Unit: Technical Assessment Unit

Public assessment report for biological products

Tetanus toxoid vaccine adsorbed

Administrative information:

Trade name of the medicinal product:	Tetanus toxoid vaccine adsorbed
INN (or common name) of the active substance(s):	Purified Tetanus Toxoid
Manufacturer of the finished product	Serum Institute of India Pvt. Ltd., (SIIPL)),212/2, Hadapsar, Pune – 411028, India
Marketing Authorization holder	Serum Institute of India Pvt. Ltd., (SIIPL)),212/2, Hadapsar, Pune – 411028, India
Applied Indication(s):	Prevention of tetanus in infants, children and adults, especially those liable to be exposed to tetanus infection and persons engaged in outdoor activities.
Pharmaceutical form(s) and strength(s):	Suspension for injection
Route of administration	I.M
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

GMP	Good Manufacturing Practices
MA	Marketing authorization
WHO	World Health Organization
Ph. Eur	European Pharmacopoeia
BP	British Pharmacopoeia
SIIPL	Serum Institute of India Pvt. Ltd
IP	Indian Pharmacopoeia
Lf/mL	Limit of Flocculation per millilitre
GMT	geometric mean titer
PMS	Post-Marketing Surveillance
IgG	immunoglobulin G
SII	Serum Institute of India

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1. General introduction about the product including brief description of the AI, its mode of action and indications:

Tetanus Toxoid Vaccine Adsorbed is used for the prevention of tetanus in infants, children and adults, especially those liable to be exposed to tetanus infection and persons engaged in outdoor activities e.g. gardeners, farm workers and athletes.
Tetanus Toxoid vaccine is also used in the prevention of neonatal tetanus by immunizing women of childbearing age, and also in the prevention of tetanus following injury
The full basic course of immunization against tetanus consists of two primary doses of 0.5 ml at least four weeks apart, followed by the third dose 6-12 months later. To maintain a high level of immunity further 0.5 ml booster doses are recommended at every feasible interval (for adults usually 5 to 10 years).

Quality aspects:

1.2.1 Introduction

As mentioned in the aforementioned section.

1.2.2 Drug Substance (Active ingredient)

- **General information**

Tetanus Toxoid Vaccine Adsorbed is prepared by detoxification of the sterile filtrate of broth cultures of *Clostridium tetani* with formalin and heat. The toxoid is purified by chemical methods and is adsorbed onto aluminum phosphate as adjuvant. Thiomersal is added as a preservative. The vaccine has the appearance of a grayish-white suspension. The vaccine meets the requirements of WHO, EP and IP when tested by the methods outlined in WHO, TRS 980 (2014), EP and IP.

Nomenclature:

- Recommended International Nonproprietary Name (INN); Purified Tetanus Toxoid

Manufacture, process controls and characterization:

Manufacturer:

Serum Institute of India Pvt. Ltd., (SIIPL),212/2, Hadapsar, Pune – 411028, India

- **Description of Manufacturing Process and Process Controls.**
  The tetanus component is purified toxoid manufactured by the chemical detoxification of exotoxin produced by *Clostridium tetani.* The *Clostridium tetani* strain Harvard 49205, giving high level of toxin production is used by SIIPL. Tetanus toxoid is prepared from the toxin produced by the growth of this strain of *Clostridium tetani* in Semi-synthetic medium using fermentation technology.
  Control of Materials.
  A summary of tests, specifications for the raw materials and animal origin used in purification of tetanus toxoid as well as Master / Working Seed System are provided in MA file.
- **Controls of Critical Steps and Intermediates.**
  In-process controls are carried out performed on the Crude Tetanus Toxoid: Description, Lf/mL and Specific toxicity.
- **Process Validation**
- All the important steps and procedures in the manufacturing have been validated and The validation protocols/reports are provided in MA file.
- **Manufacturing Process Development.**
- The preparation of Tetanus Toxoid is based solely on W.H.O. recommended procedures. There are no changes in the constitution of the product.
- **Specification**
- The specification of tetanus toxoid bulk are based on WHO TRS No. 980, British Pharmacopoeia (BP), Indian Pharmacopoeia (IP), European Pharmacopoeia (Ph.Eur.), and selected in-house requirements, ensuring adequate evaluation of the quality, purity, safety, and suitability of the bulk tetanus toxoid for vaccine manufacture.
  - **Analytical Procedures.**

  Details of the test methods are provided.
  - **Reference Standards or Materials.**
    COAs of working / reference standards are used in analysis of purified tetanus toxoid are enclosed.
  - **Container closure system**
    Purified Tetanus Toxoid is stored in a sterile glass bottles (Borosil) of 20 L capacity at 2-8°C. The glass bottles are closed with sterile silicon bungs.
    Stability of drug substance

  Recommended storage condition: 2-8°C.

2.2.3 Drug product:

- **Manufacture of the drug product:**

- Description of manufacturing process and process controls along with manufacturers and responsibilities

Manufacturer:

Serum Institute of India Pvt. Ltd., (SIIPL),212/2, Hadapsar, Pune – 411028, India

- Control of critical steps and intermediates

The manufacturing process is controlled through critical process parameters, in process testing and release testing.

A summary of the critical process parameters and tests for the finished product is provided in the dossier.

- Process validation and / or evaluation.

All critical manufacturing processes are validated.

All critical process steps, critical process parameters, in-process checks are monitored.

Product specification:

- Analytical procedures for excipients are described in Ph. Eur, BP, IP and in-house SOPs and performed accordingly.
- All specifications for the final product are in compliance with WHO and Pharmacopoeial specifications (IP, BP and Ph. Eur.)
- No excipients of human origin are added during formulation of Tetanus Toxoid Vaccine Adsorbed.
- No novel excipients have been used in the formulation of Tetanus Toxoid Vaccine Adsorbed.

- **Reference Standards or Materials.**

  At SIIPL, the Working Standard of Tetanus Toxoid which is used to test Purified Tetanus Toxoid is calibrated using International Reference Standard.

  Container closure system.

  Primary packaging consists of a 1 mL one-point-cut (OPC) Type I glass ampoule intended for a single-dose presentation.

  The selected Type I glass container is suitable for sterile injectable products and provides adequate protection of vaccine quality during storage and use.

  Stability of the drug product.

  2°C to 8°C for 36 months.

1. **Non –clinical aspect:**

The company justified for not submitting non clinical studies (module IV) as TT vaccine manufactured by Serum Institute of India Ltd. Was licensed in 1972, by the Indian Drug Regulatory Authorities is now a WHO- pre-qualified vaccine and a total quantity of 61,037,439 dose of TT vaccine alone have been used in various countries from 1999 to 2007

The safety of TT Vaccine is established by studies such as "specific toxicity" and "abnormal toxicity" which are conducted on each and every batch of the TT vaccine before being released into the market.

The toxicity studies are adequate to identify and characterize the potential toxic effects of a vaccine in order to conclude that it is reasonably safe.

The safety tests done on animals on each batch of vaccine manufactured and extensive human use of this vaccine which has proven the safety, the animal toxicity data is not applicable.

2. **Clinical aspect:**

➢ **Clinical Overview:**

Tetanus Toxoid Vaccine Adsorbed manufactured by Serum Institute of India Pvt. Ltd is used for getting protection against Tetanus. This contains tetanus toxoid ≥ 5 flocculation units (Lf) i.e. ≥ 40 IU. It also has Aluminium phosphate and preservative Thiomersal (0.01%).
Clinical development program included one phase IV post marketing surveillance study to assess immunogenicity and reactogenicity of Tetanus Toxoid (Adsorbed) manufactured by Serum Institute of India Ltd., Pune (India) in pregnant women at 28 - 36 weeks of gestation **in addition to** Post-Marketing Surveillance (PMS) study to assess the safety of Tetanus Toxoid manufactured by Serum Institute of India Ltd., Pune in India.

Study (PMS/TT/2005)

The submitted phase IV study (PMS/TT/2005) was conducted to evaluate safety and efficacy of Tetanus Toxoid (Adsorbed) in special population group **(pregnant women).** Safety and Efficacy of this toxoid was assessed in **300 pregnant women (at 28-36 weeks of gestation)** by monitoring and follow up of women for adverse events**.** The dose, dosage schedule used in this study was as per **WHO recommendations.** All women received two doses of SIIPL's Tetanus Toxoid 0.5 mL 4 weeks apart.

➢ **Clinical efficacy:**

- There was significant increase in Anti-tetanus IgG Antibody titers when serum titers at 6-8 weeks post vaccination were tested and compared with pre-vaccination titers. Analysis of data revealed that there were **21 women who were seronegative** (Anti tetanus IgG titer < 0.01 IU/ml) at pre-vaccination. **All these women developed protective antibody titer at post vaccination (2.2300 IU/ml)**. **This increase in titer is statistically and clinically significant**.

- 271 women were seropositive (Antitetanus IgG titer > 0.01 IU/ml) at pre-vaccination Post vaccination geometric mean titer in this group was 4.3261 IU/ml. This increase in titers is statistically as well as clinically significant.

- When results of all 300 women were considered, prevaccination GMT was 0.3071 IU/ml which increased to 4.1305 IU/ml. **this increase was statistically and clinically significant**. From results it can be inferred that all the women attained protective titers at peripartum period, it can also be concluded that due to placental transfer of protective antibodies, the neonates of these pregnant women can also get protection against tetanus.

➢ **Clinical immunogenicity:**

Immunogenicity was assessed as apart of efficacy.

➢ **Clinical safety:**

The safety of **Tetanus Toxoid** manufactured by **Serum Institute of India Ltd.** was evaluated in a post-marketing surveillance (PMS) program involving **1,385 vaccinated subjects** in India. Overall, the vaccine demonstrated a favorable safety profile and was well tolerated in both children and adults.
In the clinical safety study conducted in pregnant women (n = 300), **16 subjects (5.3%)** experienced one or more local adverse events, while **13 subjects (4.3%)** reported one or more systemic adverse events. The most frequently reported local reactions were **redness (3.6%)**, **pain (3.0%)**, and **swelling (3.0%)** at the injection site. The most common systemic adverse events were **rash (2.6%)**, **pruritus (1.6%)**, **dizziness (1.0%)**, and **fever (0.6%)**.
All reported adverse events were **mild, transient, and resolved spontaneously or with supportive treatment**. No neurological adverse events, immediate hypersensitivity reactions, or vaccine-related serious adverse events were reported during the study. The incidence and severity of adverse events were consistent with the established safety profile of tetanus toxoid vaccines reported in the literature.
Overall, the available clinical and post-marketing safety data indicate that **Tetanus Toxoid manufactured by Serum Institute of India Ltd. is safe and well tolerated**, with no new or unexpected safety concerns identified.

➢ **Benefit-Risk analysis:**

The tetanus toxoid (adsorbed) vaccine demonstrated immunogenicity in pregnant women, with all participants achieving protective antibody levels after the two-dose vaccination schedule. The vaccine was well tolerated, with only mild and expected local and systemic adverse reactions and no serious vaccine-related safety concerns. Overall, the clinical

benefits of preventing maternal and neonatal tetanus outweigh the identified risks, resulting in a favorable benefit-risk profile.

- **Overall Conclusion:**

The clinical study demonstrated that tetanus toxoid (adsorbed) vaccine is immunogenic, inducing protective anti-tetanus antibody levels in all vaccinated pregnant women. The vaccine was generally well tolerated, with an acceptable safety profile and no serious vaccine-related adverse events. These findings support the continued use of tetanus toxoid vaccine for active immunization during pregnancy to protect both mothers and newborns against tetanus.
Based on the available clinical evidence, tetanus toxoid (adsorbed) vaccine demonstrates a favorable efficacy and safety profile for active immunization of pregnant women to protect both mothers and newborns against tetanus

General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.