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

HEPLISAV B 20 micrograms solution for injection in pre-filled syringe
Hepatitis B vaccine (recombinant DNA, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml) contains:

Hepatitis B surface antigen (HBsAg)[1,2] 20 micrograms

[1]Adjuvanted with 3000 micrograms cytidine phosphoguanosine (CpG) 1018 adjuvant, a 22-mer phosphothioate oligonucleotide (PS-ODN) comprising microbial DNA-like-unmethylated CpG motifs
[2] Produced in yeast cells (*Hansenula polymorpha*) by recombinant DNA technology

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.
Clear to slightly opalescent, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HEPLISAV B is indicated for active immunisation against hepatitis B virus infection (HBV) caused by all known subtypes of hepatitis B virus in adults 18 years of age and older.

The use of HEPLISAV B should be in accordance with official recommendations.

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

4.2 Posology and method of administration

Posology

Adults:

The vaccine is administrated intramuscularly.

Primary vaccination:

Adults: Two doses of 0.5 ml each: an initial dose followed by a second dose 1 month later.

Adults with severe renal impairment (eGFR < 30 ml/min) including patients undergoing haemodialysis: Four doses of 0.5-ml each: an initial dose followed by a second dose 1 month later, a third dose 2 months after the initial dose, and a fourth dose 4 months after the initial dose.

Booster dose
The need for a booster dose has not been established. Subjects who are immunocompromised or who have chronic renal failure may require a booster dose. A 0.5-ml booster dose should be given when antibody levels decrease below recommended levels. See section 4.4

Elderly population
No dose adjustment is required. See section 5.1.

Paediatric population
The safety and efficacy of HEPLISAV B in children less than 18 years of age have not been established. No data are available.

Method of administration

HEPLISAV B should be injected intramuscularly (IM) in the deltoid region. Injection into the gluteal region (buttocks) should be avoided.

4.3 Contraindications

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

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

Hypersensitivity to yeast.

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.

HEPLISAV B should not be administered intravenously, subcutaneously, or intradermally.

As with all injectable vaccines, appropriate medical treatment and supervision should be readily available in case of rare anaphylactic reactions following the administration of the vaccine.

As with other vaccines, the administration of HEPLISAV B should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, is not a contraindication for immunisation.

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.

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

Because of the long incubation period of hepatitis B, it is possible for unrecognised HBV infection to be present at the time of immunisation. HEPLISAV B may not prevent HBV infection in such cases.

HEPLISAV B will not prevent infection caused by other pathogens known to infect the liver such as hepatitis A, hepatitis C, and hepatitis E viruses.

There are very limited data on the immune response to HEPLISAV B in individuals who did not mount a protective immune response to another hepatitis B vaccine.

Immunodeficiency

Immunocompromised persons may have a diminished immune response to HEPLISAV B. There are very 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. See section 4.2.

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 HBV infection can be severe in these patients: the HEPLISAV B vaccination should thus be considered on a case by case basis by the physician.

Renal Impairment

As patients with Chronic Kidney Disease (CKD) who are pre-haemodialysis or receiving haemodialysis are particularly at risk of exposure to HBV and have a higher risk of becoming chronically infected, attention should be given to ensure that a protective antibody level is maintained as defined by national recommendations and guidelines. See section 4.2.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

As there are no data on co-administration of HEPLISAV B with other vaccines, the concomitant use of HEPLISAV B with other vaccines is not recommended.

Concomitant administration of HEPLISAV B with hepatitis B immunoglobulin (HBIG) has not been studied. However, in circumstances where HEPLISAV B is administered with a standard dose of HBIG, these should be given at separate injection sites.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are a limited amount of data from the use of HEPLISAV B vaccine in pregnant women.

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

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

Breast-feeding

It is unknown whether HEPLISAV B is excreted in human milk. A risk to the breastfed newborns/infants cannot be excluded.

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

Fertility

No data on the effect of HEPLISAV B on fertility in humans are available.

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

HEPLISAV B may have a moderate influence on the ability to drive and use machine. Some of the effects mentioned under section 4.8 “Undesirable Effects” (e.g., malaise) may affect the ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile:

The clinical trials safety profile is based on data from 9365 subjects followed in 3 pivotal studies.

In two studies, 3777 of the 9365 subjects were monitored for local and systemic post-injection reactions using diary cards for a 7-day period starting on the day of vaccination. The most common adverse reactions seen were the post-injection reactions injection site pain, headache, malaise, fatigue, and myalgia.

The reactogenicity profile of HEPLISAV B in 119 subjects on haemodialysis was generally comparable to that seen in healthy subjects.

Tabulated list of 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.

System Organ Class	Frequency	Adverse Reactions
Nervous System Disorders	Very Common	Headache[1]
	Rare	Dizziness
	Rare	Paraesthesia
Musculoskeletal and Connective Tissue Disorders	Very Common	Myalgia[1]
General Disorders and Administration Site Conditions	Very Common	Malaise[1], fatigue[1], injection site pain[1]
	Common	Injection site swelling, injection site erythema, fever[1]
	Uncommon	Injection site pruritus[2]
Gastrointestinal disorders	Uncommon	Gastrointestinal symptoms[3]
Immune system disorders	Uncommon	Hypersensivity[4]
	Very Rare	Anaphylaxis[2]

1. Local and systemic adverse reactions collected using diary cards.
2. Adverse reactions reported post-authorisation.
3. Includes the individual preferred terms of nausea, vomiting, diarrhoea and abdominal pain.
4. Includes the individual preferred terms of urticaria, pruritus, and rash.

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

Cases of overdose have been been reported during post-marketing surveillance. Adverse events reported following overdosage were similar to those reported with normal vaccine administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, Viral Vaccines, Hepatitis Vaccine, ATC code: J07BC01

Mechanism of action

HEPLISAV B is comprised of recombinant hepatitis B surface antigen and the CpG 1018 adjuvant, which is a 22-mer PS-ODN immunostimulatory sequence.

HEPLISAV B induces specific antibodies against HBsAg (anti-HBs).

The biological actions of CpG 1018 are exerted locally at the injection site and draining lymph nodes. The adjuvant CpG 1018 component of HEPLISAV B has the following effects: (1) Activates plasmacytoid dendritic cells (pDCs) through the pattern recognition receptor Toll-like receptor 9; (2) converts pDCs into highly efficient antigen-presenting cells that present the processed HBsAg to CD4+ T cells; and, (3) promotes Th1 T-cell differentiation through the production of IFN-alpha and IL-12. This activation results in a high and sustained antibody response, likely due to the rapid generation of large numbers of anti-HBs-secreting plasmacytes and HBsAg-specific memory B and T cells.

Immune responses to HEPLISAV B

No efficacy trials were conducted due to the application of the well-established immune correlate of protection to the immune response (anti-HBs concentration ≥ 10 mIU/ml correlates with protection against HBV infection). The immunogenicity of HEPLISAV B was evaluated in 3 randomised, active controlled, observer-blinded, multicentre phase 3 clinical trials (HBV-10 with 3:1 randomisation, HBV-16 with 4:1 randomisation, and HBV-23 with 2:1 randomisation) including 9365 adults aged 18 to 70 years given HEPLISAV B, and 3867 adults given the comparator hepatitis B vaccine (Engerix-B 20 mcg HBsAg). HEPLISAV B was given as a 2-dose schedule at 0 and 1 month and Engerix-B was given using a 3-dose schedule at 0, 1, and 6 months.

Baseline characteristics were balanced between the treatment arms for age, sex, race, ethnicity, and body mass index (BMI). In the pooled analysis including all 3 trials, the mean age was 49.3 and 49.4 in the HEPLISAV B arm and Engerix-B arms, respectively and there were 50.8% and 51.5% female participants who received HEPLISAV B and Engerix-B, respectively.

The trials evaluated the seroprotection rates (SPR: percentage of vaccinated persons whose anti-HBs antibody levels were ≥ 10 mIU/ml after vaccination) after the second dose of HEPLISAV B compared to after the third dose of Engerix-B. The SPR and peak geometric mean concentration (GMC) after a 2-dose schedule of HEPLISAV B were statistically significantly higher than after a 3-dose schedule of Engerix-B (lower bound of the 95% confidence interval of the difference in SPRs between HEPLISAV B and Engerix-B was greater than 0%; lower bound of the 95% confidence interval of the ratio of GMCs between HEPLISAV B and Engerix-B was greater than 1.0) in all 3 trials (Table 1, Table 2).

Table 1 Comparison of Seroprotection Rates Between HEPLISAV B and Engerix-B at Peak Weeks in Pooled Trials HBV-23, HBV-16 and HBV-10 (mITT Population)

HEPLISAV B			Engerix-B			Difference
N	n	SPR (%) (95% CI)	N	n	SPR (%) (95% CI)	(HEPLISAV B - Engerix-B) (95% CI)
8701	8327	95.7 (95.3 - 96.1)	3643	2898	79.5 (78.2 - 80.8)	16.2 (14.8 - 17.6)

N = number of evaluable subjects; n = number of seroprotected subjects; SPR = Seroprotection Rate, CI = confidence interval.
Seroprotection is defined as anti-HBs ≥ 10 mIU/mL.
Peak week comparison is for HEPLISAV B at Week 24 and Engerix-B at Week 28.
The confidence intervals on seroprotection rates are calculated using the two-sided Clopper-Pearson method.
The confidence interval on the difference between treatment groups is calculated using the Miettinen and Nurminen method without stratification.

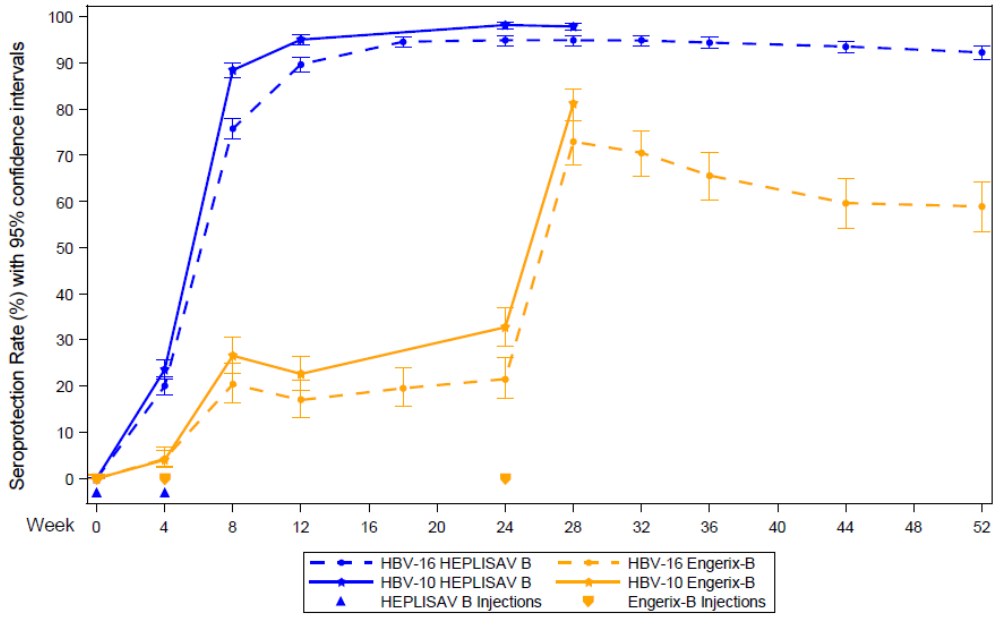
Table 2 Comparison of Anti-HBs Geometric Mean Concentrations at Peak Weeks Between HEPLISAV B and Engerix-B in Pooled Trials HBV-23, HBV-16 and HBV-10 (mITT Population)

HEPLISAV B		Engerix-B		GMC Ratio
N	GMC (95% CI)	N	GMC (95% CI)	(HEPLISAV B / Engerix-B) (95% CI)
8701	329.1 (317.1 - 341.5)	3642	262.3 (236.4 - 291.1)	1.3 (1.1 - 1.4)

Peak week for HEPLISAV B is Week 24. Peak week for Engerix-B is Week 28.

SPR results were collected at each study visit in two of the pivotal trials, HBV-10 (week 4 to 28) and HBV-16 (week 4 to 52). HEPLISAV B induced significantly higher SPRs than Engerix-B across all study visits in both studies (Figure 1).

Figure 1 Seroprotection Rates by Visit in Trials HBV-16 and HBV-10 (Per Protocol Population)



In all three trials, SPRs induced by HEPLISAV B were statistically significantly higher than those induced by Engerix-B in older adults, men, obese individuals, smokers and subjects with type 2 diabetes mellitus (Table 3).

Table 3 Comparison of Seroprotection Rates Between HEPLISAV B and Engerix-B at Peak Weeks by Category in Pooled Trials HBV-23, HBV-16 and HBV-10 (mITT Population)

	HEPLISAV B			Engerix-B			Difference
Category	N	n	SPR (%) (95% CI)	N	n	SPR (%) (95% CI)	(HEPLISAV B - Engerix-B) (95% CI)
All subjects	8701	8327	95.7 (95.3 - 96.1)	3643	2898	79.5 (78.2 - 80.8)	16.2 (14.8 - 17.6)
Age Group (years)							
18 - 29	527	526	99.8 (98.9 - 100.0)	211	196	92.9 (88.5 - 96.0)	6.9 (4.1 - 11.2)
30 - 39	1239	1227	99.0 (98.3 - 99.5)	545	483	88.6 (85.7 - 91.2)	10.4 (7.9 - 13.4)

40 - 49	2377	2310	97.2 (96.4 - 97.8)	963	771	80.1 (77.4 - 82.5)	17.1 (14.6 - 19.8)
50 - 59	2712	2578	95.1 (94.2 - 95.8)	1120	872	77.9 (75.3 - 80.3)	17.2 (14.7 - 19.8)
≥ 60	1846	1686	91.3 (90.0 - 92.6)	804	576	71.6 (68.4 - 74.7)	19.7 (16.4 - 23.1)
Sex							
Male	4274	4055	94.9 (94.2 - 95.5)	1765	1361	77.1 (75.1 - 79.1)	17.8 (15.7 - 19.9)
Female	4427	4272	96.5 (95.9 - 97.0)	1878	1537	81.8 (80.0 - 83.6)	14.7 (12.9 - 16.5)
BMI Stratum							
< 30 kg/m^2	4904	4728	96.4 (95.9 - 96.9)	2069	1756	84.9 (83.3 - 86.4)	11.5 (10.0 - 13.2)
≥ 30 kg/m^2	3789	3591	94.8 (94.0 - 95.5)	1570	1140	72.6 (70.3 - 74.8)	22.2 (19.9 - 24.5)
Smoking Status							
Smoker	2634	2538	96.4 (95.6 - 97.0)	1130	852	75.4 (72.8 - 77.9)	21.0 (18.4 - 23.6)
Non-smoker	6067	5789	95.4 (94.9 - 95.9)	2513	2046	81.4 (79.8 - 82.9)	14.0 (12.4 - 15.7)
Type 2 Diabetes Status and Age Group (Years)							
With T2D 20 - 39	38	37	97.4 (86.2 - 99.9)	16	12	75.0 (47.6 - 92.7)	22.4 (5.1 - 47.5)
40 - 49	163	151	92.6 (87.5 - 96.1)	67	49	73.1 (60.9 - 83.2)	19.5 (9.2 - 31.7)
50 - 59	334	303	90.7 (87.1 - 93.6)	160	108	67.5 (59.7 - 74.7)	23.2 (15.6 - 31.4)
≥ 60	377	320	84.9 (80.9 - 88.3)	165	97	58.8 (50.9 - 66.4)	26.1 (17.9 - 34.5)

BMI = body mass index; CI = confidence interval; N = number of evaluable subjects; n = number of seroprotected subjects; SPR = Seroprotection Rate; T2D = type 2 diabetes.
Seroprotection is defined as anti-HBs = 10 mIU/mL.
Peak week comparison is for HEPLISAV B at Week 24 and Engerix-B at Week 28.
The confidence intervals on seroprotection rates are calculated using the two-sided Clopper-Pearson method.
The confidence interval on the difference between treatment groups is calculated using the Miettinen and Nurminen method without stratification

Haemodialysis

In a phase 1, open-label, single arm, multicentre study of 119 adults with end-stage renal disease who were undergoing haemodialysis, participants received a 4-dose regimen of HEPLISAV B at 0, 1, 2, and 4 months. The mean age was 59.9 years and 60.5% were male, 39.5% were female.

The primary analysis evaluated the SPR 5 months after the first dose of HEPLISAV B. In 75 participants who received all 4 doses of HEPLISAV B, the SPR was 89.3% (95% confidence interval [CI]: 80.1%, 95.3%). In secondary analyses, 81.3% (95% CI: 70.7%, 89.4%) of subjects had an anti-HBs concentration ≥100 mIU/mL. The geometric mean concentration of anti-HBs was 1061.8 mIU/mL (95% CI: 547.2, 2060.2).

In a phase 3, randomised, open-label, multicentre study of 116 adult subjects with haemodialysis-dependent CKD who were non-responders to previous hepatitis B vaccination, participants received a 1-dose booster regimen of HEPLISAV B or Fendrix, or a double booster dose of Engerix-B.

Week 4 SPR in the HEPLISAV B group (42.1% n=16/38) was higher than the SPR in the Engerix-B group (18.9%, n=7/37) and the Fendrix group (29.3%, n=12/41). At Week 12, the SPR was 24.3% (n=9/37) in the HEPLISAV B group, 13.9% (n=5/36) in the Engerix-B group, and 26.8% (n=11/41) in the Fendrix group.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with HEPLISAV B in all subsets of the paediatric population for the prevention of hepatitis B virus infection (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Renal Impairment
The CpG 1018 adjuvant is cleared from plasma within 24 hours in renally-impaired adults after a single dose of 3000 micrograms. Dose adjustment is not required.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies consisting 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
- sodium dihydrogen phosphate dihydrate
- polysorbate 80 (E 433)
- water for injections

For adjuvants, see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must 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.
Keep the pre-filled syringe in the outer carton in order to protect from light.

6.5 Nature and contents of container

0.5 ml of solution in a pre-filled syringe (Type I glass) with tip cap (synthetic isoprene-bromobutyl rubber blend) and plunger stopper (chlorobutyl rubber). The tip cap and stopper of the pre-filled syringe do not contain natural rubber latex.

Pack sizes of 1 and 5 pre-filled syringes without needle.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

HEPLISAV B is a clear to slightly opalescent, colourless to slightly yellow liquid and should be essentially free of visible particles. Do not administer if it appears otherwise.

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

7. MARKETING AUTHORISATION HOLDER

Dynavax GmbH
Eichsfelder Strasse 11
D-40595 Düsseldorf
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1503/001
EU/1/20/1503/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 February 2021

10. DATE OF REVISION OF THE TEXT

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 OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER 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 OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Dynavax GmbH
Eichsfelder Strasse 11
D-40595 Düsseldorf
Germany

Name and address of the manufacturer responsible for batch release

Dynavax GmbH
Eichsfelder Strasse 11
D-40595 Düsseldorf
Germany

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 Agency's web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

1 pre-filled syringe without needle
5 pre-filled syringes without needle

1. NAME OF THE MEDICINAL PRODUCT

HEPLISAV B 20 micrograms solution for injection in pre-filled syringe
Hepatitis B vaccine (recombinant DNA, adjuvanted)
For adult use

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) contains:
20 micrograms of hepatitis B surface antigen adjuvanted with 3000 micrograms CpG 1018 adjuvant.

3. LIST OF EXCIPIENTS

Sodium chloride
Disodium phosphate dodecahydrate
Sodium dihydrogen phosphate dihydrate
Polysorbate 80
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
5 pre-filled syringes without needle
1 pre-filled syringe without needle

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular (IM) use
Read the package leaflet before use.

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

Keep out of the 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.
Keep the pre-filled syringes in the outer carton in order to protect from light.
Keep the pre-filled syringe in the outer carton 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

Dispose of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dynavax GmbH
Eichsfelder Strasse 11
D-40595 Düsseldorf
Germany

12. MARKETING AUTHORISATION NUMBERS

EU/1/20/1503/001
EU/1/20/1503/002

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

Pre-filled syringe label

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

HEPLISAV B
20 mcg injection
Hepatitis B vaccine

2. METHOD OF ADMINISTRATION

IM

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 ml)

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

HEPLISAV B 20 micrograms solution for injection in pre-filled syringe
Hepatitis B vaccine (recombinant DNA, adjuvanted)

▼This medicine 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 HEPLISAV B is and what it is used for

HEPLISAV B is a vaccine for use in adults 18 years of age and older to protect against infection with the hepatitis B virus.

HEPLISAV B 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, fever, and feeling very tired), dark urine, pale stools (faeces), yellowing of the skin and eyes (jaundice). However, some people with hepatitis B do not look or feel ill.

How HEPLISAV B works

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

- HEPLISAV B contains an adjuvant, a substance which improves the body's production of antibodies and makes the protection last for longer.

- A course of two injections of HEPLISAV B is required to provide full protection against hepatitis B.

- HEPLISAV B is not used to treat a person who is already infected with the hepatitis B virus, including people infected with the hepatitis B virus and have become carriers for infection.

2. What you need to know before you receive HEPLISAV B

Do not receive HEPLISAV B:
- If you are allergic to any of the components of this vaccine, including yeast (listed in section 6). Signs of an allergic reaction may include itchy skin, rash, shortness of breath and swelling of the face or tongue.
- If you have had a sudden life-threatening, allergic reaction after receiving HEPLISAV B in the past.

HEPLISAV B should not be given if any of the above apply to you. If you are not sure, talk to your doctor, <pharmacist> or nurse before vaccination with HEPLISAV B.

Warnings and precautions
Talk to your doctor, <pharmacist> or nurse before receiving HEPLISAV B:
- If you have any allergies to any of the components of HEPLISAV B (see section 6).
- If you have had any health problems after having a vaccine in the past.
- Fainting can occur after, or even before, any injection. Therefore tell the doctor, <pharmacist> or nurse if you fainted with a previous injection.
- If you are ill with a high fever, your doctor, <pharmacist> or nurse will 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 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.

HEPLISAV B does not protect you against other liver infections such as hepatitis A, C, and E.

As with any vaccine, HEPLISAV B may not protect all people who are vaccinated.
If you are not sure if any of the above apply to you, talk to your doctor, <pharmacist> or nurse before receiving HEPLISAV B.

Children and adolescents
Since HEPLISAV B has not been tested fully in young people under 18 years of age, it should not be used in this age group.

Other medicines and HEPLISAV B
Tell your doctor, <pharmacist> or nurse if you are taking, have recently taken or might take any other medicines or vaccines.

If HEPLISAV B is given at the same time as an injection of hepatitis B "immuno-globulins", which would be given to provide immediate, short-term protection against hepatitis B infection, your doctor, <pharmacist> or nurse will make sure that the two are injected into different parts of the body.

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

It is unknown whether HEPLISAV B is excreted in human milk. A risk to the suckling child cannot be excluded. Discuss with your doctor or nurse if you should discontinue breast-feeding or abstain from HEPLISAV B vaccination taking into account the benefit of breast-feeding for the child and the benefit of vaccination for you.

Driving and using machines
You may feel tired or get a headache after receiving HEPLISAV B. If this happens, do not drive or use any tools or machines.

HEPLISAV B contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium free'.

3. How HEPLISAV B is given

The doctor, <pharmacist> or nurse will give HEPLISAV B as an injection into your muscle, usually in your upper arm.

For adults, the course of vaccination is 2 injections:
- The first injection on a date agreed upon with your doctor or nurse.
- The second injection 1 month after the first injection.

For adults with a kidney problem including those receiving haemodialysis, the course of vaccination is 4 injections:
- The first injection on a date agreed upon with your doctor or nurse.
- The second injection 1 month after the first injection.
- The third injection 2 months after the first injection
- The fourth injection 4 months after the first injection

Your doctor will tell you if you need any extra or "booster" injections in the future.

If you forget a return visit to receive HEPLISAV B
Talk to your doctor and arrange another visit.

Make sure you complete the injections or you may not be fully protected. Once you have had the first injection of HEPLISAV B, the following injection(s) must also be HEPLISAV B (not another type of hepatitis B vaccine).

4. Possible side effects

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

Side effects that occurred during clinical trials with HEPLISAV B were as follows:

Serious side effects
Very rare (may affect up to 1 in 10,000 people)
You should seek immediate treatment if you get any signs of a serious allergic reaction.
The signs may include: face swelling, low blood pressure, difficulty breathing, loss of consciousness, fever, joint stiffness and a skin rash. Such reactions usually start very soon after injection.

Other side effects

Very Common (may affect more than 1 in 10 people)
- Headache
- Muscle aches
- Feeling tired
- Pain at the spot where the injection was given
- Feeling unwell (malaise)

Common (may affect up to 1 in 10 people)
- Swelling or redness at the spot where the injection was given
- Fever

Uncommon (may affect up to 1 in 100 people)
- Feeling sick (nausea)
- Being sick (vomiting)
- Diarrhoea
- Abdominal (belly) pain
- Allergic reactions (hives, rash and itchiness)
- Itching at the spot where the injection was given

Rare (may affect up to 1 in 1,000 people)
- Dizziness
- Pins and needles

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 medicine.

5. How to store HEPLISAV B

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 and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C). Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What HEPLISAV B contains
One dose (0.5 ml) contains:

Active substances:

Hepatitis B surface antigen (HBsAg)[1,2] 20 micrograms

[1]Adjuvanted with 3000 micrograms CpG 1018 adjuvant, a 22-mer immunostimulatory sequence oligonucleotide
[2]Produced in yeast cells (*Hansenula polymorpha*) by recombinant DNA technology
Substance CpG 1018 is included in this vaccine as an adjuvant. Adjuvants are substances included in certain vaccines to accelerate, improve and/or prolong the protective effects of the vaccine.

The other ingredients are:
- sodium chloride
- disodium phosphate dodecahydrate
- sodium dihydrogen phosphate dihydrate
- polysorbate 80 (E 433)
- water for injections

What HEPLISAV B looks like and contents of the pack
HEPLISAV B is a clear to slightly milky, colourless to slightly yellow liquid for injection in pre-filled syringe.

HEPLISAV B is available in packs of 1 and 5 pre-filled syringes without needles.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Dynavax GmbH
Eichsfelder Strasse 11
D-40595 Düsseldorf
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien, България, Česká republika, Danmark, Eesti, Ελλάδα, España, France, Hrvatska, Ireland, Ísland, Italia, Κύπρος, Latvija, Lietuva, Luxembourg/Luxemburg, Magyarország, Malta, Nederland, Norge, Österreich, Polska, Portugal, România, Slovenija, Slovenská republika, Suomi/Finland, Sverige, United Kingdom (Northern Ireland)
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This leaflet was last revised in {**MM/YYYY**}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

HEPLISAV B:

- is a clear to slightly opalescent, colourless to slightly yellow solution and should essentially be free of visible particles. Discard if the content appears otherwise.
- should be injected intramuscularly (IM) in the deltoid region of the upper arm.
- should not be administered in the gluteal region (buttocks).
- should not be administered intravenously, subcutaneously, or intradermally.
- should not be given to subjects with hypersensitivity to the active substance or to any of the excipients.
- should not be given to subjects suffering from acute severe febrile illness. The presence of a minor infection such as a cold is not a contraindication for immunisation.
- must not be mixed with any other vaccines in the same syringe.

As with all injectable vaccines, appropriate medical treatment should be readily available in case of rare anaphylactic reactions following the administration of HEPLISAV B.

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