SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sci-B-Vac 2.5 µg /0.5 ml

Sci-B-Vac 5µg/0.5 ml

Sci-B-Vac 10µg/1 ml

Hepatitis B vaccine (recombinant, adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:
Sci-B-Vac 2.5µg/0.5ml contains hepatitis B surface antigen 2.5 µg/0.5ml [1,2, 3]
Sci-B-Vac 5µg/0.5ml contains hepatitis B surface antigen 5 µg/0.5ml [1,2, 3]
Sci-B-Vac 10µg/ml contains hepatitis B surface antigen 10 µg/ml [1,2, 3]

[1] Hepatitis B surface antigen (S [83%], pre-S2 [11%] and pre-S1 [6%])

[2] Adsorbed on 500 micrograms of Al^{3+} as aluminium hydroxide, hydrated per ml of vaccine

[3] 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

Sci-B-Vac is indicated for active immunization against hepatitis B virus (HBV) infection.
Immunization against hepatitis B is expected, in the long term, to reduce not only the incidence of the disease, but also its chronic complications such as massive hepatic necrosis, cirrhosis of the liver and hepatocellular carcinoma.
Vaccination with Sci-B-Vac is recommended for all ages in those subjects who are or will be at increased risk of infection with HBV. In areas of high prevalence of infection, the majority of the population is at high risk, especially neonates and children. In high risk areas, infection occurs primarily through mother to child and horizontal transmission. Therefore, vaccination should be targeted to prevent such transmission. In areas of intermediate and low prevalence, vaccination is recommended for neonates, infants and adolescents, as well as subjects who are or will be at increased risk of infection, such as:

- Health care personnel
- Frequent recipients of blood products
- Infants born to HBsAg-positive mothers
- Personnel and residents of public health institutions
- Persons at increased risk of the disease due to their sexual practices
- Travelers to areas with high endemicity of HBV
- Persons originating from areas of high endemicity
- Users of illicit injectable drugs

- Military personnel, police personnel and anybody who through their work or personal lifestyle may be exposed to HBV
- Family members and others in intimate contact with persistent HBsAg-positive individuals.

Persons who develop anti-HBs antibodies following active infection with the hepatitis B vaccine are protected against the disease if they are re-exposed to the virus.
Clinical trials have shown that Sci-B-Vac induced protective levels of antibody in up to 100% of healthy adults who received the recommended three-dose regimen of 10 µg/dose.
Sci-B-Vac is highly immunogenic in children. The specific antibody titers tend to be an order of magnitude higher in children than in adults when the recommended doses are administered. Children tend to achieve seroprotection more frequently than adults.

4.2 Posology and method of administration

Posology

Sci-B-Vac is a sterile suspension for intramuscular injection.
Adult Formulation, 10 µg/ml: each 1 ml dose contains 10 µg hepatitis B surface antigen; recommended for children above the age of 10 years and adults.
Pediatric Formulation (option 1) 2.5 µg/0.5 ml: each 0.5 ml dose contains 2.5 µg hepatitis B surface antigen; recommended for neonates, infants and young children.
Pediatric Formulation (option 2) 5 µg/0.5 ml: each 0.5 ml dose contains 5 µg hepatitis B surface antigen; recommended for neonates, infants and young children in highly endemic areas.
In each formulation, the hepatitis B surface antigen is adsorbed onto approximately 0.5 mg of aluminum per ml of vaccine.

Method of administration
Sci-B-Vac should be injected intramuscularly into the deltoid muscle in adults and children or in the anterolateral thigh in neonates, infants and young children. The vaccine may be administered subcutaneously to persons who are at high risk of hemorrhage due to thrombocytopenia or bleeding disorders. **Do not inject into the gluteal muscle.**
Vaccination Schedule: The vaccination regimen for all subjects consists of three (3) doses of vaccine given according to the following schedule: first dose at elected date; second dose 1 month after the first dose; third dose 6 months after the first dose.
Booster Dose: The duration of the protective effect of Sci-B-Vac against HBV is unknown at present. A booster dose may be considered when the anti-HBs titer falls below 10 mlU/ml.

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. Sci-B-Vac 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.

Caution and appropriate care should be exercised in administering the vaccine to individuals with severe compromised cardiopulmonary status or to others in whom a febrile or systemic reaction could pose a significant risk.

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 Sci-B-Vac . 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 Sci-B-Vac 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 Sci-B-Vac .

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 Sci-B-Vac with other vaccines. The concomitant use of Sci-B-Vac with other vaccines is not recommended.

When concomitant administration of Sci-B-Vac 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 Sci-B-Vac 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 Sci-B-Vac 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 Sci-B-Vac.

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

Sci-B-Vac 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

Pediatric Use: Sci-B-Vac has been shown to be well tolerated and highly immunogenic in infants and children of all ages. Newborns also respond well; maternally transferred antibodies do not interfere with the active immune response to the vaccine.

The clinical trial safety profile of Sci-B-Vac 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 Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml.
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.

In a series of studies, 2313 doses of Sci-B-Vac were administered to 771 healthy adults who were monitored for 5 days after each dose. The following adverse reactions were reported:

Incidence Equal to or Greater Than 1% of Injections:
Local Reaction (Injection Site): Injection site reactions consist of soreness and include pain, tenderness, pruritus, erythema, ecchymosis, swelling, warmth and nodule formation. These reactions were mild and resolved within two days after vaccination.
Additional complaints included fatigue/weakness, headache, fever (37.8ºC), malaise, nausea, diarrhoea pharyngitis and upper respiratory infection.

Incidence Less Than 1% of Injections:
Sweating, aching, sensation of warmth, light-headedness, chills, flushing, vomiting, abdominal pains/cramps, dyspepsia, diminished appetite, rhinitis, influenza, cough, vertigo/dizziness, paresthesia, pruritus, rash (non-specified), angioedema, urticaria, arthralgia including monarticular, myalgia, back pain, neck pain, shoulder pain, neck stiffness, lymphadenopathy, insomnia/disturbed sleep, earache, dysuria and hypotension.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

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
Sci-B-Vac 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 Sci-B-Vac 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. Sci-B-Vac 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 Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml compared to Engerix B at Day 196, 4 weeks after receiving the third dose in all adults age ≥18 years and (2) superiority of Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml 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 (Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml minus Engerix B) was greater than -5%. Superiority was met if the lower bound of the 95% CI of the difference in SPR (Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml minus Engerix B) was greater than 0%.

The study met both co-primary endpoints. The SPR in subjects ≥18 years of age in the Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml 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 Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml 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 Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml and engerix B at Day 196

Study population and subgroups	Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml			engerix B			Difference in SPR (Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml - 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 Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml 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. Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml 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 Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml 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 Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml was non-inferior to Engerix-B. Non-inferiority of Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml 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 Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml 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 Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml 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 Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml and Engerix B in Adults Age 18-45

Timepoint	Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml Pooled			Engerix B			Difference in SPR (Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml – 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 Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml includes the Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml Lots A, B, and C

The safety and immunogenicity of Hepatitis B vaccine (recombinant, adsorbed) 10µg/1 ml 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.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of the hepatitis B surface antigen used in Sci-B-Vac 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
Disodium phosphate dodecahydrate
Potassium chloride
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

The expiry date of the product is indicated on the packaging materials.

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

0.5 or 1 mL suspension in a single-dose glass vial, fitted with a rubber stopper and sealed with an aluminum CCS seal flip off.

Pack size: 1 or 25 vials.
Not all pack sizes may be marketed.

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 turbid when mixed, clear colourless upper solution and white precipitate upon settling.

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. MANUFACTURER AND MARKETING AUTHORISATION HOLDER

SciVac Ltd.,
Gad Feinstein Rd.,
POB 580,
Rehovot 7610303,
Israel

8. MARKETING AUTHORISATION NUMBERS

Sci-B-Vac 2.5 µg/0.5 ml: 117-49-29023-00

Sci-B-Vac 5µg/0.5 ml: 140-12-32004-00

Sci-B-Vac 10µg/1 ml: 117-46-29024-00

Revised in Februaty 2023 according to MOH guidelines.