Unit: Technical Assessment Unit

Public assessment report for biological products

(Hepatitis B Vaccine (rDNA) (pediatric) 1 dose & 10 doses)

Administrative information:

Trade name of the medicinal product:	Hepatitis B Vaccine (rDNA) (pediatric) 1 dose & 10 doses
INN (or common name) of the active substance(s):	**Each dose of 0.5ml contains:** ▪ Purified Hepatitis B Surface Antigen 10 µg. ▪ Preservative Thiomersal 0.005 %. ▪ Produced in hansenula polmorph (yeast) Adsorbed on aluminum hydroxide (AL +++) 0.25 mg to 0.40 mg.
Manufacturer of the finished product	Serum Institute of India Pvt. Ltd., 212/2, Hadapsar, Pune 411028 Maharashtra State - India.
Marketing Authorization holder	Serum Institute of India Pvt. Ltd., 212/2, Hadapsar, Pune 411028 Maharashtra State - India.
Applied Indication(s):	Indicated for immunization against Hepatitis B.
Pharmaceutical form(s) and strength(s):	Suspension for intramuscular injection
Route of administration	Intramuscular Injection (IM)
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

1. **AI** – Active Ingredient AI – Active Ingredient
2. **HBsAg** – Hepatitis B surface Antigen
3. **rDNA** – Recombinant Deoxyribonucleic Acid
4. **MA file** – Marketing Authorization file
5. **Ph. Eur.** – European Pharmacopoeia
6. **BP** – British Pharmacopoeia
7. **IP** – Indian Pharmacopoeia
8. **WHO TRS** – World Health Organization Technical Report Series
9. **IHRS** – In-House Reference Standard
10. **MWCB** – Master Working Cell Bank

11. **SOP** – Standard Operating Procedure
12. **SIIPL** – Serum Institute of India Pvt. Ltd.
13. **S protein** – Small surface protein (Hepatitis B virus)
14. **RH** – Relative Humidity
15. **kDa** – Kilodalton
16. **µg** – Microgram
17. **mg** – Milligram
18. **mL** – Milliliter
19. **L** – Liter
20. **°C** – Degrees Celsius
21. **Al^{3+}** – Trivalent aluminium ion
22. **rDNA** – Recombinant DNA
23. **HBV** – Hepatitis B virus
24. **HBsAg** – Hepatitis B surface antigen
25. **ED50** – median effective dose of vaccine
26. **GMT** – Geometric Mean Titres

Table of contents

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

Hepatitis B Vaccine (rDNA), Suspension for Injection, is a non-infectious recombinant vaccine indicated for immunization against Hepatitis B. The vaccine contains the purified

Hepatitis B surface antigen (HBsAg) produced in Hansenula polymorpha yeast cells genetically engineered to express the viral surface antigen gene. The antigen is subsequently purified and adsorbed onto aluminium hydroxide as an adjuvant. Thiomersal is included as a preservative.

The vaccine is supplied as a whitish, turbid aqueous suspension of HBsAg adsorbed onto aluminum hydroxide, which may settle on standing and should be shaken before use. It is stored at 2–8°C and must not be frozen. The product is available as single-dose paediatric vials and ten dose paediatric vial.

For the paediatric presentation, each 0.5 mL dose contains:

- 10 µg purified Hepatitis B surface antigen.
- 0.005% Thiomersal.
- Aluminium hydroxide (0.25–0.40 mg).

2. Quality aspects:

2.2.1 Introduction.

Mentioned above in the general information.

2.2.2 Drug Substance (Active ingredient):

Purified Hepatitis B Surface Antigen 10 µg.

- **General information**

The hepatitis B virus surface antigen (HBsAg) is produced in the recombinant yeast Hansenula polymorpha by successive steps of fermentation, harvest, purification and maturation. The antigen is existing as a particle composed of proteins and lipids (60% proteins and 40% lipids by weight). The protein component is the hepatitis B virus small surface protein (S protein) which is a membrane protein comprised of 226 amino acids with a molecular weight of 25.348 kDa. The lipid component consists of yeast lipids mainly phospholipids. [1,2,3,4]. The 15 N-terminal amino acids determined by Edman degradation sequence analysis are: Met-Glu-Asn-Ile-Thr-Ser-Gly-Phe-Leu-Gly-Pro-Leu-Leu-Val-Leu.

- **International Name (Latin):** Vaccinum hepatitidis B (ADNr).
- **European Pharmacopoeia:** Hepatitis B Vaccine (rDNA); (bulk = purified HBsAg protein).
- **Indian Pharmacopoeia:** Hepatitis B Vaccine (rDNA); (bulk = purified antigen).

- **Manufacture, process controls and characterization:**

  The active substances (Purified Hepatitis B Surface Antigen) are manufactured by Serum Institute of India Pvt. Ltd., 212/2 Hadapsar, Pune- 411 0028, India.

  Manufacturing process:

  The process includes: (1) Fermentation, (2) harvest and (3) Purification. Full details are available in the MA file.

- **Characterization.**

The Hepatitis B surface antigen (HBsAg) drug substance is a glycoprotein-based macromolecule associated with lipids. A comprehensive analytical program confirmed its identity, structure, and physicochemical properties using multiple orthogonal methods.

- **Specification**

  The tests performed on the drug substance comply with the requirements of ICH Q6B guideline, IP, Ph. Eur, and In-house practices.

  Detailed SOPs are provided with their validation report. Full specification data are available in the MA file.

- **Reference Standards or Materials, (HBsAg Aqueous Bulk, SIIPL).**

In- house reference standard (IHRS) of HBsAg (Aqueous) Bulk currently is purified HBsAg (aqueous) bulk.

- The Storage Condition of current n- house reference standard (IHRS) is 2°C -8°C.

Full details are available in the MA file.

- **Container closure system**

HBsAg bulk is stored in 10 L sterile Schott Duran Borosilicate Glass bottles with pouring ring and screw cap closures. The bulk is sterile filtered into the sterile Schott Duran Borosilicate Glass bottle. After filtration is complete bottle is closed with sterile cap and 'Parafilm' is wrapped on the bottle cap. Bottle containing HBsAg Bulk is stored in cold room at +2°C to +8°C. Full details are available in the MA file.

- **Stability of drug substance**

- Hepatitis-B Surface Antigen (Aqueous) Bulk, shelf life is 36 months.

- Real time stability study storage temperature: +2°C to +8 °C.
- Accelerated stability study storage temperature: + 25°C ± 2 °C / 60 % RH ± 5% RH.

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**
  Mentioned above in the general introduction.
- **Pharmaceutical Development including brief description on Components of drug product.**
  - **Formulation development:** Recombinant Hepatitis B surface antigen (HBsAg) expressed in Hansenula polymorpha yeast and formulated as an aqueous suspension for injection.
  - **Physicochemical and biological properties:** HBsAg antigen maintains required viability and quality; annual testing confirmed suitability until viability decline detected after 2 years for MWCB-02.
  - **Manufacturing process development:** Process originated at Rhein Biotech, transferred to TVL, then acquired by SIIPL with further cell bank development, scale-up, and validation of production batches.
  - **Container closure system:** Filled in Type I glass vials or snap-off ampoules, sealed with Bromo butyl rubber stoppers and aluminum seals; stability and integrity confirmed through studies.
  - **Microbiological attributes:** Sterile product; container integrity demonstrated via stability and microbial challenge tests, with no sterility failures in over 15 years of market use.
  - **Compatibility:** Common vaccine excipients and closures; stability studies in upright and inverted positions show no adverse interaction with the stopper or container.

- **Manufacture of the drug product:**
  - **Description of manufacturing process and process controls along with manufacturers and responsibilities.**
    The vaccine is manufactured, packaged, tested, and released by Serum Institute of India Pvt. Ltd., 212/2, Hadapsar, Pune 411028 Maharashtra State - India.
    Full details and description of the process are provided in the MA file. Each step of the process is controlled through defined in-process controls (IPCs).

- **Control of critical steps and intermediates**

  Controls of Critical Steps and Intermediates including tests and acceptance criteria are provided and they ensure that the process is controlled.
- **Process validation and / or evaluation.**

  Process Validation and Evaluation of Hepatitis B Vaccine (rDNA) were performed on three consecutive batches. All parameters and final bulk results met the acceptance criteria. Full Protocol and Reports are available in the MA file.

- **Product specification:**

  Release specifications for the Finished Product comply with Ph Eur, BP, IP, and WHO, TRS 978. Detailed SOPs. Full specifications are available in MA file.

  No excipient of human or animal origin are added during formulation of the Drug Product. No novel excipient has been used in the formulation of Drug Product.

- **Reference Standards or Materials.**

  An Internal reference standard is used for testing of the Hepatitis B vaccine (rDNA). Analysis of internal reference standard is included in the MA file.

- **Container closure system.**

  The Hepatitis B vaccine (rDNA)vaccine is filled in clear tubular vial type I glass vial, closed with grey Bromo butyl rubber stopper and sealed with aluminium seal having PMS blue colored flip-off cap. Full specifications are available in the MA file.

- **Stability of the drug product.**
  - Shelf life (unopened) is 3 years.
  - Unopened vials: Store at temperature 2 - 8°C.
  - Opened vials: Store at temperature 2 - 8°C for 28 days.
  - Don't freeze, discard if vaccine has been frozen.

3. Non –clinical aspect:

Hepatitis B Vaccine (rDNA) is a non-infectious recombinant DNA Hepatitis B vaccine. It contains purified surface antigen of the virus obtained by culturing genetically engineered Hansenula polymorpha yeast cells having the surface antigen gene of the Hepatitis B virus.

Hepatitis B vaccine (recombinant) stimulates active immunity to hepatitis B virus (HBV) infection. Hepatitis B surface antigen (HBsAg) s it promotes the production of antibody to HBsAg (anti-HBs) which neutralizes the HBV so that its infective or pathogenic properties are inhibited.

The candidate product, being a vaccine and considering its well-established efficacy and safety profile in clinical practice over many years, only selective nonclinical studies were conducted.

The main objective of non-clinical toxicity studies was to assess acute and subacute toxicity of this product. Accordingly, one single toxicity study (on Swiss mice) and two subacute toxicity studies (on Swiss mice and albino rats) were conducted.

Single dose toxicity study was conducted on albino Swiss mice and animals were observed for 7 days after injecting the vaccine. Control group received solution devoid of HBsAg protein. There was no detectable sign of toxicity and there was no death.

In both subacute studies, the vaccine was administered in low, medium and high dose based on the median effective dose of vaccine (ED50). Thus, low dose was 3 times ED50, medium dose was 6 times ED50 and high dose was 12 times ED50. There were no major abnormalities in any of the parameters and it is concluded that vaccine is safe for administration.

The results of the above toxicity studies demonstrated that the vaccine was found to be safe and was well tolerated. There was no death in any of the studies and there was no abnormality that could be specifically related to the dose of the vaccine or gender of animal.

4. Clinical aspect:

Clinical Overview

The recombinant Hepatitis B vaccine (Genevac-B) has been developed by Serum Institute of India Ltd. for the prevention of Hepatitis B infection. The vaccine is administered via the intramuscular route in a three-dose schedule, either at 0, 1, and 2 months or 0, 1, and 6 months. Its clinical development program is extensive, comprising 17 studies, including controlled and uncontrolled trials, as well as dose- and schedule-comparison studies and post-marketing evaluations. These studies encompassed a wide range of populations, including

infants, children, adolescents, adults, and special populations such as patients with chronic renal failure. The clinical program primarily focused on evaluating immunogenicity (efficacy) and safety (reactogenicity). Given the well-established nature of recombinant Hepatitis B vaccines and their long history of use, no additional biopharmaceutic or clinical pharmacology studies were conducted.

Clinical Efficacy

Clinical efficacy of the recombinant Hepatitis B vaccine (Genevac-B), was primarily assessed through the measurement of anti-HBs antibody levels, with titres ≥10 mIU/ml considered protective against Hepatitis B infection.

Across multiple clinical studies, the vaccine demonstrated consistently high seroconversion rates ranging from approximately 95% to 100%, and seroprotection rates between 92% and 100%. The observed efficacy was comparable to established reference vaccines, including Engerix-B and Shanvac-B.

The vaccine was shown to be effective across all age groups, from infants to adults, and across both recommended vaccination schedules (0, 1, 2 months and 0, 1, 6 months), with the latter associated with higher antibody titres.

Adequate efficacy was also demonstrated in special populations, including patients with chronic renal failure when higher doses were administered.

Clinical Safety

The clinical safety profile of Genevac-B was found to be favorable and consistent across all studies. The vaccine was generally well tolerated, with most adverse events being mild, transient, and self-limiting in nature. The most commonly reported events included injection site pain, fever, and localized swelling. Importantly, no vaccine-related serious adverse events were reported. The safety profile was comparable to that of Engerix-B and Shanvac-B, with no clinically significant changes observed in liver function, renal function, or hematological parameters. Additionally, the safety profile remained consistent irrespective of dose (0.5 ml versus 1.0 ml) or vaccination schedule.

Clinical Immunogenicity

Immunogenicity data demonstrated a strong and consistent immune response, with high geometric mean titres (GMTs) observed across studies and rapid antibody development following vaccination. The vaccine was immunogenic in all evaluated populations, including infants, children, adolescents, and adults. Comparable immunogenicity was observed between the 0.5 ml and 1.0 ml doses, while both vaccination schedules were effective, with the 0, 1, and

6-month schedule producing higher GMT values. Overall, the vaccine was shown to induce robust and sustained protective antibody responses.

Overall Conclusion and Benefit–Risk Analysis

Based on the totality of clinical evidence, Genevac-B is highly immunogenic, clinically effective, and well tolerated. Its performance is comparable to other established Hepatitis B vaccines, supporting its use across a broad population, including all age groups, with flexible dosing and scheduling options.

The benefit-risk profile of the vaccine is favorable. The benefits include strong protection against Hepatitis B infection, high seroconversion and seroprotection rates, and demonstrated efficacy across diverse populations and immunization schedules. The risks are minimal and primarily limited to mild, transient adverse events such as injection site reactions and low-grade fever. No significant safety concerns have been identified. Overall, the benefits of vaccination clearly outweigh the minimal risks, supporting the use of Genevac-B in routine immunization programs.

5. General Conclusion and Recommendations if any:

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