The most frequent effects, according to the total doses administered, were pain at the injection site (27.8%), sneezing (20.5%), nasal discharge (6.8%), slight local burning at the site of inoculation (6.8%), nasal pruritus (5.1%), mild fever less than 38 °C (4.4%) and malaise (4.4%). All these symptoms disappear spontaneously in the first hours without treatment. In any case, it is recommended to consult the doctor before the appearance of any undesirable manifestation.

So far, in the studies carried out, no reactions of greater intensity or serious adverse events have been reported. In other vaccines against hepatitis B anaphylaxis and other types of immediate hypersensitivity reactions are reported in a very low proportion, which take place in the first hours after the administration of the vaccine.

There is no confirmed scientific evidence that hepatitis B vaccines cause diseases of the central or peripheral nervous system, such as Guillain-Barré syndrome, optic neuritis, multiple sclerosis or other demyelinating diseases, chronic fatigue syndrome, rheumatoid arthritis or autoimmune diseases. It is recommended to evaluate the suitability of using an effective treatment for chronic hepatitis B and its sequelae through therapeutic vaccination against the risk, not scientifically confirmed, of inducing any of these diseases.

DOSAGE AND MODE OF ADMINISTRATION

• *First cycle:* **HeberNasvac®** for intranasal application by dispersant: (0.10 mg AgsHB + 0.10 mg AgcHB) / dose of 1.0 mL. Apply one dose every two weeks until completing 5 doses.

• *Second cycle (one month after the end of the first cycle):* **HeberNasvac®** for intranasal application by dispersant: (0.10 mg AgsHB + 0.10 mg AgcHB) / dose of 1.0 mL and simultaneously **HeberNasvac®** for subcutaneous injection: (0.10 mg AgsHB + 0.10 mg AgcHB) / dose of 1.0 mL. One dose of each is applied every two weeks until the 5 combined doses of both routes of administration are completed.

INTERACTIONS WITH OTHER MEDICATIONS

HeberNasvac® is a therapeutic vaccine that has been shown to be safe and effective as monotherapy. Its simultaneous application with other specific therapies for the treatment of hepatitis B still needs to be studied. Co-administration with antivirals or with immunomodulatory therapies such as interferon or pegylated interferon is not recommended.

USE IN PREGNANCY AND LACTATION

Vaccination with **HeberNasvac®** of pregnant women is not recommended, but in case of high-risk situations or other special cases, the doctor may consider administration. It is not necessary to terminate the pregnancy in case of vaccination of the pregnant woman. Breastfeeding is not a contraindication for treatment with **HeberNasvac®**.

EFFECTS ON DRIVING VEHICLES AND MACHINERY

Although the reactogenicity of **HeberNasvac®** is very low, local symptoms such as pain at the injection site, sneezing and nasal discharge or itching may occur, which, if they become intense in people with Under threshold, they could affect your ability to drive and use machines.

Center for Genetic Engineering and Biotechnology

Distinctive company of Cuban biotechnology which develops, produces, markets and exports innovative products, for key areas of the biomedical, veterinary, agricultural, aquaculture and industrial sectors, for one health. It has a portfolio of research and development (R&D) projects and products, protected by patents. Its more than 30 products marketed in more than 35 countries, include first and only drugs of its kind, to treat diseases that do not have other effective therapeutic solutions. Several of its medicines are inserted into national programs to offer comprehensive health care. We work with social responsibility and in harmony with the environment.

CIGB CENTRO DE INGENIERÍA GENÉTICA Y BIOTECNOLOGÍA

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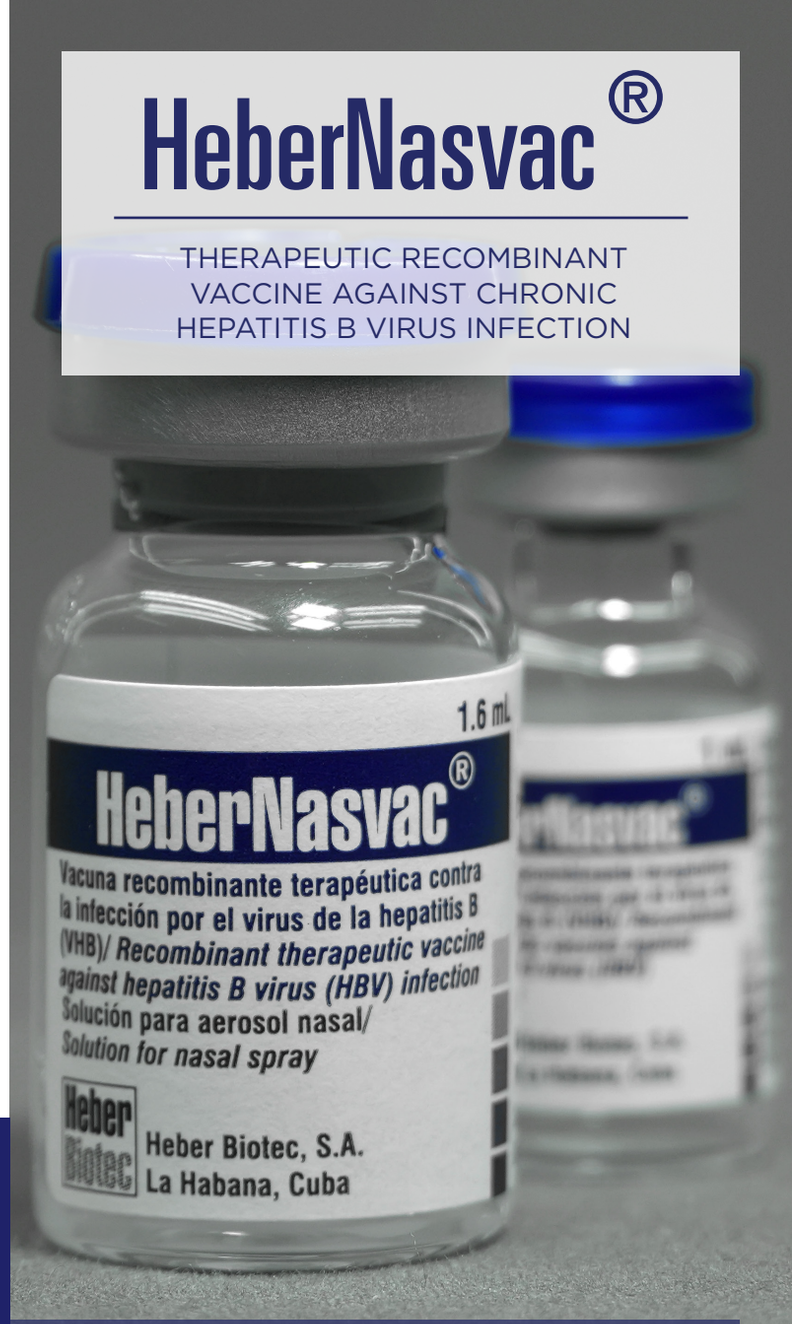
HeberNasvac®

THERAPEUTIC RECOMBINANT VACCINE AGAINST CHRONIC HEPATITIS B VIRUS INFECTION



SAFETY AND WELFARE

HeberNasvac®

Therapeutic recombinant vaccine against chronic hepatitis B virus infection

SAFETY AND WELFARE

- VACCINE FOR IMMUNOTHERAPY AGAINST CHRONIC HEPATITIS B VIRUS INFECTION AND FOR PREVENTION OF ITS POSSIBLE CONSEQUENCES.
- IT IS ADMINISTERED THROUGH THE INTRANASAL (MUCOSAL) AND PARENTERAL (SUBCUTANEOUS) PATHWAYS.
- IT INDUCES A STRONG IMMUNE RESPONSE.

PHARMACEUTICAL FORM

Nasal spray solution and subcutaneous injection solution.

STRENGTH

AgsHB 100 µg/mL + 100 µg/mL hepatitis B virus nucleocapsid antigen (AgcHB).

PRESENTATION

- Cases per 1; 5; 10 or 25 clear glass vials with 1.6 mL each of nasal spray solution.
- Cases per 1; 5; 10 or 25 clear glass vials with 1 mL each of subcutaneous injection solution.

COMPOSITION

HeberNasvac® has the same composition in its nasal spray presentation as in the subcutaneous injection solution. Each dose of 1 mL contains hepatitis B virus surface antigen (AgsHB) 0.10 mg; hepatitis B virus nucleocapsid antigen (AgcHB) 0.10 mg; disodium hydrogen phosphate (Na_2HPO_4); sodium hydrogen phosphate dihydrate (NaH_2PO_4 x $2H_2O$); disodium salt of ethylenediamine-tetraacetic acid dihydrate (EDTA); sodium chloride (NaCl); water for injection c.s.

SHELF LIFE AND STORAGE CONDITIONS

It is stable during 36 months. Store and transport at 2 to 8 °C (Refrigeration). Do not freeze.

INDICATIONS

HeberNasvac® is indicated for active immunotherapy against chronic hepatitis B virus infection and for the prevention of its possible consequences, such as liver cirrhosis, chronic liver failure and primary hepatocarcinoma. It should be applied to patients before these complications arise, as its usefulness and risk-benefit ratio in those who already suffer them have not yet been studied. It is not recommended for use in children under 18 years of age, since clinical experience with this product, due to its novelty, is based exclusively on adults.

Only for adults and under medical prescription

CONTRAINDICATIONS

It should not be administered to patients with febrile conditions, acute or chronic decompensated diseases, and should be expected to improve the clinical picture to start or continue treatment.

Do not administer to people allergic to any component of the vaccine, or who have suffered a serious adverse reaction to a previous dose.

HeberNasvac® should not be administered to patients with ALAT or ASAT enzyme levels above 500 IU/L. Nor should it be administered to patients with hepatocellular carcinoma, liver cirrhosis or a history of liver transplantation.

PRECAUTIONS

It is recommended to use with caution in cases of patients in whom chronic hepatitis B concomitates with other liver conditions of another nature, for example alcoholism, autoimmune hepatitis, toxic hepatitis, Wilson disease, hemochromatosis and coinfection with hepatitis C virus.

HeberNasvac® produces a known transient increase in ALAT enzymes during or after treatment, which is associated with its mechanism of action. Periodic monitoring of liver function should be considered during and after treatment.

The safety and effectiveness of **HeberNasvac®** in pediatric patients has not yet been established.

A sufficient number of patients over 65 years of age have not been evaluated to determine whether they respond differently to younger individuals.

In patients with compromised immune response, such as those receiving immunosuppressive therapies (eg. corticosteroids, cytotoxic agents, among others), in patients undergoing hemodialysis treatment and those suffering from HIV/AIDS immunodeficiencies or other causes, the property of **HeberNasvac®** to achieve an effective immune response.

Vaccination with **HeberNasvac®** of pregnant women is not recommended. It is not necessary to terminate the pregnancy in case of unintentional vaccination of the pregnant woman.

As with any vaccine, an epinephrine solution (1:1000) should be available, ready for immediate use in a rare and unexpected case where an anaphylactic reaction or another acute hypersensitivity reaction may occur.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Although **HeberNasvac®** is a transparent and essentially homogeneous solution, some small particles of protein agglomerates can be observed, characterized by particles inherent in the product. The product should be discarded if a change in color occurs.

It should not be mixed in the bulb or syringe with any other vaccine.

Do not administer intravenously.

UNDESIRABLE EFFECTS

Clinical studies show that the **HeberNasvac®** therapeutic vaccine is highly safe. Adverse effects occur only in a small number of people, are mild and short-lived.