SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Name of the product: Hepatitis-B Vaccine (r-DNA)
Strength:
a) Each pediatric dose of 0.5 mL contains
Hepatitis B surface Antigen (HBsAg)…….. ≥10 µg
b) Composition: Each adult dose of 1.0 mL contains
Hepatitis B surface Antigen (HBsAg)……... ≥20 µg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition: Each pediatric dose of 0.5 mL contains
Hepatitis B surface Antigen (HBsAg)…….. ≥10 µg
Aluminum Hydroxide Gel equivalent to Aluminum (Al^{+++})….. 0.25 mg
Thiomersal IP ……..…….. 0.025 mg
Phosphate Buffered Saline ……..…… q.s. to 0.5 mL

b) Composition: Each adult dose of 1.0 mL contains
Hepatitis B surface Antigen (HBsAg)……... ≥20 µg
Aluminum Hydroxide Gel equivalent to Aluminum (Al^{+++})…… 0.5 mg
Thiomersal IP…….. 0.05 mg
Phosphate Buffered Saline…….……. q.s. to 1.0 mL

3. PHARMACEUTICAL FORM

Suspension for injection. White or almost white, transparent liquid. Free from particulate matter by visual observation.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Revac-B+ ® is indicated for the immunization of persons against infection by Hepatitis B virus and its common subtypes. It can also be administered to hepatitis C and D virus-infected patients to protect them against co-infection with hepatitis B virus.

Revac-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 hepatocellular carcinoma. In addition, for various groups of individuals, as listed below **Revac-B+®** immunization is an essential requirement:

- Healthcare personnel
- Patients prone to infection due to unscreened or improperly tested blood transfusions
- Hemophiliacs and patients on hemodialysis.
- 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 or hostels
- Household contacts of persons with acute or chronic HBV infection
- Infants born to HBV carrier mothers.
- Organ transplant recipients
- Others: Police, armed forces and other regimented personnel.

4.2 Posology, Schedule and Method of Administration
20µg/mL is the dose for adults and children above 10 years of age.
10µg/0.5mL is recommended for neonates, infants and children below 10 years of age.

A. Primary immunization schedule:
Indian Academy of Pediatrics recommends the following for children:

1. At Birth
2. At 6 weeks of age
3. At 6 months: The final (3rd or 4th) dose is administered no earlier than age 24 weeks and at least 16 weeks after the first dose.

As per the Universal Immunisation Program, the hepatitis B vaccine is provided as part of the pentavalent vaccine at 6. 10 & 14 weeks apart from the birth dose.

Adults: An interval of 30 days given between the administration of the FIRST and SECOND doses, followed by the THIRD dose 180 days after the first dose.

B. Special recommendations:

- To neonates born to HBV-infected mothers, the recommended pediatric dose schedule:
  1st dose on selected date
  2nd dose 30 days after the first dose
  3rd dose 60 days after the first dose
  One booster dose to be administered 1 year after the first dose

Hepatitis B Immunoglobulins may also be given to comprised neonates on advice from a medical practitioner.

- To persons involuntarily exposed by accident to HBV infection:
  The schedule of immunization stated above is recommended at the the pediatric dose level for children and at the adult dose for others.

- Immuno-compromised patients will require additional doses as per the schedule given:
  1st dose of 40 µg (2mL), on the first day
  2nd dose of 40 µg (2mL), 30 days after the first dose
  3rd dose of 40 µg (2mL), 60 days after the first dose
  4th dose of 40 µg (2mL), 180 days after the first dose

C. Method of Administration

Revac-B+® should be injected deep intramuscularly into the deltoid region in adults and in the Antero-lateral aspect of the thigh in neonates, infants and young children.

Revac-B+® should not be injected into the gluteal muscle. This route of administration may result in lower immune response. Under no circumstance **Revac-B+®** should be given intravenously.

4.3 Contraindications

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

4.4 Special warning and Precautions for use

- Do not administer intravenously, intradermally, or subcutaneously.
- Like all other vaccines, supervision and appropriate medical treatment should always be available to treat anaphylactic reactions following immunization.
- Epinephrine injection (1:1000) must be immediately available in case of an acute anaphylactic reaction or any allergic reaction due to any vaccine component.
- The vaccinee should remain under medical supervision for at least 30 minutes after vaccination.

While using the multi-dose vial, care must be taken to use a separate sterile syringe and needle to administer every dose. Used multi-dose vial that contains the remaining vaccine must be stored at the recommended storage temperature and reexamined carefully before reuse. A multi-dose vial of **Revac-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 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
- An aseptic technique has been used to withdraw all doses

Before use, **Revac-B+ ®** should be well shaken to obtain a uniform, whitish translucent suspension. The vial should be visually checked for the presence of any particulate matter or other coloration, prior to its administration. If in doubt, do not use the contents of the vial.

Revac-B+ ® can be administered simultaneously with BCG, DTP, OPV and measles vaccines that are extensively used in the Universal Immunization Program (UPI). **Revac-B+ ®** should always administered at a different injection site in the event of its use along with UPI vaccines.

Revac-B+ ® should not be mixed with other vaccines.

NOTE: Because of the longer incubation period, hepatitis-the hepatitis B virus takes a long time to manifest symptoms; some subjects may receive the vaccine while the infection remains unrecognized. In such cases, the vaccine may not prevent the onset of hepatitis due to the hepatitis B virus.

Revac-B+ ® 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 Interactions with Other Medicinal Products

The simultaneous administration of **Revac-B+ ®** and a standard dose of HepBIg does not result in lower anti-HBs antibody concentrations provided that they are administered at separate injection sites.

Revac-B+® can be given concomitantly with *Haemophilus influenzae* type b, BCG, hepatitis A, polio, measles, mumps, rubella, diphtheria, tetanus and pertussis vaccines, human papillomavirus (HPV)

Different injectable vaccines should always be administered at different injection sites.

Revac-B+ ® may be used to complete a primary immunization course started either with plasma-derived or with other genetically-engineered hepatitis B vaccines, or, if it is desired to administer a booster dose, it may be administered to subjects who have previously received a primary immunization course with plasma-derived or with other genetically-engineered hepatitis B vaccines.

4.6 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 fetus. No contraindication was recorded for the use of the vaccine in lactating mothers. However, the decision to immunize pregnant and lactating mothers may be made 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 **Revac-B+ ®** on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Revac-B+® is well tolerated.
Inflammation at the injection site 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, pruritis, urticaria, arthralgia, myalgias and similar associated symptoms and side effects.

4.9. Overdose

No data available

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Not Applicable

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Pre-clinical safety data

A 60-day repeat dose non-clinical toxicity study in mice and guinea pigs was conducted to obtain information on the chronic toxicity of the hepatitis B vaccine in mice and guinea pigs after administration of the vaccine by intramuscular route dosing on 0, 7th and 14th day. Food consumption, body weight, biochemical, hematology parameters were estimated, and all parameters were normal. No detectable signs of pain, edema or inflammation were observed at the site of injections. Based on the results, **Revac-B+®** was safe at the doses used in chronic toxicity studies in mice and guinea pigs.

Clinical Study Data
A phase 3 clinical trial was conducted to study the reactogenicity and immunogenicity of yeast-derived Hepatitis B vaccine in 196 healthy adults. Blood samples were collected and immunogenicity was tested on Day 30, 60 and 90 and **Revac-B+ ®** was safe & and immunogenic comparable to other commecrial vaccine.

A multi-center post marketing surveillance was conducted to establish the safety of **Revac-B+ ®** produced in *Pichia pastoris* in 1185 subjects aged from less than 1 month to about 70 years. The adverse events commonly seen were minor local reactions, such as pain at the site of injection. Pruritus and systemic reactions like fever (3.2%) within levels observed in similar studies earlier. This study thus conclusively establishes that the recombinant Hepatitis B vaccine, **Revac-B+ ®** produced in *Pichia pastoris* is safe for all age groups including neonates. No unexpected adverse vaccine reactions were observed during the study.

A post-marketing study evaluated safety and boosting effect in children receiving one booster dose of **Revac-B$^{+®}$** in subjects aged between 5 and 6 years. Serum samples were subjected to ELISA tests (AUSAB) and the titers were expressed as mIU/mL. An increase in the antibody titers from less than 1.0 mIU/mL to a value >1mIU /mL was considered seroconverted. A four-fold increase in the titer was considered significant. A titer of greater than 10 mIU/mL is considered seroprotective. No unexpected or untoward reactions have been reported.

Another post-marketing study evaluate the safety and immunogenicity of infants receiving their first two doses of **Revac-B$^{+®}$** on day 1 and day 30 in 282 subjects, aged between 3 and 6 months. Vaccine administration: The mean titer value increased from 0.47 m IU in the first sample to 155.24 mIU/mL. The phase 4 study in infants proved the immunogenicity of **Revac-B$^{+®}$** as high as 99% seroconversion.2% of subjects showed local reactions during the study The results conclusively establish that the recombinant Hepatitis B vaccine (**Revac-B$^{+®}$**) produced in *Pichia pastoris* by Bharat Biotech is safe and immunogenic in children and adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

- Aluminum Hydroxide Gel equivalent to Aluminium (Al^{+++})
- Thiomersal IP
- Phosphate Buffered Saline

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf Life

The expiry date of the vaccine is indicated on the label and carton of the product.

6.4 Special Precautions for Storage

Store at +2°C to +8°C. Shake well before use. Do not freeze. Discard if frozen.
Keep out of reach of children.
Experimental data at the production and R&D laboratories, have shown the formulation to be stable and potent for 36 months at +2°C to +8°C.
The vaccine's exposure to higher temperatures, 37°C for 1 month and 45°C for 1 week, did not result in the loss of its immunogenicity.

6.5 Nature and contents of the container

Revac-B+® is presented in USP type 1 glass vial. The content, upon storage, may present a fine white with a clear colourless supernatant. Once shaken, the vaccine is slightly opaque.
Pediatric Single dose : ……. 0.5 mL
Pediatric Multi-dose: …….. 2.5 mL
Pediatric Multi dose: ……. 5 mL
Adult Single dose: ……. 1 mL
Adult Multi-dose : …… 10 mL

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bharat Biotech International Limited, situated

Sy. No. 230, 231 & 235, Genome Valley,

Turkapally, Shamirpet Mandal,

Medchal, Malkajgiri District, Telangana State, India, Pin: 500078.

8. MARKETING AUTHORISATION NUMBER
12-30/86-DC

9. DATE OF FIRST MARKETING AUTHORISATION
14 OCT 1998

10. DATE OF REVISION
July 2023