ANNEX I

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-S1 [11%] and pre-S2 [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. PreHevbrio 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 national reporting system listed in Appendix V.

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%).

Study Sci-B-Vac-002 in adults age 18-45 years

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

3 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 aluminum seal with a plastic coloured flip-off top.

Pack size: 10 vials

6.6 Special precautions for disposal and other handling

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)

EU/1/22/1641/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

{DD month YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

SciVac Ltd.
13 Gad Feinstein Road
POB 580, Rehovot, 7610303
Israel

Name and address of the manufacturer(s) responsible for batch release

MIAS Pharma Limited
Suite 2, Stafford House
Strand Road, Portmarnock
County Dublin, D13 H525
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 mL contains10 mcg of Hepatitis B Surface Antigens (S, pre-S1, pre-S2).

3. LIST OF EXCIPIENTS

Excipients: Sodium chloride, Potassium chloride, Disodium phosphate dodecahydrate , Potassium dihydrogen phosphate, Aluminium hydroxide gel, Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
10 x 1 mL single-dose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Read package leaflet before use.
Shake well before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1641/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

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

2. METHOD OF ADMINISTRATION

IM

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

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

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What PreHevbri is and what it is used for

PreHevbri is a vaccine which prevents infection caused by the hepatitis B virus. It is used in adults to protect from all known types of hepatitis B virus.

PreHevbri may also protect against hepatitis D which can only occur in people who have hepatitis B infection.

What is hepatitis B
- Hepatitis B is an infectious illness of the liver caused by a virus. Hepatitis B virus infection can cause serious liver problems such as “cirrhosis” (scarring in the liver) or liver cancer.
- Some people infected with the hepatitis B virus become carriers, which means that they may not feel ill but continue to have the virus in their body and they can still infect other people.
- The disease spreads by the hepatitis B virus entering the body through contact with an infected person’s body fluids, such as in the vagina, blood, semen, or spit (saliva). A mother who is a carrier of the virus can also pass the virus to her baby at birth.
- The main signs of the illness include mild signs of flu (such as headache and fever, feeling very tired, dark urine, pale stools [faeces], and yellowing of the skin and eyes [jaundice]). However, some people with hepatitis B do not look or feel ill.

How PreHevbri works

When a person is given the PreHevbri vaccine, it helps the body’s natural defence system (immune system) produce specific protection (antibodies) against the hepatitis B virus.

- PreHevbri contains a substance (called an ‘adsorbent’) which improves the body’s production of antibodies and makes the protection last for longer.
- A course of three injections of PreHevbri is required to provide full protection against hepatitis B.
- PreHevbri is not used to treat a person who is already infected with the hepatitis B virus including anyone who has previously been infected and who is now a carrier of the virus.

- Prehevbri is a ‘3-antigenic’ vaccine, which contains small amounts of the three antigens (pre-S1, pre-S2, S) from the ‘outer coating’ of the hepatitis B virus. This ‘outer coating’ is not infectious and cannot make you ill.

2. What you need to know before you receive PreHevbri

You must NOT receive PreHevbri:
- if you are allergic to the active substance or any of the other ingredients of this vaccine (listed in section 6). Signs of an allergic reaction may include breathing difficulty, swelling, light-headedness, fast heartbeat, sweating, and loss of consciousness.
- if you have ever previously had a sudden, life-threatening allergic reaction to any vaccine against hepatitis B.

You must not receive PreHevbri if either of the above apply to you. If you are not sure, talk to your doctor, pharmacist or nurse before receiving PreHevbri.

Warnings and precautions
- Your doctor, pharmacist or nurse will make sure that appropriate medical treatment is readily available in case you should develop a sudden and rare anaphylactic reaction (a very severe allergic reaction with symptoms such as breathing difficulty, swelling, light-headedness, fast heartbeat, sweating, and loss of consciousness) after you have been given the vaccine. This reaction may occur when any vaccine is injected, including PreHevbri. **Seek <u>urgent</u> medical attention** if you develop any of these symptoms after you are given the injectionas this could be a life-threatening allergic reaction.
- Fainting can occur following, or even before, any needle injection, therefore tell the doctor, pharmacist or nurse if you fainted with a previous injection.
- If you are ill with a high fever, tell your doctor, pharmacist or nurse as they may delay the vaccination until you are feeling better. A minor infection such as a cold should not be a problem, but your doctor, pharmacist or nurse will decide if you could still be vaccinated.
- If you have low blood platelets or any blood-clotting disorders, then bleeding or bruising may occur after you are given the injection. Tell your doctor, pharmacist or nurse if you have any of these conditions.
- PreHevbri may not prevent hepatitis B infection if you already have an unrecognised hepatitis B infection at the time of vaccine administration.
- As with any vaccine, PreHevbri may not protect all people who are vaccinated.
- PreHevbri does not protect you against other liver infections such as hepatitis A, C, and E.
- If you are on dialysis for a kidney problem or if you have a weakened immune system your doctor may need to do a blood test to check if the vaccination has worked well enough to protect you against hepatitis B.

If you have any concerns or you are not sure about any of the above, talk to your doctor, pharmacist or nurse before receiving PreHevbri.

Children and adolescents
PreHevbri has not been fully tested in children under 18 years of age, it should not be used in this age group.

Other medicines and PreHevbri
Tell your doctor, pharmacist or nurse if you are taking, have recently taken, or might take any other medicines, including any other vaccine.

In addition to PreHevbri, you may be given an injection of hepatitis B 'immuno-globulins'. This will give you immediate short-term protection against hepatitis B infection. If this happens your doctor, pharmacist or nurse will make sure that the two injections are given in different parts of the body.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before being given this vaccine.

It is unknown whether PreHevbri is excreted in human milk. A risk to the suckling child cannot be excluded. Discuss with your doctor or nurse whether the risks and benefits of breast-feeding your child outweigh the benefit of vaccination and whether you should stop breast-feeding.

Driving and using machines
PreHevbri is unlikely to have any effect on the ability to drive and use machines. If you feel tired, or have a headache or feel dizzy after having the vaccine, do not drive or use any machines until you feel well again.

PreHevbri contain sodium and potassium
This vaccine contains less than 1 mmol sodium (23 mg) per dose, i.e. that is to say is essentially 'sodium-free'.

This vaccine contains less than 1 mmol potassium (39 mg) per dose, i.e. that is to say is essentially 'potassium-free'.

3. How PreHevbri is given

PreHevbri will be given to you as an injection by a doctor, pharmacist or nurse. The vaccine will usually be injected into a muscle in your upper arm.

You will be given a total of three injections. Each injection will be given on separate visits:
- 1st injection: on a date agreed with your doctor, pharmacist or nurse;
- 2nd injection: 1 month after the 1st injection;
- 3rd injection: 6 months after the 1st injection.

The recommended dose for each injection is 10 micrograms (1 mL of suspension for injection).

If you forget a scheduled dose of PreHevbri
If you miss a scheduled dose, talk to your doctor, pharmacist or nurse to arrange another visit to receive the missed dose.

Make sure you receive the complete course of three injections or you may not be fully protected.

If you have any further questions on the use of this vaccine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, this vaccine can cause side effects, although not everybody gets them.

Very common (may affect more than 1 in 10 people):
- feeling very tired;
- pain or tenderness at the injection site;
- itching at the injection site;
- muscle pain;
- headache.

Common (may affect up to 1 in 10 people):
- diarrhoea;
- feeling or being sick;
- stomach pain;

- redness, bruising or swelling at the injection site;
- rash;
- dizziness;
- joint pain;
- fever.

Uncommon (may affect up to 1 in 100 people):
- swollen lymph nodes;
- hives or itchy skin;
- flushing or hot flushes.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this vaccine.

5. How to store PreHevbri

Keep this vaccine out of the sight and reach of children.

Do not use this vaccine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Store vials in a refrigerator (2°C to 8°C). Store in the original package in order to protect from light. Do not freeze.

Do not throw away any vaccines via wastewater. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. These measures will help protect the environment.

6. Contents of the pack and other information

What PreHevbri contains

One dose (1 mL) contains:
- Active substances: 10 micrograms of hepatitis B surface antigens (S [83%], pre-S1 [11%] and pre-S2 [6%]) [1, 2]

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

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

- The other ingredients are sodium chloride, potassium chloride, disodium phosphate dodecahydrate, potassium dihydrogen phosphate, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), water for injections.

What PreHevbri looks like and contents of the pack
PreHevbri is a clear, colourless suspension with a fine white deposit. When the vial is shaken the suspension forms a slightly white opaque suspension.

PreHevbri is supplied in vials containing 1 mL. Each vial is for single use only.

Packs of 10 single-dose vials are available.

Marketing Authorisation Holder
VBI Vaccines B.V.
Delflandlaan 1
Queen's Tower, No. 714
1062EA Amsterdam
Netherlands

Manufacturer
MIAS Pharma Limited
Suite 2, Stafford House
Strand Road, Portmarnock
County Dublin, D13 H525
Ireland

For any information about this vaccine, please contact the Marketing Authorisation Holder.

This leaflet was last revised in MM/YYYY.

Other sources of information

Detailed information on this vaccine is available on the European Medicines Agency web site: http://www.ema.europa.eu, and on the website of {name of Member State Agency (link)}.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Storage
- Vials should be stored in a refrigerator (2°C to 8°C)).Store in the original carton in order to protect from light.
- Do not freeze .

Preparation
- The vaccine should be used under aseptic conditions.
- 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 physical aspect being observed, discard the vaccine.
- The vial should be shaken well prior to administration.

Administration
- PreHevbri should be injected intramuscularly into the deltoid muscle.
- Do not inject PreHevbri into the gluteal muscle, or intradermally or intravascularly.
- Each vial is for single use only.
- PreHevbri must not be mixed with other medicinal products.

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