SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Product Name: Hepatitis B Vaccine (r DNA) IP
Brand Name: EnivacHB®
Strength: One pediatric dose is 0.5 ml
Pharmaceutical Form: Injectable Vaccine

EnivacHB® Vaccine (rDNA) is sterile, opaque, uniform suspension of Hepatitis B surface antigen adsorbed on Aluminum hydroxide to which thiomersal is added as a preservative. Surface antigen of the Hepatitis B Virus (HBV) is obtained from cultures of transformed yeast by the insertion in its genome of the gene coding for the surface antigen (HBsAg) using recombinant DNA procedures. The production process of Enivac HB® vaccine complies with WHO recommendations.

The final product has the appearance of a white or almost white suspension which may sediments at the bottom of the container on storage separating into two phases: a clear supernatant essentially protein-free composed of phosphate buffered saline (PBS) with the preservative substance dissolved in it and aluminum hydroxide gel with adsorbed antigen. When shaken, a white or almost white suspension is formed, lasting for some minutes, which is the form in which the product is to be administered.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

The composition per ml of vaccine is as follows:

Components	Quantity
Purified Surface Antigen (HBsAg)	20 mcg
Aluminum content (Al^{+++}) (As Aluminum hydroxide gel) IP	0.50 mg
Thiomersal IP	0.05 mg
Phosphate Buffer Saline	qs

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications:

EnivacHB® Vaccine is indicated for active immunization against Hepatitis B virus.

4.2 Posology and method of administration:

Dosage:

There are multiple options for administration of hepatitis B vaccine and the guidelines of the national immunization programme should be consulted. The choice of vaccination schedule should depend on national policy, taking into account the local epidemiological situation and programmatic considerations. The minimum recommended interval between vaccine doses is four weeks. Longer dose intervals may increase the final anti-HBs titres but do not affect seroconversion rates (Cell Discov. 2023 Jul 28;9:79. doi:10.1038/s41421-023-00585-5). For routine primary immunization, a total of three doses is generally adequate. However, where a birth dose is included as per the national immunization programme, a four-dose schedule may also be followed.

EnivacHB has been assessed for safety and immunogenicity in healthy infants (≥6 weeks of age) as a three-dose primary vaccination course administered at 6, 10 and 14 weeks of age (0, 4 and 8-week interval).

EnivacHB has also been evaluated for safety and immunogenicity in healthy adults aged 17–35 years.

Recommended schedules for vaccination can be divided into those that include a birth dose and those that do not. Schedules with a birth dose call for the first vaccination at birth (within 24 hours), followed by a second and third dose at the time of the first and third doses of diphtheria-tetanus-pertussis (DTP) vaccination, respectively. Alternatively, a four-dose schedule may be used where the birth dose is followed by three additional doses. These doses may be administered either as monovalent hepatitis B vaccine or as part of a combination vaccine (e.g. with DTP and/or Hib), according to the schedule recommended for those vaccines. These schedules prevent most perinatally acquired hepatitis B virus infections.

Administration:

The liquid vaccine vial should be shaken before use to homogenize the suspension. It should be injected intramuscularly into anterolateral aspect of thigh in infants, or into the deltoid muscles of older children or adults. An injection into a child's buttocks may cause injury to the sciatic nerve and is not recommended. A sterile syringe and sterile needle must be used for each injection.

4.3 Contraindications:

Known hypersensitivity to any component of the vaccine, or a serve reaction to a previous dose. The vaccine will not harm individuals currently or previously infected with hepatitis B virus.

Immuno deficiency:
Individuals infected with human immunodeficiency virus (HIV), both asymptomatic and symptomatic, should be immunized with hepatitis B vaccine according to standard schedules.

4.4 Special warnings and precautions for use:

EnivacHB® vaccine must be stored between +2ºC and +8ºC. It must not be frozen.

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

EnivacHB® vaccine can be given safely and effectively at the same time as BCG, DTP, Measles, polio (OPV or IPV), *Haemophilus influenzae* type b, or yellow fever vaccines or vitamin A supplementation. If EnivacHB® vaccine is given at the same time as other vaccines, it should be administered at separate site:
1. (*https://www.cdc.gov/pinkbook/hcp/table-of-contents/chapter-6-vaccine-administration.html)*,
2. (https://acvip.org/professional/columns/general-instructions).

It should not be a mixed in the vial or syringe with any other vaccine unless it is licensed for use as combination product (e.g DTP-Hep B/DTPHepHib). Concomitant vaccine such as DTP have been administered during the clinical trial of EnivacHB®.

4.6 Pregnancy and lactation:

Safety and effectiveness have not been established in pregnant women and nursing mothers. However, the decision to immunize pregnant and lactating mothers may be taken by the physician in the context of case specific high-risk factors.

4.7 Effects on ability to drive and use machines:

No studies on the effect of EnivacHB® on ability to drive and use machines have been performed.

4.8 Undesirable effects:

The vaccine is very well tolerated. In placebo-controlled studies, with exception of local pain, reported events such as myalgia and transient fever have not been more frequent than in the placebo group. Reports of severe analphylactic reactions are very rare. Available data do not indicate a casual association between hepatitis B vaccine and Guillain-Barre syndrome, or demyelinating disorders including multiple sclerosis, nor is there any

epidemiological data to support a causal association between hepatitis B vaccination and chronic fatigue syndrome, arthritis, autoimmune disorders, astma, sudden infant death syndrome, or diabetes.

4.9 Overdose:

Not Applicable, as EnivacHB® vaccine is to be administered as per the pediatric immunization schedule under the direct supervision of physicians.

5. PHARMACOLOGICAL INFORMATION:

5.1 Mechanism of action:

Hepatitis B: Hepatitis B virus is one of several hepatitis viruses that cause systemic infection, with major pathology in the liver. Antibody concentrations of ≥10 mIU/mL against HBsAg correlate with protection against hepatitis B virus infection.

5.2 Pharmacodynamic properties:

Pharmacotherapeutic group:

ATC (Anatomical Therapeutic Classification) Code of EnivacHB® vaccine is J07BC01. In the clinical study (Study I) the EnivacHB® vaccine has been found to be safe & highly immunogenic. The vaccine showed sero-protection rate (antiHBs ≥ 1mIU/ml) in 97.87% of the subjects.

Study I:

A prospective, open labelled study to assess the immunogenicity and Reactogenicity of indigenously produced Hepatitis B vaccine was performed in Indian Adults.

During the study period, 58 subjects were screened. Six subjects tested positive for anti HBs and were excluded from the study. 52 subjects were enrolled in the study out of which 5 subjects did not come back after dose 1 and were lost to follow up and 47 subjects completed the study and were statistically analyzed.

Demography: Out of 47 subjects analyzed, 16 were males and 37 were females. The age of the subjects ranged from 17 years to 35 years and the average age was 20.60 years (***Table 1***).

Table 1: Baseline parameters and interval between doses:

Parameter	Value
Male : Female	14 : 33
Mean age at recruitment	20.60 Years
Interval between dose 1 & 2 (Mean)	30.91 Days
Interval between dose 2 & 3 (Mean)	31.91 Days

Immunogenicity: The investigational vaccine (EnivacHB®) showed a very good immunologic response and caused a statistically significant (p=0.000) increase in GMT from 0.214 prevaccination to 2440.92 1 month post vaccination (95% CI; 1372.0 – 3509.42 mlU/ml). The vaccine demonstrated 100% (47/47) seroconversion. 97.87% (46/47) of subjects developed protective levels of anti HBs (seroprotection) out of which 89.36% (42/47) achieved an antibody titer of ≥ 100 mlU/ml (hyper response) (Table 2, 3 and 4). One subject responded poorly to the vaccine (low responder) and showed an antibody titer of 8.60 mlU/ml 1 month after the 3rd dose.

Table 2: Geometric Mean Titers of Anti HBs before and after 3 doses of Hepatitis B vaccine (95% C1; 1372.00 – 3509.42):

Antibody	Baseline	Post Immunization	P value
AntiHBs	0.214 mlU/ml	2440.92 mlU.ml	0.00

Table 3: Proportion of subjects having protective antibodies before starting immunization (baseline) and one month after 3rd dose:

Titer	Baseline	Post Immunization
AntiHBs > 10 mlU/ml	0	97.87%

Table 4: Proportion of subjects showing sero conversion, seroprotection and hyper response:

	Seroconversion < 10 IU/ml	Seroprotection ≥ 10 IU/ml	Hyper response ≥ 100 IU/ml
Baseline (Pre Immunization)	Nil	Nil	Nil
Post Immunization	47 (100%)	46 (97.87 %)	42 (89.36%)

Reactogenicity: The investigational vaccine Enivac HB showed a very favorable tolerability profile. Except for mild pain at injection site, no other local or systemic vaccine related adverse effect was noted in any of the subject. No other adverse event was reported in the study (***Table 5***).

Table 5: Post vaccination record after dose 1, 2 & 3.

	Dose 1		Dose 2		Dose 3	
	N	%	N	%	N	%
Fever	00	00	00	00	00	00
Pain at site of injection	49	92.45	49	92.45	49	92.45

	Dose 1		Dose 2		Dose 3	
	N	%	N	%	N	%
Erythema/redness at the site of injection	00	00	00	00	00	00
Swelling	00	00	00	00	00	00
Nausea/Vomiting	00	00	00	00	00	00
Rash	00	00	00	00	00	00
Body Ache	00	00	00	00	00	00
Fatigue	00	00	00	00	00	00
Any other	00	00	00	00	00	00

Results:

Indigenously produced recombinant DNA Hepatitis B vaccine of Panacea Biotec Ltd. (EnivacHB®) appeared to be a highly immunogenic and safe vaccine in the 0, 1 and 2 months accelerated schedule. Indigenous EnivacHB showed a seroprotection rate of 97.87% with 89.36% of subjects showing hyper response. The vaccine appeared to be very well tolerated.

Study II:

Another study was performed to demonstrate the immunogenicity and reactogenicity of EnivacHB® in comparison to a licensed comparator Engerix B in healthy infants at 6, 10, 14 weeks of age (Study No: Panbio/CR/0882004/CT).

It was a prospective, open-labelled, randomized, comparative, multicenter study. There were 751 subjects enrolled in the study (379 subjects in the EnivacHB® group and 372 in the Engerix group).

Non-inferiority of EnivacHB® to Engerix B, in terms of anti-HBs immune response one month after the 3-dose primary vaccination course, was demonstrated. The seroprotection rate (defined as the percentage of subjects in the respective vaccine group with anti-HBs antibody concentration ≥ 10 mIU/ml) was 100% for EnivacHB® and 94.9% for Engerix B. The treatment difference in seroprotection rate (Engerix B minus EnivacHB®) was -5.1% with an upper 95% confidence limit of 3.1%, which is well within the pre-specified non-inferiority margin of 10%.

The GMT for EnivacHB® (951 mIU/ml) was more than 3.5 times that for Engerix B (269 mIU/ml). The 95% upper confidence limit for the GMT ratio (Engerix B/EnivacHB®), adjusted for pre-vaccination titre levels, was 0.36, which is well below 1, demonstrating the superiority of EnivacHB® to Engerix B in terms of anti-HBs immune response measure by GMT. The superiority of the EnivacHB® group to the Engerix B group was also evident from the reverse cumulative distribution curves.

The incidence of each solicited local symptom and each solicited general symptom at each dose and over all doses were similar for the groups, with p-values indicating no statistically significant difference between the groups. The most frequent local symptom was pain (13.2% overall in the EnivacHB® group and 15.1% overall in the Engerix group). The most frequent general symptom was fever (32.7% overall in the EnivacHB® group and 32.3% overall in the Engerix B group).

There were no subjects with redness, lump, or swelling > 20 mm, or pain that interfered with movement of the injected limb. In both groups, there were relatively few subjects with severe general symptoms, and relatively few subjects with local or general symptoms that were related (i.e. with a possible, probable, or definite relationship) to the study vaccine. In most cases, the symptoms were attributable to other concomitant vaccinations such as DTP vaccination.

The incidence of unsolicited adverse events was similar for the two groups, with 23 (6.1%) in the EnivacHB® group and 22 (5.9%) in the Engerix B group reporting any adverse event. The most frequently reported unsolicited symptom was pyrexia (8 (2.1%) in the EnivacHB® group and 6 (1.6%) in the Engerix group).

Most of the unsolicited adverse events were mild. There was only one subject in each group with an unsolicited AE related (i.e. with a possible, probable, or definite relationship) to the study vaccine.

There were no deaths. There were 7 (1.8%) subjects with serious adverse events in the EnivacHB® group and none in the Engerix B group. In all 7 cases, the subject recovered completely before the end of the study. In all of those 7 cases, the investigator concluded that there was no reasonable possibility that the SAE could have been caused by the study vaccine.

Overall, based on the results of this study, it can be concluded that EnivacHB® is at least non-inferior to Engerix B in terms of anti-HBs immune response, with a Reactogenicity profile similar to that of Engerix B.

5.3 Pharmacokinetic properties:

Not Applicable.

6. PRECLINICAL SAFETY DATA (NON-CLINICAL PROPERTIES):

6.1 Animal Toxicology or Pharmacology:

Panacea Biotec manufactured the EnivacHB by utilizing the WHO prequalified Hepatitis B from Panacea Biotec Ltd., Lalru.

This antigen component is well established and has proven safety. The EnivacHB was found to be safe and immunogenic in the pre-clinical toxicology studies conducted on it comprising of acute toxicity in Swiss mice and guinea pigs, single dose toxicity and pharmacodynamics study in Swiss mice and local tolerance study in rabbits.

7. DESCRIPTION:

EnivacHB®, Hepatitis B Vaccine (rDNA) IP is a uniform suspension (after shaking) free from any extraneous particles. The vaccine contains Hepatitis B surface antigen adsorbed on aluminium hydroxide gel which is further suspended in Phosphate buffer saline to which thiomersal is added as a preservative. The Hepatitis B surface antigen (HBsAg) is produced from culture of genetically-engineered yeast cells (*Pichia pastoris*) which carries the gene coding for the major surface antigen of the Hepatitis B Virus (HBV). The production process of EnivacHB® vaccine complies with WHO recommendations. The final vaccine is presented in USP type 1 glass vials closed with

bromobutyl rubber stoppers and flip-off seal and as single paediatric dose in prefilled injection devices.

8. PHARMACEUTICAL PARTICULARS

8.1 List of Excipients:

- Aluminum Hydroxide gel
- Thiomersal
- Phosphate Buffer Saline

8.2 Incompatibilities:

The vaccine should not be mixed in the vial or syringe with any other vaccines unless it is licensed for use as a combined product.

8.3 Shelf-Life:

36 months from the date of manufacturing, when stored at 5°C ± 3°C.

9. NATURE AND CONTENTS OF CONTAINER (PACKAGING INFORMATION):

9.1 Storage and Handling Instructions:

9.1.1 Special precautions for storage:

EnivacHB® vaccine must be stored between +2°C and +8°C. It must not be frozen. Multi dose vials of hepatitis B vaccine 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 maximum of 4 weeks.

- The expiry date has not been 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 withdrawal all doses

9.1.2 Special precautions for disposal:

Once the vaccine has been administered, the injection equipment (syringes and needles) and the vaccine containers (vials) should be disposed of according to standard procedures for medical/biomedical waste.

9.1.3 Nature and contents of the container:

EnivacHB® vaccine is to be filled in tubular, colorless glass vials and stoppered with bromo butyl rubber closures and finally sealed with flip off aluminium seals as well as in Pre-filled syringe of USP type 1 glass stoppered with plunger stopper in below mentioned presentations:

Vial Presentations:
Pediatric:
Single dose vial containing 0.5 ml vaccine.
Multi-dose vial containing 2.5 ml vaccine
Ten paediatric doses vial containing 5.0 ml vaccine
Adult:
Single dose vial containing 1.0 ml vaccine
Ten doses vial containing 10.0 ml vaccine

Prefilled Syringe Presentations:
Pediatric: Single dose Prefilled Syringe containing 0.5 ml vaccine**.**
Adult: Single dose Prefilled Syringe containing 1.0 ml vaccine.

10. PATIENT COUNCELLING INFORMATION:

Registered Medical Practitioners may counsel the parents (and/or infant/child's caretaker as applicable) of the potential benefits and undesirable effects of vaccination with EnivacHB®. Parents (and/or infant/child's caretaker) may also be informed about posology (including vaccination schedule if applicable), method and route of administration and storage information of EnivacHB® vaccine as applicable. Registered Medical Practitioners may also choose to inform the parents (and/or infant/child's caretaker) about the special warnings and precautions for use, drug interactions, and any relevant contra-indications associated with EnivacHB® vaccine.

11. MARKETING AUTHORIZATION HOLDER:

Panacea Biotec Ltd.
Malpur, Baddi, Distt Solan,
Himachal Pradesh – 173205, India
Tel. : 01795-674036
E-mail : corporate@panaceabiotec.com
Website: https://www.panaceabiotec.com

12. MARKETING AUTHORIZATION NUMBER:

License No. : MB/07/632

13. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

The details of the manufacturing authorization certificates obtained from Licensing Authority, India for EnivacHB® vaccine manufactured at Vaccine Formulation Plant (VFP), Baddi, Himachal Pradesh, India are as mentioned below:

- Date of first authorization: September 29, 2007
- Renewal of the authorization: granted on September 29, 2012 valid up to 28.09.2017
- Renewal of the authorization: granted on September 29, 2017 valid up to 28.09.2022
- Retained up to September 28, 2027