Summary of Product Characteristics (SmPC)

1. Name of the Medicinal Product:

Brand Name:

Revac-B+®

Generic Name:

Hepatitis B Vaccine (rDNA) BP

Revac-B+® is a sterile suspension containing purified, non-infectious major surface antigen of the Hepatitis-B virus and is manufactured by recombinant DNA technology. The antigen is adsorbed onto high affinity aluminium hydroxide gel molecules and hence the suspension appears almost white and translucent.

Revac-B+® fulfils WHO Requirements for Hepatitis-B Vaccine made by recombinant DNA technique.

Recombinant Technology:

The Hepatitis-B Surface Antigen (HBsAg) is produced 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. HBsAg expressed in yeast cells is purified by complex physical, chemical and biochemical process. 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 R&D processes characterised and confirmed than these 20-24nm spherical particles resemble the natural HBsAg protein in their antigenic properties. The efficacy and safety of the formulated **Revac-B+®**is ensured through stringent adherence to the highest standards of the bio-process control and consistent Quality Assurance measures. **No substance of human origin is used in the manufacture of the HBsAg protein.**

2. Qualitative and Quantitative Composition:

a) Composition: Each Paediatric dose of 0.5mL contains

Hepatitis B surface Antigen(HBsAg)	≥10 µg
Aluminium hydroxide gel equivalent to Aluminium(Al^{+++})	0.25 mg
Thiomersal BP	0.025 mg
Phosphate buffered saline	q.s to 0.5 ml

b) Composition: Each adult dose of 1.0ml contains

Hepatitis B surface Antigen(HBsAg)	≥20 µg
Aluminium hydroxide gel equivalent to Aluminium(Al^{+++})	0.5 mg
Thiomersal BP	0.05 mg
Phosphate buffered saline	q.s to 1.0 ml

3. Pharmaceutical Form:

Suspension for injection.

4. Clinical Particulars:

4.1 Therapeutic indications:

Revac-B+® is indicated for immunization of persons against infection by hepatitis-B virus and its common sub-types. It can also be given 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
- Haemophiliacs and patients on haemodialysis

- Travellers 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 HBV infection
- Infants born to HBV carrier mothers
- Organ transplant receivers
- Others: Police, armed forces and other such regimented personnel.

4.2 Posology and method of administration:

Posology:

20µg/mL is the dose for adult and children above 10 years of age.

10µg/0.5mL is recommended for neonates, infants and children below the 10 years of age.

A. <u>Primary immunization schedule</u>:

Indian Academy of Pediatrics recommends as follows for children:

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

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

Adults: An Interval of 30 days should be given between FIRST and SECOND doses, followed by the third dose 180 days after the first dose.

B. <u>Special recommendations</u>:

To neonates born to HBV infected mothers the recommended paediatric 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 compromised neonates on advice from the medical practitioner.

- To persons involuntarily exposed by accident to HBV infection:

The schedule of the immunization stated at (B) is recommended at paediatric dosage level for children and as adult dose for others.

- Immuno-compromised patients will require additional dosage 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

Method of Administration:

Revac-B+®should be injected deep intramuscularly into the deltoid region in adults and in the anterio-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 circumstances should **Revac-B+®**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 components of the vaccine. Avoid immunization during severe febrile illness.

4.4 Special warnings and special 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 any anaphylactic reactions following immunisation.

Epinephrine injection (1:1000) must be immediately available in case of any acute anaphylactic reactions or any allergic reactions occurs due to any component of the vaccine.

The vaccine should remain under medical supervision for atleast 30minutes after the vaccination.

While using the multi dose vial care must be taken to use separate sterile syringe and needle for the administration of every dose. Used multi dose vial that contains remaining vaccine must be stored at recommended storage temperature and rexamine carefully prior to reuse. A multi dose vial of **Revac-B**$^{+®}$from which one or more doses of vaccine have been removed during an immunisation session may be used in subsequent immunisation sessions for upto maximum of 4weeks, provide that all the following conditions are met.

- The expiry date has not passed.
- The vaccine are stored under appropriate cold chain conditions.
- The vaccine vials septum has not been submerged in water.
- Aseptic technique has been used to withdraw all doses

Before use, **Revac-B**$^{+®}$should be well shaken to obtain a uniform, Whitish Translucent suspension. Vial should be visually checked for the presence of any particulate matter or any other coloration, if any prior to its administration. If in doubt do not use the contents of the vial.

Revac-B$^{+®}$can be administered at the same time as BCG, DTP & OPV &Measles vaccines that are extensively used in the Universal Immunisation Programme (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 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.

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 Interaction 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 influenza 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 immunisation course started either with plasma derived or with other genetically-engineered hepatitis B vaccine or if it is desired to administer a booster dose, it may be administered to the subjects who have previously a primary immunisation 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 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 the 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.

4.7 Adverse Reactions

Revac-B+® is well tolerated

Inflammation 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 physicist are dizziness, headache, nausea, abdominal pain, rash, pruritus, arthralgia, myalgias and simisal associated symptoms and side-effects.

4.8 Over dose

Not Applicable**.**

5.0 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 repeated non clinical toxicity study in mice and guinea pigs were conducted is to obtain information on the chronic toxicity of 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, haematology parameters were estimated and all parameters normal. No detectable signs of pain, edema or inflammation were observed at site of injections based on the results, **Revac-B$^{+®}$**was safe at the doses used in chronic toxicity study in mice and Guinea pigs.

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 commercial 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 all age group including neonates. No unexpected adverse vaccine reactions were observed during the study.

A post marketing study was conducted to evaluate 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 (AUSAB) and the titres were expressed as mIU/mL. An increase in the antibody titres from less than 1.0 mIU/mL to a value >1mIU/mL was considered to be seroconverted. A four – fold increase in the titer than 1.0mIU/mL to a value >1mIU/mL was considered to be seroconverted. A fourfold increase in the titer was considered significant. A titer of greater than 10mIU/mL is considered sero protective. No unexpected or untoward reactions have been reported.

Another post-marketing study was conducted to evaluate safety and immunogenicity in infants receiving their first two doses of **Revac-B$^{+®}$** on day 1 and day 30 in 282 subjects, aged between 3 and 6 moths vaccine administration the mean titer value increased from 0.47mIU in the first sample to 155.24mIU/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.

6.0 Pharmaceutical Particulars

6.1 List of excipients:

Aluminium hydroxide gel equivalent to Aluminium (Al^{+++})

Thiomersal BP

Phosphate buffered saline

6.2 Incompatibility:

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 Storage:

Store at +2°C to 8°C. Shake well before use. Do not freeze. Discard if frozen. Keep out of reach of Children.

6.5 Nature and content of container Presentation:

Revac-B+® is presented in USP type 1 glass vial. The content upon storage may present a fine white deposit with a clear colourless supernatant. Once shaken the vaccine is slightly opaque.

Paediatric single dose	: 0.5 mL
Paediatric Multi-dose	: 2.5mL
Paediatric Multi-dose	: 5.0 mL
Adult single dose	: 1.0 mL
Adult Multi-dose	: 10.0 mL

6.6 Special precautions for disposal

Not Applicable.

Safety, Stability and Potency

Revac-B+® contains highly purified HbsAg in a formulation that consistently conforms to pharmacopoeia standards.

Experimental data both 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.

Exposure of vaccine to higher temperature at 37°C for 1 month & 45°C for 1 week did not result in the loss of its immunogenicity.

7.0 Marketing Authorization Holder and Manufacturing Site Address:

Name of the Company	: Bharat Biotech International Limited
Address of the Site & Corporate Office	: Genome Valley, Shameerpet Mandal, Medchal District-500 078, Telangana India.
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