1. NAME OF THE MEDICINAL PRODUCT (GENERIC NAME)

BEVAC® (Hepatitis B Vaccine (rDNA))

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose contains

	Paediatric Dose (0.5 mL)	Adult Dose (1.0 mL)
Purified HBsAg	≥ 10 µg	≥ 20 µg
Aluminium hydroxide gel equivalent to Al^{+++}	0.25 mg	0.5 mg
Thiomersal I.P. (as preservative)	0.025 mg	0.05 mg

Recombinant HBs Antigen produced in *pichia pastoris (Yeast)*

3. PHARMACEUTICAL FORM (DOSAGE FORM AND STRENGTH)

Suspension for intramuscular injection. Each Paediatric dose of 0.5 ml contains 10µg of Purified HBsAg and Adult dose of 1.0 ml contains Purified HBsAg 20µg of Purified HBsAg.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

BE's Hepatitis B Vaccine is indicated for active immunization against infection caused by Hepatitis B virus.

4.2 Posology and method of administration

The liquid vaccine vial should be shaken well before use to homogenize the suspension. BEVAC® should be injected deep intramuscularly into the deltoid muscle region in adults and in the antero-lateral aspect of the upper/mid-thigh in neonates, infants and young children. BEVAC® should not be injected into the gluteal muscles. It is not recommended for intradermal or intravenous administration.

Hepatitis B is recommended primarily for neonates, infants and young adults not only for the prevention of the disease but also to protect them from probable hepatitis B virus - induced carrier state, cirrhosis and hepato-cellular carcinoma. It can also be given to hepatitis C and D virus infected patients to protect them against co-infection with hepatitis B virus. In addition, for various groups of individuals as listed below, Hepatitis B vaccine immunization is an essential requirement:

- Healthcare personnel.

- Patients prone to infection due to unscreened or improperly tested blood transfusions.
- Haemophiliacs and patients on haemodialysis.
- Travelers to specified high endemic areas.
- Residents in high endemic areas.
- Persons in contact with infected sexual partners.
- Drug addicts.
- Personnel and residents of community homes and hostels.
- Household contacts of persons with acute or chronic Hepatitis B virus infection.
- Infants born to Hepatitis B virus carrier mothers.
- Organ transplant receivers.
- Others: Police, Armed forces and such other regimented personnel.

Dosage:

Pediatric dose vaccine: 10 µg dose in 0.5mL is indicated for neonates, infants and children below 10 years of age

Adult dose vaccine: 20 µg dose in 1mL is indicated for adults and children ≥ 10 years of age.

PRESENTATIONS

Paediatric : Single dose vial of 10 µg/ 0.5 mL

: Multi dose vial of 5 mL

Adult : Single dose vial of 20 µg/ 1 mL

: Multi dose vial of 10 mL

Immunization Schedule:

Primary immunization schedule:

Any one of the following is recommended as a Primary Schedule (IAP Guidelines) for Routine Immunization

Age	Schedule – 1 (IAP & WHO)	Schedule – 2 (IAP & WHO)	Schedule – 3 (IAP)
Birth	NA*	1st dose**	At Birth – 1st dose**
6 Weeks	1st dose	2nd dose	1 Month – 2nd dose
10 Weeks	2nd dose	NA*	6 Months – 3rd dose

14 Weeks	3rd dose	3rd dose	------
Booster	Booster doses are not recommended.		

*NA – Not Applicable

**Monovalent Hepatitis B vaccine MUST BE USED for the birth dose.

In order to prevent HBV transmission from mother to infant, the first dose of Hepatitis B vaccine needs to be given as soon as possible after birth (preferably within 24 hours). This must be followed by a second and third dose at the time of the first and third diphtheria-tetanus-pertussis (DTP) vaccination.

Temporary immunity may be obtained using Hepatitis B immune globulin (HBIG) for post-exposure prophylaxis. As a rule, HBIG should be used as an adjunct to hepatitis B vaccine when given at birth, but at a different injection site. However, in full-term newborns, the protection against perinatally acquired infection achieved by immediate (<24 hours) hepatitis B vaccination is not significantly improved by the addition of HBIG.

Schedule for Preterm infants:

Age	**Alternate Schedule (WHO) (For Preterm infants with < 2000g Birth weight)**
Birth	1st dose**
6 weeks	2nd dose
10 weeks	3rd dose
14 weeks	4th dose

**Monovalent Hepatitis B vaccine MUST BE USED for the birth dose.

Alternatively, for preterm infants, to prevent perinatal transmission, a four-dose schedule may be used; if the birth weight is <2000 grams, the vaccine dose at birth should not be counted towards the primary series, and three additional doses should be given. These doses may be given either as monovalent vaccine or as a combination (e.g. with DTP and/or Hib) following the schedules commonly used for DTP vaccines. These schedules will prevent most perinatally acquired infection.

Booster Doses:

In immunocompetent individuals Hepatitis B vaccine induces an effective immunological memory that lasts life-long and protects against symptomatic acute illness and development of chronic infection on exposure to the virus. Boosters of Hepatitis B vaccine are, therefore, not necessary under usual circumstances.

Catch-up Vaccination:

Catch-up vaccination with Hepatitis B vaccine of older age groups, including adolescents and adults should be considered only if the continuity of the infant vaccination programme can be ensured. If a higher proportion of chronic infections may be acquired among older children, adolescents and adults; catch-up immunization for these groups may be considered.

Schedule for older children and adults:

For older children and adults, the preferred schedule is 0, 1 and 6 months, 0 being the elected dose for first dose.

Immunization in special situation:

a) Immunocompromised Individuals

It is recommended that (by Advisory Committee on Immunization Practices-ACIP) adults with HIV infection receive Hepatitis B vaccination (3doses). Immunosuppressive illnesses such as advanced HIV infection, chronic liver disease, chronic renal failure and diabetes are associated with reduced immunogenicity of the vaccine.

b) Unresponsive Individuals

Persons unresponsive to the primary series of Hepatitis B (serum anti-HBsAg concentration less than 10 ml U/L), may require revaccination of a fourth or fifth dose, or a new complete course of immunization at the discretion of the medical practitioner.

Method of administration:

The liquid vaccine vial should be shaken well before use to homogenize the suspension. Hepatitis B should be injected deep intramuscularly into the deltoid muscle region in adults and in the antero-lateral aspect of the upper/mid-thigh in neonates, infants and young children. Hepatitis B should not be injected into the gluteal muscles. It is not recommended for intradermal administration.

4.3 Contraindications

Hepatitis B vaccine is generally well tolerated. However, the vaccine should not be administered or repeated to persons known to be hypersensitive to any of the components of the vaccine. Avoid immunization during severe febrile illness.

4.4 Special warnings and precautions for use

It is suggested that the medical practitioners ascertain the pre-immunization hypersensitivity status of the subject. In general, biologicals are known to cause reactions occasionally. Sympathomimetic drug like adrenalin may be kept readily available in case of rare anaphylactic reactions due to the vaccine. While using the multi-dose vial, care must be taken to use separate sterile syringe and needle for the administration of every dose.

Before use, Hepatitis B vaccine should be well shaken to obtain a uniform, whitish translucent suspension. Vaccine should be visually checked for the presence of any particulate matter or other colouration, if any, prior to its administration. If in doubt, do not use the contents of the vial.

NOTE: Because of the long incubation for hepatitis-B virus to manifest the symptoms, some subjects may receive the vaccine while the infection stays unrecognized. In such cases, the vaccine may not prevent the onset of hepatitis due to hepatitis - B virus. BEVAC® will not prevent hepatitis caused by other viruses such as hepatitis A, hepatitis C and hepatitis D and other agents known to infect the liver.

4.5 Interaction with other medicinal products and other forms of interaction (Drug Interactions)

Hepatitis B vaccine can be administered safely and effectively at the same time as BCG, DTP, Measles, polio (OPV or IPV), *Haemophilus influenzae* type b, or yellow fever vaccines that are extensively used in the Expanded Programme on Immunization (EPI), worldwide or vitamin A supplementation. If Hepatitis B 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 (e.g. DTP Hep B/ DTP Hep B-Hib).

4.6 Use in special populations (such as pregnant women, lactating women, pediatric patients, geriatric patients etc.) (Pregnancy and Lactation)

Routine vaccination of pregnant women with recombinant Hepatitis-B vaccine is not recommended due to inadequate data on its effects on the foetus. No contraindication was recorded for the use of the vaccine in lactating 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 Effect on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable Effects

Hepatitis B vaccine has proven for low reactogenicity and is well tolerated. Soreness at the site of injection or a febrile reaction may be observed in some subjects. In rare cases of post vaccinal hypersensitivity, the common symptoms that are quickly recognized by the physician are: dizziness, headache, nausea, abdominal pain, rash, pruritus, urticaria, arthralgia, myalgias and similar associated symptoms and side effects.

Clinical Trial Experience: The safety of BE's Hepatitis B vaccine was established in controlled clinical trials in individuals ranging from neonates vaccinated within 24 hours of birth to adults of 35 years of age. Within each system organ class (SOC) the adverse reactions are ranked under headings using the following convention:

Very common	≥ 10%
Common	≥ 1% and < 10%
Uncommon	≥ 0.1% and < 1%
Rare	≥ 0.01% and < 0.1%

Very Common:

- Injection site swelling

Common (may affect up to 1 in 10 people)

- Pyrexia
- Injection site pain
- Irritability postvaccinal

Uncommon (may affect up to 1 in 100 people)

- Injection site erythema
- Decreased appetite
- Somnolence

Summary of safety profile:

Phase III Clinical Study (BECT001):

In a Phase III clinical study (BECT001) conducted in 166 subjects aged 5-35 years to evaluate, record and analyse the tolerability, safety, immunogenicity and efficacy of the indigenous Hepatitis B vaccine(r-DNA), the Vaccine was found to be safe and well tolerated.

In total of 166 enrolled subjects, 5 (4.13%) subjects who received BE's Hepatitis B vaccine(r-DNA) Vaccine had experienced adverse reactions which were mainly solicited in nature, i.e., pain at injection site, injection site swelling and injection site redness. These are very much within the level of adverse reactions reported in the literature.

Phase IV Clinical Study (BECT058):

In a Phase-IV (BECT058), non-inferiority study conducted in 468 subjects to evaluate the immunogenicity and safety of BE's monovalent Hepatitis-B (rDNA) vaccine when administered as a first dose to neonates within 24 hours of birth followed by a dose at 6 and 14 weeks of age in comparison with a licensed comparator, 68 of the 234 subjects (29.06%) who had received BE's Hepatitis-B (rDNA) vaccine reported 148 events and 82 of the 234 subjects (35.04%) who had received the licensed comparator reported 193 adverse events.

The most commonly reported adverse events were Pyrexia [55 AEs in 55 (23.5%) subjects], Injection site pain [36 AEs in 36 (15.4%) subjects], Injection site swelling [36 AEs in 36 (15.4%) subjects], Irritability postvaccinal [12 AEs in 12 (5.1%) subjects], Injection site erythema [6 AEs in 6 (2.6%) subjects], Somnolence [2 AEs in 2 (0.9%) subjects] and Decreased appetite [1 AEs in 1 (0.4%) subjects] in BEVAC arm and Pyrexia [72 AEs in 71 (30.3%) subjects], Injection site pain [48 AEs in 48 (20.5%) subjects], Injection site swelling [41 AEs in 41 (17.5%) subjects], Irritability postvaccinal [20 AEs in 20 (8.5%) subjects], Injection site erythema [10 AEs in 10 (4.3%) subjects], Somnolence [1 AEs in 1 (0.4%) subjects] and Decreased appetite [1 AEs in 1 (0.4%) subjects] in licensed comparator arm. All the reported adverse events were mild to moderate in their intensity and are related to the study vaccine. All the reported adverse events are solicited in nature. There were no SAEs and no deaths reported in the study.

Post Marketing Surveillance Study (BECT082):

In a multicentre single arm, post marketing surveillance study (BECT082) conducted in 500 subjects to evaluate the safety of BE's monovalent recombinant Hepatitis-B vaccine when administered to 6-8 weeks old infants in 6-10-14 weeks dosing schedule, 185 subjects (37.0%) reported 238 adverse events.

The most commonly reported adverse events were Pyrexia [97 (19.4%) subjects with 117 events], Injection site pain [45 (9.0%) subjects with 46 events], Injection site erythema [39 (7.8%) subjects with 40 events], Injection site swelling [17 (3.4%) subjects with 17 events] and Irritability postvaccinal [12 (2.4%) subjects with 16 events].

Consolidated table of clinical safety of BEVAC® across clinical studies:

Age cohort	Study	MedDRA System Organ Class	Frequency	Adverse reactions
Neonates (<24 hours of age) N=468 BEVAC (N=234) Comparator: GENEVAC-B (N=234)	BECT058 (Phase IV)	General disorders and administration site conditions	Very common	Pyrexia, Injection site pain, Injection site swelling
			Common	Injection site erythema, Irritability postvaccinal
		Metabolism and nutrition disorders	Uncommon	Decreased appetite
		Nervous system disorders	Uncommon	Somnolence
Infants (6-8 weeks of age) N=500	BECT082 (post-marketing surveillance)	General disorders and administration site conditions	Very common	Pyrexia
			Common	Injection site pain, Injection site swelling, Injection site erythema, Irritability postvaccinal
		Metabolism and nutrition disorders	Uncommon	Decreased appetite
		Nervous system disorders	Uncommon	Somnolence

Children, Adolescents and Adults (5 to 35 years*. N=163) BEVAC (N=121) Comparator: ENGERIX-B (N=42)	BECT001 (Phase III)	General disorders and administration site conditions	Common	Injection site pain, Injection site swelling, Injection site redness

*Children (5–10 years) no. of subjects=25; Adolescents (11–20 years) no. of subjects =78; Adults (21 to 35 years) no. of subjects =60

4.9 Overdose

No case of overdose has been reported. There is no specific treatment for an overdose with BE's Hepatitis B vaccine. In the event of an overdose, the individual should be monitored and provided with symptomatic treatment as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Antibodies produced by vaccination target the outer protein coat or surface antigen. This immune response helps in the protection against Hepatitis B virus infection.

5.2 Pharmacodynamics Properties

Pharmacotherapeutic group: Viral vaccines, Hepatitis vaccines, ATC code: J07BC01

Immunological Properties: In clinical trials, BE's Hepatitis B vaccine induced specific antibodies in the vaccines against hepatitis B virus. Three doses of BE's Hepatitis B vaccine immunization elicited high protective antibody levels in the recipients.

Under no circumstances, BE's Hepatitis B vaccine should be given intravenously.

Efficacy and immunogenicity data:

Phase III Clinical Study (BECT001):

In a Phase III clinical study (BECT001) conducted in 166 subjects aged 5-35 years to evaluate, record and analyse the tolerability, safety, immunogenicity and efficacy of the indigenous Hepatitis B vaccine(r-DNA), immunogenicity of the vaccine was found to be comparable to that of the licensed comparator.

Immunogenicity Conclusions

Data on immunogenicity very well concluded that both the study drug i.e., BEVAC® and the licensed comparator were highly immunogenic. The percent seroconversion data depicted a 100% seroconversion response by the 30th day after the 1st injection in both BEVAC® and the licensed comparator arms. The indigenously developed recombinant Hepatitis-B vaccine was found to be safe and well tolerated.

Post Marketing Surveillance Study (BECT058):

In the multicentre single blind, parallel randomized phase-IV non-inferiority study to evaluate the immunogenicity and safety of Biological E's monovalent Hepatitis-B (rDNA) vaccine (BEVAC®) when administered as a first dose to neonates within 24 hours of birth followed by a dose at 6 and 14 weeks of age in comparison with a licensed comparator, immunogenicity of the BEVAC® was found to be comparable to that of the licensed comparator.

Immunogenicity Conclusions

Analysis of immunogenicity parameters indicate that BEVAC® when administered in a three-dose schedule (0-6-14 weeks) was found to be highly immunogenic which was comparable with the licensed comparator vaccine.

The Primary immunogenicity objective of demonstrating non-inferiority of BEVAC® in terms of difference in proportion of subjects seroprotected (protective threshold value ≥10 mIU/mL) against licensed comparator, was met.

Summary of Immunogenicity of BEVAC® across Clinical Studies:

Parameter	BECT001	BECT058
Study population	Healthy children, adolescents and adults BEVAC: 121* ENGERIX-B: 42*	Healthy neonates BEVAC: 219* GENEVAC-B: 222*
Age group	5–35 years	≤24 hours after birth
Vaccination schedule	0, 30 and 60 days	0, 6 and 14 weeks
Comparator vaccine	ENGERIX-B	GENEVAC-B
Assessment time point	Day 30, Day 60 and Day 90	Day 126
Final seroprotection post-vac (Anti-HBs ≥10 mIU/mL)	BEVAC: 100% (121/121) ENGERIX-B: 100% (42/42)	BEVAC: 98.2% (215/219) GENEVAC-B: 99.1% (220/222)

Overall conclusion	BEVAC was immunogenic, achieving 100% seroconversion by Day 30 and 100% seroprotection following completion of the vaccination schedule..	BEVAC induced high seroprotection (98.2%) following the three-dose infant schedule and demonstrated non-inferior immunogenicity compared with the licensed comparator vaccine.

* Per Protocol population

5.3 Pharmacokinetic Properties

Evaluation of pharmacokinetic properties is not required for vaccines.

6. PRECLINICAL SAFETY DATA (NON-CLINICAL PROPERTIES)

6.1 Animal Toxicology or Pharmacology

A 14-day acute toxicity study (Single dose toxicity study) and 60-day chronic toxicity study (Repeat dose toxicity study) were conducted on Hepatitis B Vaccine (rDNA) in mice and rabbits. The objective of the study was to evaluate the potential toxicity of a single dose and repeated doses of Hepatitis B vaccine when administered intramuscularly to mice and rabbits.

A summary of the toxicological effects found in relevant studies conducted in different animal species:

Single dose – No abnormalities detected.

Repeated dose – No abnormalities observed.

Carcinogenicity – No carcinogenicity observed.

Reproductive toxicity - Nil

Genotoxicity (mutagenicity) – No Genotoxicity /Mutagenicity observed.

The study results revealed that that Hepatitis B vaccine was safe during the single and repeat dose toxicity studies in mice and rabbits.

7. DESCRIPTION

Hepatitis B Vaccine is a sterile suspension containing highly purified, non-infectious major surface antigen of the Hepatitis-B virus produced by recombinant DNA technology. The antigen is adsorbed onto high affinity aluminum hydroxide gel particles and hence the suspension appears almost white and translucent. BEVAC® is available in paediatric dose vials

(containing 10 µg HBsAg / dose) as well as adult dose vials (containing 20 µg HBsAg / dose). The vaccine meets the requirements of WHO and IP.

Recombinant technology: The hepatitis-B surface antigen (HBsAg) has been developed in genetically engineered yeast cells of Pichia pastoris which carry the gene that codes for the major surface antigen protein of the hepatitis-B virus (HBV). HBsAg expressed in yeast cells is purified by complex physical, chemical and biochemical processes. The resultant highly purified surface antigen assembles spontaneously into spherical particles of an average diameter of 20-24nm containing non-glycosylated polypeptides in a lipid matrix. An extensive and rigorous in-house R&D process characterized and confirmed that these 20-24nm spherical particles resemble the natural HBsAg protein in their antigenic properties. The efficacy and safety of the formulated Hepatitis B Vaccine is ensured through stringent adherence to the highest standards of bio-process control and consistent quality assurance measures. No substance of human origin is used in the manufacture of HBsAg protein.

8. PHARMACEUTICAL PARTICULARS

8.1 List of Excipients

Purified HBsAg

Aluminium Hydroxide gel equivalent to Al^{+++}

Thiomersal BP

8.2 Incompatibilities

Vaccine should not be mixed in the vial or syringe with any other vaccine unless it is licensed for use as a combined product (e.g. DTP Hep B/ DTP Hep B-Hib).

8.3 Shelf Life

3 years from the date of manufacture.

9. NATURE AND CONTENTS OF CONTAINER

The vaccine is filled in USP Type I glass vials closed bromobutyl rubber stoppers and sealed with aluminium flip-off seals. The vaccine is offered in following presentations.

For Paediatric use:

Single dose vial of 0.5 mL

Two dose vial of 1 mL

Five dose vial of 2.5 mL

Ten dose vial of 5 mL

For Adult use:

Single dose vial of 1 mL

Ten dose vial of 10 mL

9.1 Storage and Handling Instructions

Handling of multi dose vial: Once opened, multi dose vials of Hepatitis B 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 a maximum of 4 weeks, provided that all of the following conditions are met:

- The expiry date has not 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 withdraw all doses
- The vaccine vial monitor (VVM) (if attached) has not reached the discard point.

9.1.1 Special Precautions for Storage

- The vaccine should be stored at a temperature between +2°C to +8°C. Do not freeze. Discard if the vaccine has been frozen. Shake well before use.

9.1.2 Special Precautions for Disposal

Discard if the vaccine has been frozen as per the approved procedures.

10. PATIENT COUNSELLING INFORMATION

BEVAC® is a sterile suspension containing highly purified, non-infectious major surface antigen of the Hepatitis B virus produced by recombinant DNA technology. The body is expected to develop an immune response against hepatitis B virus which would help in prevention of hepatitis B infection.

Common adverse events that have been reported with the BE.'s BEVAC® are soreness at the site of injection, injection site swelling, injection site erythema, irritability postvaccinal or a febrile reaction. In rare cases of post vaccinal hypersensitivity, the common symptoms that are quickly recognized by the physician are: dizziness, headache, nausea, abdominal pain, rash, pruritus, urticaria, arthralgia, myalgias, decreased appetite, somnolence and similar associated symptoms and side effects.

If you experience any side effect(s), please contact/visit your health provider/Vaccinator/ Officer supervising your vaccination or immediately go to the nearest hospital.

11. MARKETING AUTHORISATION HOLDER

Biological E. Limited

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Manufacturing Site Address:

M/s. Biological E. Limited

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Web site: www.biologicale.com

12. DETAILS OF MARKETING AUTHORISATION NUMBER(S) (DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE)

Permission No: MF-197/2013 (Regularization)
Date of first authorisation: 05/09/2013

13. DATE OF REVISION

09/07/2026