunization be completed with reinforcing doses upon starting school and at intervals subsequently of about ten years (Harrison & Fulginiti, 1980b).

5.2.2 Drug Concentration Levels

- Therapeutic Drug Concentration

  - ➢ A randomized, double-blind trial of pasteurized human tetanus immunoglobulin (P-HTIG) (Pasteur Merieux Connaught; Lyon, France) defined tetanus antibody titers greater than 0.1 international units/milliliter (IU/ml) as seroprotective. Patients injected with P- HTIG (500 IU) and placebo (n=24) or tetanus-diphtheria (Td) vaccine (purified diphtheria toxoid, not less than 2 IU/dose or purified tetanus toxoid not less than 20 IU/dose) (n=24) reached antibody titers of 0.1 IU/ml in 1.64 ± 1.62 and 1.47 ± 2.13 days respectively. After 3 days 80% of patients in both groups had antibody titers considered seroprotective. The antibody titer Cmax was 0.313 ± 2.49 IU/ml and Tmax was 4.46 ± 1.92 days for the P-HTIG plus placebo patients compared to Cmax of 15.2 ± 2.42 IU/ml and Tmax of 18.80 ± 1.40 days for the P-HTIG plus Td patients (Forrat et al, 1998).

  - ➢ Circulating toxoid antibody levels of 0.01 units/mL are reported to be therapeutic and meet the international standard set by the World Health Organization (Simonsen et al, 1987; Peebles et al, 1969)

6. Pharmaceutical Particulars:

6.1 List of Excipients:

Aluminium Phosphate ($ALPO_4$)$^{\$}$
Thiomersal B.P (Preservative)
$ Prepared from Solution I ($AlCl_3 6H_2O$ + NaCl) & Solution II (Na_3PO_4 $12H_2O$ + Na_2HPO_4)

6.2 Incompatibilities

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

6.3 Shelf Life:

Three years from the date of manufacture.

6.4 Special precaution for storage:

The vaccine should be stored at a temperature between 2^{o}C to 8^{o}C
Do not freeze.
Discard if the vaccine has been frozen

6.5 Nature and contents of the container

1 dose ampoule and vial of 0.5 ml
10 dose vial of 5 ml
20 dose vial of 10 ml

7. MARKETING AUTHORISATION HOLDER

Plot No. 1, Biotech Park, Phase-II, Kolthur Village, Shameerpet,
Medchal-Malkajgiri District, Telangana State, INDIA - 500078

Registered Office: Biological E. Limited
18/1&3, Azamabad, Hyderabad – 500020, Telangana, INDIA.

8. MARKETING AUTHORISATION NUMBER(S)

India MF-196/2013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04.09.2013 (INDIA) - Regularization

10. DATE OF REVISION OF THE TEXT

August 2023