SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

PreHevbri 10 micrograms suspension for injection
Hepatitis B vaccine (recombinant, adsorbed)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (1 mL) contains:

Hepatitis B surface antigens (S [83%], pre-S2 [11%] and pre-S1 [6%]) [1, 2]
10 micrograms

[1] Adsorbed on 500 micrograms of Al^{3+} as aluminium hydroxide, hydrated

[2] Produced in Chinese Hamster Ovary cells by recombinant DNA technology

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection (injection)
Clear, colourless with a fine white deposit.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PreHevbri is indicated for active immunisation against infection caused by all known subtypes of the hepatitis B virus in adults.

It can be expected that hepatitis D will also be prevented by immunisation with PreHevbri as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

The use of PreHevbri should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Vaccination schedule
The vaccination schedule consists of 3 doses (1 mL each) given according to the following schedule: first dose at an elected date; second dose 1 month after the first dose; third dose 6 months after the first dose.

Booster dose
The need for a booster dose has not been established. No data are available.

Elderly population
No dose adjustments are required in elderly persons aged 65 years and older (see section 5.1).

Paediatric population
The safety and efficacy of PreHevbri in children have not yet been established. Limited data are available.

Method of administration
PreHevbri should be injected intramuscularly (IM) into the deltoid region.
Do not inject intravascularly, subcutaneously or intradermally.

For instructions on handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

History of severe allergic reaction, such as anaphylaxis, after a previous dose of any hepatitis B vaccine.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

As with all injectable vaccines, appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

Vaccination should be postponed in subjects suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia, and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury.

Hepatitis B has a long incubation period. PreHevbri may not prevent hepatitis B infection in individuals who have an unrecognised hepatitis B infection at the time of vaccine administration.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

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

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in subjects receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these subjects.

Immunodeficiency

Immunocompromised persons may have a diminished immune response to PreHevbri. There are limited data available among immunocompromised population. Attention should be given to ensure that a protective antibody level is maintained as defined by national recommendations and guidelines.

Patients with chronic liver disease or with HIV infection or hepatitis C carriers should not be

precluded from vaccination against hepatitis B. The vaccine could be advised since hepatitis B infection can be severe in these patients: the PreHevbri vaccination should thus be considered on a case by case basis by the physician.

Hepatitis B surface antigen (HBsAg) derived from hepatitis B vaccines has been transiently detected in blood samples following vaccination. Serum HBsAg detection may not have diagnostic value within 28 days after administration of PreHevbri.

Renal impairment

Pre-haemodialysis and haemodialysis patients are at risk of exposure to hepatitis B virus and have a higher risk of becoming chronically infected. Attention should be given to ensure that a protective antibody level is achieved and maintained as defined by national recommendations and guidelines.

Excipients with known effect

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. is essentially 'sodium-free'.

Potassium

This medicinal product contains less than 1 mmol potassium (39 mg) per dose, i.e. is essentially potassium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

There are no data on co-administration of PreHevbri with other vaccines. The concomitant use of PreHevbri with other vaccines is not recommended.

When concomitant administration of PreHevbri and immune globulin is required, they should be given with different syringes at separate injection sites.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of the vaccine in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Vaccination during pregnancy should only be performed if the benefit/risk ratio at individual level outweighs possible risks for the foetus.

Breast-feeding

It is unknown whether PreHevbri is excreted in human milk.

A risk to the breastfed newborn/infant cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to abstain from PreHevbri vaccination taking into account the benefit of breast-feeding for the child and the benefit of vaccination for the woman.

Fertility
There are no data on fertility in humans from the use of PreHevbri.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

PreHevbri has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 (e.g. fatigue, headache, dizziness) may temporarily affect the ability to drive or operate machines.

4.8 Undesirable effects

Summary of safety profile
The clinical trial safety profile of PreHevbri is based on two Phase 3 controlled clinical trials (Sci-B-Vac-001 and Sci-B-Vac-002) in which 2 920 adults received at least one dose of PreHevbri.

Local and systemic post-injection reactions were monitored using diary cards for a 7 -day period starting on the day of each vaccination (solicited adverse events).
The most common solicited local reactions were injection-site pain (72.2%), tenderness (71.2%) and local pruritus/itching (12.2%). Most common solicited systemic reactions were myalgia (41.7%), fatigue (37.5%), and headache (36.3%).

The frequency and severity of solicited adverse events generally declined or remained similar with successive vaccinations.

Tabulated list of adverse reactions
The information in the table below is taken from data from the two pivotal studies and includes both solicited and spontaneously reported adverse reactions.

The frequency of adverse reactions is defined as follows:
Very common: (≥1/10)
Common: (≥1/100 to <1/10)
Uncommon: (≥1/1000 to <1/100)
Rare: (≥1/10,000 to <1/1000)
Very rare: (<1/10,000)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse Reactions by System Organ Class and Frequency

System Organ Class	Adverse Reaction	Frequency
Blood and Lymphatic System Disorders	Lymphadenopathy	Uncommon
Gastrointestinal Disorders	Diarrhoea[1], nausea/vomiting[1]	Common
	Abdominal pain	Common
General Disorders and Administration Site Conditions	Injection site pain[1], injection site tenderness[1], injection site pruritus[1], fatigue[1],	Very Common
	Injection site swelling[1], injection site redness[1]	Common
	Injection site bruising	Common
	Fever[1]	Common
Nervous System Disorders	Headache[1]	Very Common
	Dizziness	Common
Musculoskeletal and Connective Tissue Disorder	Myalgia[1]	Very Common
	Arthralgia	Common
Skin and Subcutaneous Tissue Disorders	Urticaria, pruritus	Uncommon
	Rash	Common
Vascular disorders	Flushing, hot flush	Uncommon

[1] Local and systemic adverse reactions collected using diary cards. Adverse events collected on the diary cards included local (pain, tenderness, erythema/redness, pruritus/itchiness and oedema/swelling) and systemic (nausea/vomiting, diarrhoea, headache, fever, fatigue and myalgia) solicited adverse events.

Additional information in special populations
Safety data are limited in immunocompromised adults, in adults previously vaccinated for hepatitis B and in adults with chronic renal failure, including patients on haemodialysis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No cases of overdose have been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hepatitis B vaccines, purified antigen ATC code J07BC01

Mechanism of action
PreHevbri contains the full antigenic composition of the hepatitis B virus surface antigen, including the small (S), middle (pre-S2) and large (pre-S1) hepatitis B surface antigens in a virus-like particle structure and confers immunity against all known subtypes of hepatitis B virus infection through the stimulation of a specific immune response, as measured by the induction of anti-HBs antibodies at a level ≥10 mIU/mL

Clinical immunogenicity
The immunogenicity of PreHevbri was evaluated in comparison with a licensed hepatitis B vaccine (Engerix-B) in two randomised, active controlled, double-blinded, multi-centre Phase 3 clinical trials in adults. PreHevbri and Engerix-B were given as a 3-dose regimen at 0, 1, and 6 months.

Study Sci-B-Vac-001 in adults age ≥18 years
The primary immunogenicity endpoint of the study was the seroprotection rate (SPR), defined as the percentage of subjects with anti-HBs levels of ≥10 mIU/mL The two co-primary analyses, tested hierarchically, were:
(1) non-inferiority of PreHevbri compared to Engerix B at Day 196, 4 weeks after receiving the third dose in all adults age ≥18 years and (2) superiority of PreHevbri compared to Engerix-B in subjects ≥45 years old at Day 196.

Non-inferiority was met if the lower bound of the 95% confidence interval (CI) of the difference in SPR (PreHevbri minus Engerix B) was greater than -5%. Superiority was met if the lower bound of the 95% CI of the difference in SPR (PreHevbri minus Engerix B) was greater than 0%.

The study met both co-primary endpoints. The SPR in subjects ≥18 years of age in the PreHevbri group was non-inferior to the Engerix B group at Study Day 196 (91.4% vs. 76.5%) and the SPR in subjects ≥45 years of age was superior to the Engerix B group at Study Day 196 (89.4% vs. 73.1%). Higher SPR and anti-HBs titres (GMC, geometric mean concentration) were noted for PreHevbri compared with Engerix-B at all time points (Table 2), with peak titres at Day 196 (1424.52 mIU/mL vs. 235.43 mIU/mL) and persistent titres at Day 336 (546.79 mIU/mL vs. 83.48 mIU/mL). Results were consistent across key subgroups based on age, gender, diabetes status, BMI, daily alcohol consumption, and smoking status, with all lower bounds of 95% CIs of the difference in SPR being above the preset margin of non-inferiority and superiority (Table 2).

Table 2: Seroprotection Rate (SPR) and Geometric Mean Concentration (GMC) of Anti-HBs Titres of PreHevbri and engerix B at Day 196

Study population and subgroups	PreHevbri			engerix B			Difference in SPR (PreHevbri – engerix B)
	N	SPR (95% CI)	GMC (mIU/mL)	N	SPR (95% CI)	GMC (mIU/mL)	Difference (95% CI)
Adults (age 18+)	718	91.36% (89.07, 93.32)	1424.52	723	76.49% (73.22, 79.53)	235.43	14.88% (11.18, 18.63)
Age 18-44	125	99.20% (95.62, 99.98)	4550.39	135	91.11% (84.99, 95.32)	727.67	8.09% (3.40, 14.22)
Age 45-64	325	94.77% (91.76, 96.92)	1558.30	322	80.12% (75.34, 84.34)	274.80	14.65% (9.75, 19.81)
Age 65+	268	83.58 (78.59, 87.81)	414.24	266	64.66% (58.59, 70.40)	64.31	18.92% (11.60, 26.14)
Diabetes (age 18+)	54	83.33% (70.71, 92.08)	448.89	60	58.33% (44.88, 70.93)	73.68	25.00% (8.37, 40.36)
BMI >30 kg/m^2 (age 18+)	269	89.22% (84.89, 92.66)	1005.16	254	68.11% (61.99, 73.80)	131.35	21.11% (14.29, 27.97)

N = number of subjects evaluated in the Per-Protocol Set; SPR = Seroprotection Rate defined as anti-HBs titres ≥10 mIU/mL in serum; GMC = Geometric Mean Concentration (adjusted)

Enrolment of subjects in Sci-B-Vac-001 to receive either PreHevbri or Engerix B was stratified by three age groups: age 18-44 years (n=125 vs. n=135 subjects), age 45-64 years (n=325 vs. n=322, and age 65+ (n=268 vs. n=266. PreHevbri achieved higher seroprotection rates in each of these groups at Day 196, four weeks after the third dose (age 18-44: 99.2% vs. 91.1%; age 45-64: 94.8% vs. 80.1%; age 65+: 83.6% vs. 64.7%).

<u>Study Sci-B-Vac-002 in adults age 18-45 years</u>

The primary endpoint of the study was to compare 3 lots of PreHevbri and Engerix-B for immune response assessed by measuring GMC of anti-HBs. The data from the three lots were combined (pooled) to demonstrate that the SPR on Study Day 196, 4 weeks after completion of the 3-dose regimen of PreHevbri was non-inferior to Engerix-B. Non-inferiority of PreHevbri

compared to Engerix B was based on the difference in SPR and the lower bound of the 2-sided 95% CI, using the preset margin of -5%.

The GMC of anti-HBs titres in the PreHevbri groups were consistent across all three lots and higher than Engerix B at all time points, including at peak at Study Day 196 (Lot A: 5979.5 mIU/mL; Lot B: 4855.3 mIU/mL; Lot C: 5553.2 mIU/mL vs. 1526.3 mIU/mL). The SPR in the pooled PreHevbri group was also higher at each time point than Engerix B and demonstrated non-inferiority at Day 196 (99.3 vs. 94.8) after the required 3-dose course (Table 3).

Table 3: Seroprotection Rate (SPR) and Geometric Mean Concentration (GMC) of Anti-HBs Titres of PreHevbri and Engerix B in Adults Age 18-45

Timepoint	PreHevbri Pooled			Engerix B			Difference in SPR (PreHevbri – Engerix B)
	N	SPR (95% CI)	GMC (mIU/mL)	N	SPR (95% CI)	GMC (mIU/mL)	Difference (95% CI)
Day 196	1753	99.26% (98.74. 99.60)	5443.07	592	94.76% (92.65, 96.41)	1526.26	4.49 (2.90, 6.63)
Day 336	1718	98.66% (98.00, 99.15)	2093.80	580	92.41% (89.95, 94.43)	473.02	6.25 (4.26, 8.74)

N = number of subjects in the Per-Protocol Set 2 (received all 3 doses at months 0, 1 and 6); SPR = Seroprotection Rate defined as % of subjects with anti-HBs titers
≥10 mIU/mL in serum; Pooled PreHevbri includes the PreHevbri Lots A, B, and C

The safety and immunogenicity of PreHevbri observed in the two pivotal studies, Sci-B-Vac 001 and Sci-B-Vac 002, are supportive of that observed in 11 adult legacy studies.

Paediatric Population
The European Medicines Agency has waived the obligation to submit the results of studies with PreHevbri in all subsets of the paediatric population for the prevention of hepatitis B virus infection.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of the hepatitis B surface antigen used in PreHevbri have not been assessed.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single-dose and repeat-dose toxicity (including local tolerance) and reproductive and developmental toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Potassium chloride
Disodium phosphate dodecahydrate
Potassium dihydrogen phosphate
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

For adsorbent, see section 2.

6.2 Incompatibilities

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

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Store in the original package, in order to protect from light.

6.5 Nature and contents of container

1 mL suspension in a single-dose glass vial, fitted with a rubber stopper and sealed with an aluminium seal with a plastic coloured flip-off top.

Pack size: 1 or 10 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The vaccine should be used under aseptic conditions.

The suspension should be shaken well prior to administration.

The suspension is slightly white opaque when mixed. Upon settling, the solution is clear and colourless with a white deposit.

The suspension should be visually inspected prior to administration. In the event of any foreign particulate matter and/or variation of the appearance being observed, discard the vaccine.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

VBI Vaccines B.V.
Delflandlaan 1
Queen’s Tower, No. 714
1062EA Amsterdam
Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 54272/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 May 2022

10 DATE OF REVISION OF THE TEXT

16/01/2024