Unit: Technical Assessment Unit

Public assessment report for biological products

Diphtheria, Tetanus, Pertussis, Hepatitis B and Haemophilus influenza type b conjugate

Administrative information:

Trade name of the medicinal product:	Diphtheria, Tetanus, Pertussis, Hepatitis B and Haemophilus influenza type b conjugate vaccine adsorbed-VACSERA
INN (or common name) of the active substance(s):	N.A.
Manufacturer of the finished product	The Egyptian Company for Production of vaccines, sera and drugs-building 60/building 1 - 51 wezaret el Zeraa St.-Agouza-Giza,Egypt. - EGYPT
Marketing Authorization holder	The holding company for biological products and vaccines (VACSERA)-building (60)/ building (1)-51 wezarat el zeraa street - agouza - Giza-Egypt - EGYPT
Applied Indication(s):	DTP-HB-Hib Vaccine Adsorbed is indicated for the active immunization of infants, at or above the age of 6 weeks against Diphtheria, tetanus, pertussis, Hepatitis B and Haemophilus Influenzae type b. In young children the EPI recommends as many antigens as possible to be administered at a single visit. DTP-HB-Hib Vaccine should NOT be used for the birth dose. In countries where pertussis is of particular danger to young infants, the combination vaccine should be started as soon as possible with the first dose given as early as 6 weeks, and two subsequent doses given at 4-week intervals. DTP-HB-Hib Vaccine can be given safely and effectively at the same time as BCG, measles, polio (OPV or IPV), and yellow fever vaccines and vitamin A supplementation. If DTP-HB-Hib Vaccine is given at the same time as other vaccines, it should be administered at a separate

	site. It should not be mixed in the vial or syringe with any other vaccine unless it is licensed for use as a combined product.
Pharmaceutical form(s) and strength(s):	Suspension for IM injection Each dose of 0.5 ml contains: Diphtheria toxoid ≥ 30 I.U Tetanus toxoid ≥ 40 I.U B. Pertussis (whole cell) ≥ 4 I.U HBsAg (rDNA) ≥10 mcg Purified capsular Hib Polysaccharide (PRP) conjugated to Tetanus Toxoid (carrier protein) 10mcg **Adsorbed on Aluminium Phosphate, Al+++ ≤1.25 mg Thiomersal 0.005%
Route of administration	I.M
Type of registration (EMA/FDA – Local)	Local

List of abbreviations

MA	Marketing Authorization
IPC	In process control
GMP	Good manufacturing practice
USP	United states pharmacopeia
BP	British pharmacopeia
CPP	Critical process parameter
SOPs	Standard operating procedures
D	Diphtheria
DTPw-HB-Hib	Diphtheria, Tetanus, Pertussis (whole cell), Hepatitis B Haemophilus influenzae type ‘b’ vaccine
HB	Hepatitis B
Hib	Haemophilus influenzae type ‘b’
IgG	Immunoglobulin G
P	Pertussis
PRP-T	Polyribosyl ribitol Phosphate — Tetanus Conjugate Vaccine
PSURs	periodic safety update reports
Pw	whole cell Pertussis
SAE	Serious Adverse Event
SIIL	Serum Institute of India Ltd
T	Tetanus

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

- The DTP-HB-Hib (Pentavalent) vaccine, adsorbed, is indicated for the active immunization of infants from six weeks of age onwards against diphtheria, tetanus, pertussis (whooping cough), hepatitis B, and *Haemophilus influenzae* type b infections.
- In accordance with the WHO Expanded Programme on Immunization (EPI) recommendations, administration of multiple antigens at a single visit is encouraged to maximize coverage and improve compliance.
- It is noted that this combined vaccine is **not intended for administration as the hepatitis B birth dose**.

- The Pentavalent vaccine manufactured by SII received **WHO Prequalification in September 2010** and was subsequently **registered by the Egyptian Drug Authority (EDA) in 2018**.

- In August 2019, the Serum Institute of India (SII) and VACSERA entered into a technology transfer agreement, which authorized VACSERA to conduct the filling and packaging of the Pentavalent vaccine. These operations are performed at VACSERA's vaccine production facility (Building 60), using ready-to-fill bulk material supplied by SII.

2. Quality aspects:

2.2.1 Introduction

-As mentioned above in the general introduction.

2.2.2 Drug Substance (Active ingredient)

The Drug Substance (DS) part was not reassessed, as it had previously undergone full evaluation and approval during the Marketing Authorization (MA) of the SII Pentavalent vaccine.

2.2.3 Drug product:

- **Description and Composition of the Drug Product**

-The DTP-HB-Hib (Pentavalent) vaccine, adsorbed, is supplied as a homogeneous liquid suspension for intramuscular injection.
It consists of purified diphtheria toxoid, purified tetanus toxoid, inactivated whole-cell pertussis organisms, purified recombinant hepatitis B surface antigen (HBsAg), and *Haemophilus influenzae* type b polysaccharide conjugated to tetanus toxoid (PRP-T). Thiomersal is added as a preservative.

****Presentations (DTP-HB-Hib adsorbed vaccine):** Ten-doses Vials (5 mL – 10 doses): Box of 25 vials.

- **Pharmaceutical Development including brief description on components of drug product**

1. Drug Substance

The drug substances used are Pool of purified Diphtheria Toxoid, Pool of purified Tetanus Toxoid, Pertussis bulk vaccine, Hepatitis B surface antigen (HBsAg) aqueous protein and Haemophilus influenzae type B conjugate bulk vaccine manufactured and supplied by SIIL.

All the provided data are satisfactory & aligned with international guidelines

2. Excipients

- Aluminium phosphate (adjuvant), Thiomersal (Preservative), Sodium chloride and TRIS buffer as inactive ingredient.

- **Formulation Development**

- SIIL, the bulk supplier, has a valid manufacturing license and is WHO pre- qualified to manufacture DTP - HB group of vaccines. Vacsera receives the bulk ready to fill from SII, So manufacturing
- process development is fully described in SII CTD DS part.

- **Overages**

- As Vacsera receives the bulk ready-to-fill from SII, **no overages are added by Vacsera.**

- SII specifies a 25% overage for the Hepatitis B component during bulk manufacture.

- **Physicochemical and Biological Properties**

- The physicochemical, immunochemical, and biological characterization performed on the Diphtheria, Tetanus, Pertussis, Hepatitis B and Haemophilus influenza type b conjugate vaccine finished product to verify the quality characteristics.
- The physicochemical, immunochemical, and biological characterization include appearance, PH, osmolarity, storage conditions, identification and potency of diphtheria toxoid, tetanus toxoid, pertussis component, hepatitis B component, Hib component.

- **Manufacturing Process Development**

- As Vacsera receives the bulk ready-to-fill from SII, manufacturing process development is fully described in Previously submitted CTD of SERUM.

- **Container closure system and their compatibility**

- The vaccine is filled and packed by VACSERA using container closure components identical in specification and source to those used by SII. Vacsera uses the primary packaging material of the same specifications as that of SII. The rubber closure is from the same supplier that provides stoppers for SII.
- Specification sheets and Extractables/Leachables studies performed by SII were submitted.

- **Microbiological Attributes**

- The DTP-HB-Hib vaccine adsorbed is a sterile product. Stability study is completed up to 30 months with no sterility test failure. Also, In-use stability study has been completed successfully for 28-days following the WHO suggestion of 28-days stability after opening.

- **Compatibility**

- Container closure components and excipients are widely used in vaccines, with no adverse compatibility issues observed. Stability data support compatibility with packaging materials.
- The Penta vaccine filled by VACSERA uses the same container closure system and supplier as Serum Institute of India

- **Manufacture of the drug product**

- **Description of manufacturing process and process controls along with manufacturers and responsibilities.**
- **Manufacturer(s):**

- **The bulk is manufactured at** Serum Institute of India Pvt. Ltd. 212/2, Hadapsar - 411028, Pune Maharashtra, India

- **The finished product is filled and released at** The Egyptian Company for Production of vaccines and drugs.51 wezaret el zeraa St, Agouza, Giza, Egypt.

- **Manufacturing process:**

- As VACSERA receives the bulk ready-to-fill from SII the manufacturing process till filling step are full provided and assessed previously in SERUM file.
- Narrative description & flow diagram of the filling and packaging process of DTP-HB-Hib vaccine adsorbed in VACSERA is well illustrated in the MA file.
- The steps are controlled through various IPCs.
- The comparability between Penta vaccine filling process at SERUM manufacturing site and VACSERA manufacturing site identifying the critical points and relevant changes for fill and packaging process is well described in the MA file.

- **Control of critical steps and intermediates**

- As VACSERA receives the bulk ready-to-fill from SII all critical steps with its CPP and in-process control for manufacturing process of bulk are full provided and assessed previously in SERUM file.

- **Process validation and / or evaluation**

- The applicant submits detailed validation protocol for fill-finished process with CPP for each step and all CPP are consistent in all 3 batches i.e. the process is consistent all over process of 3 batches.
- Any deviation or defect are mentioned and justified.
-The process was performed aseptically and comply with GMP.

- **Product specification**

- The analytical tests provided for testing the final product ensures its purity, strength and quality.
- The presented data complies with the relevant WHO TRS, however the potency test have received a complete waiver for the potency testing of Hepatitis B component by in vivo method. Moreover, bacterial endotoxin in Pentavalent vaccine was deleted as per SII technical advice.
-All analytical procedures of DTPHB-Hib Vaccine, adsorbed for all tests either done by VACSERA or by SII and for sterility test done by MUP are provided with its validation reports.
-Process validation batches were tests in both VACSERA and SERUM QC labs and results were compared and found comparable and fulfilling all the acceptance criteria**.**
-No specific impurities of DTP-HB-Hib vaccine are measured in the final product. These are measured by SII in the drug substance level.
- All specifications for the final product are in compliance with WHO and Pharmacopeial specifications (IP).
-The justification of In-house Specifications was verified through method validation.
- The data provided was sufficient to ensure the consistency of production of the drug product.
- The excipients are compendial, and complies with their relevant monographs.
- No novel excipients or excipient of animal or human origin are added.

- **Reference Standards or Materials**

- List of references were provided in the MA file with their type and storage condition.

- COAs for all reference standard are provided.

➢ **Container closure system**

-VACSERA utilizes primary packaging materials with the same specifications as those used by SII. Additionally, the rubber closure is sourced from the same supplier that provides stoppers to SII.
-The Extractables and Leachable (E&L) study performed by SII was provided
- Primary container: each vial **made of clear transparent tubular glass (Type 1) closed with grey bromo Butyl Rubber plunges(v-50) symmetrical with clean and smooth surface and violet flip off seal.**

➢ **Stability of the drug product**

Based on available stability data

- **Approved Shelf Life:**

  - 30 months

- **Approved Storage Conditions:**

- Store at refrigerator (2 - 8℃)
- Transportation should also be at (2 - 8℃).
- Don't freeze
- The liquid vaccine vial should be shaken before use to homogenize the suspension.
- Once opened multi dose vial should be kept between (2℃ - 8℃) and multidose vials of Diphtheria, Tetanus, Pertussis, Hepatitis B and Haemophilus influenza type b conjugate vaccine absorbed from which one or more doses of vaccine have been removed during an immunization session may be used in subsequent immunization session for up to a maximum of 28 days.

3. Non –clinical aspect

➢ **Pentavalent vaccine (DTwP-HepB-Hib-Conjugate Vaccine)** is a liquid suspension, with five individual vaccines conjugated into one which contains: inactivated purified diphtheria **(D)** and tetanus **(T)** toxoids, whole-cell pertussis bacteria (**WP**), recombinant hepatitis B surface antigen (**HBsAg**) and highly purified, non-infectious Haemophilus Influenzae Type b **(Hib)** capsular polysaccharide chemically conjugated to tetanus toxoid (as carrier protein) to enhance its immunogenicity, particularly in infants whose immune systems do not respond robustly to polysaccharides alone. It is indicated for the active immunization of infants, at or above the age of 6 weeks, against diphtheria, tetanus, whooping cough, Hepatitis B and Haemophilus Influenzae type b infections. It is WHO prequalified for sale to United Nations agencies on 26/5/2010.

➢ **Pharmacology (PD, safety pharmacology & PK studies):** Not applicable. All the antigens in the pentavalent vaccine have been previously evaluated separately in clinical trials by SIIPL. These vaccines were already licensed and WHO prequalified. Furthermore, such studies are not applicable for SIIPL DTwP-HepB-Hib vaccine since its administration does not employ a new delivery system and

does not contain novel adjuvants or excipients. This is consistent with the international guidelines for vaccines (WHO TRS 927, 2005; WHO TRS 987, 2014).

- **Toxicology:** Two single dose toxicity studies and three repeat-dose toxicity studies were performed on pentavalent-Vaccine in rats and rabbits, and the local tolerance and injection-site evaluations were conducted across all studies. There is no safety concerns observed except irritation at the site of injection, which reflects inflammatory responses. The result from single dose toxicity studies indicates that LD50 of the study vaccines was found to be more than 1 ml, which is 2X the human dose. Regarding Genotoxicity, Carcinogenicity, Reproductive and Developmental Toxicity, no studies have been conducted. This is consistent with the guidelines for vaccines (WHO TRS 927, 2005 and WHO, TRS 987, 2014).

- **Overall conclusion:** Based on the toxicology data, pentavalent vaccine has an acceptable safety and tolerability profile. Its safety was found to be comparable to that of the reference marketed vaccine, Easy Five.

4. Clinical aspect:

The clinical development program is mainly based on the phase III comparative clinical trial to assess the immunogenicity and reactogenicity of the DTPw-HB-Hib (PRP-T) vaccine (adsorbed) by SIIL, proposed for the active immunization of infants, at or above the age of 6 weeks against Diphtheria, tetanus, whooping cough, Hepatitis B and Haemophilus Influenzae type b infections against DTPw-HB-Hib Vaccine (Panacea Biotec Ltd.) (reference product).

- **<u>Clinical Efficacy: (Immunogenicity)</u>**

Immunogenicity of the vaccines was determined on the basis of IgG antibody titres against each of five components of vaccine. (D, T, P, HBs and Polyribosyl Ribitol Phosphate of Hib). Per protocol population was considered for immunogenicity analysis.

- In SIIL group, seroprotection was 100% for Diphtheria, Tetanus, Hepatitis B and Haemophilus influenzae type ‘b’. For pertussis, percentage positive vaccine response was 95.3 %.
- In Panacea group, there was 100% seroprotection for Diphtheria, Tetanus, Haemophilus influenzae type ‘b’ and Hepatitis B. For pertussis, positive vaccine response was 96.5%.
- Non-inferiority of SIIL vaccine to Panacea vaccine was concluded for all five components including long-term protection, wherever applicable.

Conclusion: This new fully liquid pentavalent vaccine DTPw-HB-Hib manufactured by Serum Institute of India Ltd., Pune has proven high immunogenicity where all (100%) infants available for immunogenicity assessment developed protective antibody titres to diphtheria, tetanus, hepatitis B and Hib disease. The vaccine response to Pertussis in either group was

more than 90%. Non-inferiority, with respect to percentage sero-protection/vaccine response, to the comparator vaccine of Panacea Biotec was demonstrated.

- **Clinical Safety:**

  The vaccinees were observed for local, systemic and neurological adverse events, and rare cases of anaphylaxis after each dose of vaccine to assess reactogenicity.

  - **Local Adverse Events:** Majority of local adverse events were mild in intensity and resolved with or without concomitant medications such as analgesics and by application of cold compresses at the injection site.
  - **Systemic Adverse Events:** were comparable between the two vaccination groups and all were mild or moderate in nature and resolved with or without concomitant medications, without any complications. Most common was Fever.
  - No Serious Adverse Event (SAE) occurred in any of the groups. There was no case of anaphylaxis or any immediate allergic reaction in any of the groups. None of the infants dropped out of the study due to adverse events to vaccine.
  - Also, during the period covered by the PSURs (2018-2021), no withdrawal or suspension of marketing authorization, or any restrictions on distribution at any of the places were reported where the vaccine is marketed. No clinical trials being carried out for the evaluation of the vaccine were suspended or stopped for safety reason. No dosage or formulation modifications were suggested in the vaccine for safety reason.

Conclusion: DTP-HB-Hib vaccine of SIIL is safe and well tolerated in infants and can be used effectively for prevention of tetanus, diphtheria, pertussis, hepatitis-B and Haemophilus influenzae type b infections in the target population.

- **Overall Conclusion:**

  DTPw-HB-Hib (PRP-T) vaccine manufactured by Serum Institute of India Ltd. is safe, immunogenic and comparable to DTPw-HB-Hib (CRM_{197}) vaccine of panacea Biotech.

5. General Conclusion and Recommendations if any:

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