SUMMARY OF PRODUCT CHARACTERISTICS
HEPATITIS B VACCINE (rDNA) I.P.

1. NAME OF THE MEDICINAL PRODUCT:
Hepatitis-B Vaccine (rDNA) I.P., GENEVAC-B

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:
Each dose of 0.5 ml (Pediatric) contains:
10 mcg of purified Hepatitis B surface antigen*
Adsorbed on Aluminium hydroxide (Al+++ 0.25 mg to 0.40 mg
Preservative : Thiomersal 0.005%
* - Produced in Hansenula polymorpha (yeast)

Each dose of 1 ml (Adult) contains:
20 mcg of purified Hepatitis B surface antigen*
Adsorbed on Aluminium hydroxide (Al+++ 0.50 mg to 0.80 mg
Preservative : Thiomersal 0.005%
* - Produced in Hansenula polymorpha (yeast)

3. PHARMACEUTICAL FORM
Suspension for Injection.
GeneVac-B (Hepatitis B Vaccine (rDNA) I.P.) 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. The Hepatitis B surface antigen (HBsAg) expressed in the cells of Hansenula polymorpha is purified through several chemical steps and formulated as a suspension of the antigen adsorbed on aluminium hydroxide and thiomersal is added as preservative. The vaccine does not contain any material of human or animal origin.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
GeneVac-B is indicated for active immunisation against Hepatitis B virus (HBV) infection in subjects considered at risk of exposure to HBV-positive material.
Immunisation against hepatitis B is expected in the long term to reduce not only the incidence of this disease, but also its chronic complications such as chronic active hepatitis B and hepatitis B associated cirrhosis and primary hepatocellular carcinoma.

In areas of low prevalence of hepatitis B, immunisation with GeneVac-B is recommended for neonates/infants and adolescents as well as for subjects who are, or will be, at increased risk of infection such as:

- health care personnel,
- patients receiving frequent blood products,
- personnel and residents of institution,
- persons at increased risk due to their sexual behavior,
- illicit users of addictive injectable drugs,
- travelers to areas with a high endemicity of HBV,
- infants born of mothers who are HBV carriers,
- persons originating from areas with a high endemicity of HBV,
- police personnel, fire brigade personnel, armed forces personnel and
- anybody who through their work or personal lifestyle may be exposed to HBV, household contacts of any of the above groups and of patients with acute or chronic HBV infection.

In areas of intermediate or high prevalence of hepatitis B, with most of the population at risk of acquiring the disease, immunisation should be offered to all neonates and young children. Immunisation should also be considered for adolescents and young adults.

The vaccine can be safely and effectively given simultaneously but at different injection site with DTP, DT, TT, BCG, Polio vaccine (OPV and IPV) and yellow fever vaccine.

4.2 Posology and method of administration

GeneVac-B should be injected intramuscularly in the deltoid region in adults and children or in the anterolateral thigh in neonates, infants and young children. The vaccine may be administered subcutaneously in patients with thrombocytopenia or bleeding disorders. The
vaccine should be well shaken before use. Only sterile needle and syringes should be used for each injection.

The vaccine should be visually inspected for any foreign particulate matter and/or variation of physical aspect prior to administration. In event of either being observed discard the vaccine.

Paediatric dose vaccine: 10 mcg dose (in 0.5 ml suspension) is recommended for neonates, infants, children and adolescents upto 19 years of age.
Adult dose vaccine: 20 mcg dose (in 1.0 ml suspension) is recommended for adults aged 20 years and above.

**Primary immunisation**
The following immunisation schedules can be recommended.:
- 6,10,14 weeks for infants
- 0,1,6 months
- 0,1,2 months (rapid schedule)
The immunisation schedule should be adapted to meet local immunisation recommendations.

**Booster dose**
The need for the booster dose in healthy individuals who have received the full primary immunization, is not recommended. It would seem advisable to recommend a booster dose when Anti-HBs antibody titres fall below 10 IU/L for all people at risk and especially for patients who are immunocompromised (HIV infected patients) or those on haemodialysis. GeneVac-B can be administered with DTPw vaccine of SIIL at separate site alone or as a combination vaccine i.e. DTPwHB (SIIL).

**Dosage recommendation for neonates born of mothers who are HBV carriers**
The 0, 1, 2 month immunisation schedule is recommended, and should start at birth. Concomitant administration of Hepatitis B immunoglobulin is not necessary, but when Hepatitis B immunoglobulin is given simultaneously with GeneVac-B a separate injection site must be chosen.
Dosage recommendation for known or presumed exposure of HBV

In circumstances where exposure to HBV has recently occurred (e.g. needles stick with contaminated needle) the first dose of GeneVac-B can be administered simultaneously with Hepatitis B immunoglobulin which however must be given at a separate injection site. The rapid immunisation schedule should be advised.

Dosage recommendation for immunocompromised persons

The primary immunisation schedule for chronic haemodialysis patients or persons who have an impaired immune system is four doses of 40 mcg at 0, 1, 2 and 6 months from the date of first dose. The immunisation schedule should be adapted in order to ensure that the anti-HBs antibody titre remains above the accepted protective level of 10 IU/L.

4.3 Contraindications

GeneVac-B should not be administered to subjects with known hypersensitivity to any component of the vaccine, or to subjects having shown signs of hypersensitivity after previous Hepatitis B Vaccine administration.

4.4 Special warnings and precautions for use

Because of the period of latency of hepatitis B infection it is possible for unrecognized infection to be present at the time of immunisation. The vaccine may not prevent hepatitis B infection in such cases.

The vaccine will not prevent infection caused by other agents such as hepatitis A, hepatitis C and hepatitis E and other pathogens known to infect the liver.

The immune response to Hepatitis B vaccines is related to age. In general, people over 40 years of age respond less well.

In haemodialysis patients and persons with an impaired immune system, adequate anti-HBs antibody titres may not be obtained after the primary immunisation course and such patients may therefore require administration of additional doses of vaccine.
As with all injectable vaccines, appropriate medication (e.g. adrenaline) should always be readily available for treatment in case of rare anaphylactic reactions following the administration of the vaccine.

Adrenaline injection (1:1000) must be immediately available should an acute anaphylactic reaction occur due to any component of the vaccine. For treatment of severe anaphylaxis the initial dose of adrenaline is 0.1-0.5 mg (0.1-0.5ml of 1:1000 injection) given s/c or i/m. Single dose should not exceed 1 mg (1ml). For infants and children the recommended dose of adrenaline is 0.01mg/kg (0.01ml/kg of 1:1000 injection). Single Paediatric dose should not exceed 0.5mg (0.5ml). The mainstay in the treatment of severe anaphylaxis is the prompt use of adrenaline, which can be lifesaving. It should be used at the first suspicion of anaphylaxis.

As with the use of all vaccines, the vaccinees should remain under observation for not less than 30 minutes for possibility of occurrence of immediate or early allergic reactions. Hydrocortisone hydrochloride and antihistaminics should also be available in addition to supportive measures such as oxygen inhalation.

Special care should be taken to ensure that the injection does not enter a blood vessel.

GeneVac-B should not be administered in the gluteal muscle or intradermally since this may result in a lower immune response.

GeneVac-B may be used to complete a primary immunisation course started either with plasma-derived or with other genetically-engineered hepatitis B vaccines, or as a booster dose in subjects who have previously received a primary immunisation course with plasma-derived or with other genetically-engineered hepatitis B vaccines.

4.5 Interaction with other medicinal products and other forms of Interaction
The vaccine can be safely and effectively given simultaneously but at different injection site with DTP, DT, TT, BCG, Polio vaccine (OPV and IPV) and yellow fever vaccine. It should not be mixed in the via or syringe with any other vaccine.
4.6 Pregnancy and lactation
Though no clinical studies have been done on Hepatitis-B vaccine in pregnancy and lactation, there are no reports of any adverse reactions in pregnant and lactating women.

4.7 Effects on ability to drive and use machines
Not applicable.

4.8 Undesirable effects
The reported undesirable events were temporally related to the administration of Hepatitis B Vaccine. They are usually mild and confined to the first few days of the vaccination. The most common reactions are mild soreness, erythema, induration, fatigue, fever, malaise, influenza-like symptoms. Less common systemic reactions include nausea, vomiting, diarrhoea, abdominal pain, abnormal liver function tests, arthralgia, myalgia, rash, pruritus, urticaria.

4.9 Overdose
Not applicable

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: rDNA vaccine.

Immune response after primary vaccination:
The vaccine induces specific humoral antibodies against hepatitis-B virus surface antigen (anti-HBsAg). Development of an antibody titre against hepatitis-B virus surface antigen (anti-HBsAg) equal to or greater than 10 IU/l measured 1 to 2 months after the last injection correlates with protection against hepatitis B virus infection.

In clinical trials, 91% - 100% of healthy infants, children, adolescents and adults given a 3 dose course of a SIIL recombinant hepatitis-B vaccine developed a protective level of antibodies against hepatitis-B virus surface antigen (≥ 10 IU/l).

In one trial, GeneVac-B was compared with Shanvac-B (Shantha Biotech, India) in 80 adults each at Hyderabad in the schedule of 3 doses of 20 μg (1 ml), given at 0,1 & 6 month. The GMT with GeneVac-B (145.61 mIU/ml) was apparently higher than with Shanvac-B (108.05
mlU/ml). Both seroconversion and seroprotection was attained in all the subjects, with both the vaccines.

A large clinical trial in 788 adults with adult doses of GeneVac-B given at 0,1 and 6 months showed that seroprotection was 95.6%.

GeneVac-B was compared with Engerix -B (GlaxoSmithKline Beecham, Belgium) & Shanvac-B (Shantha Biotech, India) in 400 adults. Post-vaccination, the seroprotection rates achieved were 99.5% (Genevac-B), 98.5% (Engerix-B) and 98.4% (Shanvac-B). The GMTs were better with GeneVac-B (735 mlU/ml), than Engerix-B (718 mlU/ml), and Shanvac-B (662 mlU/ml).

Two trials in adolescents compared 3 doses of 1 ml and 0.5 ml of GeneVac-B. All the subjects with both dose strengths showed seroprotection.

In a pediatric trial, children of 6-12 Years age group were given 10 μg of GeneVac-B, at 0,1 & 6 months. A high mean titre of 1619 mlU/ml was observed after the 3 dose series. All subjects achieved seroprotective titres

A comparison with Engerix-B was done in 173 infants, when the subjects were given 3 doses at 6,10,14 weeks of age, along with DTP vaccine. The GMTs of antibodies were 229 mlU/ml with GeneVac-B, and 167 mlU/ml with Engerix-B. 95% of subjects were seroprotected with both vaccines.

In a Double-blind. Randomized comparative trial between GeneVac-B and Engerix-B, 3 doses of vaccines were administered in 262 subjects at birth, 6 weeks and 14 weeks of age. Infants showed 96.97 % seroprotection with GeneVac-B and 95.38 % with Engerix-B. The mean titres achieved were 383.35 mlU/ml (GeneVac-B) & 285.43 mlU/ml (Engerix-B).

In another randomized comparative trial between GeneVac-B and Engerix-B, 3 doses of vaccines were administered in 118 subjects at 6, 10 and 14 weeks of age. Infants showed 98.36 % seroprotection with GeneVac-B and 98.25 % with Engerix-B. The mean titres achieved were 273.46 mlU/ml (GeneVac-B) & 266.26 mlU/ml (Engerix-B).
In yet another randomized comparative trial between GeneVac-B and Engerix-B, 3 doses of vaccines were administered in 126 subjects at 6, 10 and 14 weeks of age. Infants showed 94.36% seroprotection with GeneVac-B and 92.72% with Engerix-B. The mean titres achieved were 149.47 mIU/ml (GeneVac-B) & 153.28 mIU/ml (Engerix-B).

GeneVac-B has been compared with Engerix-B in an immunocompromised population of chronic renal failure in 4 doses of double strength i.e. 40 μg (2 ml) at 0, 1, 2 & 6, months. The seroprotection rates (Anti HBs ≥ 100 mIU/ml) and the GMTs were 82% & 78%, and 321 mIU/ml & 274 mIU/ml, with GeneVac-B and Engerix-B, respectively.

**Reduced risk of Hepatocellular Carcinoma**

Hepatocellular carcinoma is a serious complication of hepatitis-B virus infection. Studies have demonstrated the link between chronic hepatitis-B infection and hepatocellular carcinoma and 80% of hepatocellular carcinomas are caused by hepatitis-B virus infection. Hepatitis-B vaccine has been recognized as the first anti-cancer vaccine because it can prevent primary liver cancer.

**5.2 Pharmacokinetic properties**

Evaluation of Pharmacokinetic properties is not required for vaccines.

**5.3 Preclinical safety data**

Acute toxicity study of GeneVac-B was conducted in Swiss albino mice. The vaccine was well-tolerated in the dose of 80 μg/kg dose intramuscularly. None of the animals in the treated group showed any toxic symptoms, which indicate the safety of the vaccine.

Subacute toxicity study of GeneVac-B was conducted in Swiss albino mice. Mice were divided into 5 groups each containing 12 animals. First group served as negative control and second group served as positive control. Remaining three groups were given low (12 μg/kg), medium (24 μg/kg) and high (48 μg/kg) doses of the vaccine intramuscularly, based on the ED50. The doses were given daily for a period of 7 days. The vaccine in the doses used did not significantly affect the parameters such as body weight, feed and water intake, hematology and clinical biochemistry. The results were supported by the histopathological studies.
Sub acute toxicity study of GeneVac-B was also conducted in Wistar albino rats. Rats were divided into 5 groups each containing 12 animals. First group serve as negative control and second group served as positive control. Remaining three groups were given low (9 μg/kg), medium (18 μg/kg), and high (36 μg/kg) doses of the vaccine intramuscularly, based on the ED50. The doses were given daily for a period of 7 days. The vaccine in the doses used did not significantly affect the parameters such as body weight, feed and water intake, hematology and clinical biochemistry. The results were supported by the histopathological studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Aluminium hydroxide (Al+++), Thiomersal

6.2 Incompatibilities
The vaccine should not be mixed in the vials or syringe with any other vaccine unless it is manufactured as combined product (e.g. DTP-HB).

6.3 Shelf life
36 months.

6.4 Special precautions for storage
The vaccine should be stored at 2°C to 8°C. Protect from light. Do not freeze.
Discard if vaccine has been frozen.

6.5 Nature and contents of container

Vials (adult or pediatric):

<table>
<thead>
<tr>
<th>Material</th>
<th>Suppliers</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1, clear tubular glass</td>
<td>Kaisha Manufacturers Pvt, Ltd, Daman</td>
<td>4 mL (fill vol. 5.0 mL)</td>
</tr>
<tr>
<td></td>
<td>Tube Glass Containers Pvt, Ltd, Badalapur</td>
<td>13 mm neck</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 mm ht</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16.5 mm dia</td>
</tr>
<tr>
<td>Rubber stopper Grey (Bromobutyl)</td>
<td>Helvoet Pharma, Belgium West Pharmaceutical Services, Singapore</td>
<td>13 mm</td>
</tr>
<tr>
<td>Aluminium flip-off seal For pediatric (Pentone process blue colour)</td>
<td>Autofits Ltd, Nashik</td>
<td>13 mm</td>
</tr>
<tr>
<td>Aluminium flip-off seal for Adult (Pentone process green colour)</td>
<td>Autofits Ltd, Nashik</td>
<td>13 mm</td>
</tr>
</tbody>
</table>
**Amopules (adult or pediatric):**

<table>
<thead>
<tr>
<th>Material</th>
<th>Suppliers</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1, clear tubular glass ampoule, white colour break for 0.5 to 1.0 mL product</td>
<td>Kaisha Manufacturers Pvt, Ltd, Daman</td>
<td>-1.0 mL (1.8 mL shoulder capacity)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-65 mm ht</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-10.25 mm dia</td>
</tr>
</tbody>
</table>

**6.6 Special precautions for disposal**

Once vaccine has been administered, the injection equipment and vaccine containers should be disposed of according to the standard procedures for medical waste.

**7. MARKETING AUTHORISATION / PREQUALIFICATION HOLDER**

SERUM INSTITUTE OF INDIA LTD,

212/2, Hadapsar, Pune – 411028, Maharashtra, INDIA.
Telephone: ++ 91-20- 26993900
Fax: ++ 91- 20-26993924 / 26993921
Website: [www.seruminstitute.com](http://www.seruminstitute.com)

**8. MARKETING AUTHORISATION NUMBER(S)**

Drug Mfg. License. No. 10 (in Form 28-D) granted by State licensing Authority (Food and Drug administration) and Central License Approving Authority (Drug Controller General of India)

**9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 21.07.2000
Date of last renewal: 01.01.2012

01/2014