1. NAME OF THE MEDICINAL PRODUCT

HBVAXPRO 5 micrograms, suspension for injection in pre-filled syringe
Hepatitis B vaccine (recombinant DNA)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml) contains:
Hepatitis B virus surface antigen, recombinant (HBsAg) * ..... 5 micrograms
Adsorbed on amorphous aluminium hydroxyphosphate sulfate (0.25 milligram Al^{+})

* produced in *Saccharomyces cerevisiae* (strain 2150-2-3) yeast by recombinant DNA technology.

This vaccine may contain traces of formaldehyde and potassium thiocyanate, which are used during the manufacturing process. See sections 4.3, 4.4 and 4.8.

Excipient(s) with known effect:
Sodium less than 1mmol (23 mg) per dose.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Suspension for injection in pre-filled syringe
Slightly opaque white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HBVAXPRO is indicated for active immunisation against hepatitis B virus infection caused by all known subtypes in individuals from birth through 15 years of age considered at risk of exposure to hepatitis B virus.

The specific at risk categories to be immunised are to be determined on the basis of the official recommendations.

It can be expected that hepatitis D will also be prevented by immunisation with HBVAXPRO 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

Individuals from birth through 15 years of age: 1 dose (0.5 ml) at each injection.

Primary vaccination:

A course of vaccination should include at least three injections.

Two primary immunisation schedules can be recommended:

0, 1, 6 months: two injections with an interval of one month; a third injection 6 months after the first administration.

0, 1, 2, 12 months: three injections with an interval of one month; a fourth dose should be administered at 12 months.

It is recommended that the vaccine be administered in the schedules indicated. Infants receiving the compressed regimen (0, 1, 2 months dosing schedule) must receive the 12 month booster to induce higher antibody titres.

Booster:

Immunocompetent vaccinees

The need for a booster dose in healthy individuals who have received a full primary vaccination course has not been established. However, some local vaccination schedules currently include a recommendation for a booster dose and these should be respected.

Immunocompromised vaccinees (e.g. dialysis patients, transplant patients, AIDS Patients)

In vaccinees with an impaired immune system, administration of additional doses of vaccine should be considered if the antibody level against hepatitis B virus surface antigen (anti-HBsAg) is less than 10 IU/l.

Revaccination of nonresponders

When persons who do not respond to the primary vaccine series are revaccinated, 15-25 % produce an adequate antibody response after one additional dose and 30-50 % after three additional doses. However, because data are insufficient concerning the safety of hepatitis B vaccine when additional doses in excess of the recommended series are administered, revaccination following completion of the primary series is not routinely recommended. Revaccination should be considered for high-risk individuals, after weighing the benefits of vaccination against the potential risk of experiencing increased local or systemic adverse reactions.

Special dosage recommendations:

Dosage recommendations for neonates born to mothers who are hepatitis B virus carriers

- At birth, one dose of hepatitis B immunoglobulin (within 24 hours).
- The first dose of the vaccine should be given within 7 days of birth and can be administered simultaneously with hepatitis B immunoglobulin at birth, but at a separate injection site.
- Subsequent doses of vaccine should be given according to the locally recommended vaccination schedule.

Dosage recommendation for known or presumed exposure to hepatitis B virus (e.g. needlestick with contaminated needle)

- Hepatitis B immunoglobulin should be given as soon as possible after exposure (within 24 hours).
- The first dose of the vaccine should be given within 7 days of exposure and can be administered simultaneously with hepatitis B immunoglobulin but at a separate injection site.

- Serologic testing is also recommended, with the administration of subsequent doses of vaccine, if necessary, (i.e. according to the serologic status of the patient) for short and long term protection.
- In the case of unvaccinated or incompletely vaccinated individuals, additional doses should be given as in the recommended immunisation schedule. The accelerated schedule including the 12 month booster dose can be proposed.

Method of administration

This vaccine should be administered intramuscularly.

The anterolateral thigh is the preferred site for injection in neonates and infants. The deltoid muscle is the preferred site for injection in children and adolescents.

Do not inject intravascularly.

Exceptionally, the vaccine may be administered subcutaneously in patients with thrombocytopaenia or bleeding disorders.

Precautions to be taken before handling or administering the product: see section 6.6.

4.3 Contraindications

- History of hypersensitivity to the active substance, or to any of the excipients, or trace residuals (e.g. formaldehyde and potassium thiocyanate), see sections 6.1 and 2.
- Vaccination should be postponed in individuals with a severe febrile illness or acute infection.

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 should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine (see section 4.8).

This vaccine may contain traces of formaldehyde and potassium thiocyanate which are used during the manufacturing process. Therefore, hypersensitivity reactions may occur (see sections 2 and 4.8).

Use caution when vaccinating latex-sensitive individuals since the syringe plunger stopper and tip cap contain dry natural latex rubber that may cause allergic reactions.

For clinical or laboratory monitoring regarding immunocompromised individuals or individuals with known or presumed exposure to hepatitis B virus, see section 4.2.

The potential risk of apnoea and the need for respiratory monitoring for 48 to 72 hours should be considered when administering the primary immunisation series to very premature infants (born $\leq$ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity (see section 4.8). As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

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

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

Caution should be exercised when prescribing to pregnant or breast-feeding women. (see section 4.6).

Excipient(s) with known effect:
This medicinal product contains less than 1mmol sodium (23 mg) per dose, and is considered to be essentially sodium free.

4.5 Interaction with other medicinal products and other forms of interaction

This vaccine can be administered:
- with hepatitis B immunoglobulin, at a separate injection site.
- to complete a primary immunisation course or as a booster dose in subjects who have previously received another hepatitis B vaccine.
- concomitantly with other vaccines, using separate sites and syringes.

The concomitant administration of pneumococcal conjugate vaccine (PREVENAR) given with hepatitis B vaccine using the 0, 1 and 6 and 0, 1, 2 and 12 month schedules has not been sufficiently studied.

4.6 Fertility, pregnancy and lactation

Fertility:
HBVAXPRO has not been evaluated in fertility studies.

Pregnancy:
There is no clinical data on the use of HBVAXPRO on pregnant women.
The vaccine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding:
There is no clinical data on the use of HBVAXPRO on breast-feeding women.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, HBVAXPRO is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

The most common side effects seen are injection-site reactions: transient soreness, erythema, induration.

b. Tabulated summary of adverse reactions

The following undesirable effects have been reported following the widespread use of the vaccine.

As with other hepatitis B vaccines, in many instances, the causal relationship to the vaccine has not been established.

Adverse reactions	Frequency
General disorders and administration site conditions	
Local reactions (injection site): Transient soreness, Erythema, Induration	Common (≥1/100 to, <1/10)
Fatigue, Fever, Malaise, Influenza-like symptoms	Very rare (<1/10,000)
Blood and the lymphatic system disorders	
Thrombocytopaenia, Lymphadenopathy	Very rare (<1/10,000)
Immune system disorders	
Serum sickness, Anaphylaxis, Polyarteritis nodosa	Very rare (<1/10,000)
Nervous system disorders	
Paresthesia, Paralysis (including Bell's palsy, facial paralysis), Peripheral neuropathies (polyradiculoneuritis, Guillain Barre Syndrome), Neuritis (including optical neuritis), Myelitis (including transverse Myelitis), Encephalitis, Demyelinating disease of the central nervous system, Exacerbation of multiple sclerosis, Multiple sclerosis, Seizure, Headache, Dizziness, Syncope	Very rare (<1/10,000)
Eye disorders	
Uveitis	Very rare (<1/10,000)
Vascular disorders	
Hypotension, Vasculitis	Very rare (<1/10,000)
Respiratory, thoracic and mediastinal disorders	
Bronchospasm-like symptoms	Very rare (<1/10,000)
Gastrointestinal disorders	
Vomiting, Nausea, Diarrhoea, Abdominal pain	Very rare (<1/10,000)
Skin and subcutaneous tissue disorders	
Rash, Alopecia, Pruritus, Urticaria, Erythema multiforme, Angioedema, Eczema	Very rare (<1/10,000)
Musculoskeletal, connective tissue and bone disorders	
Arthralgia, Arthritis, Myalgia, Pain in extremity	Very rare (<1/10,000)
Investigations	
Elevation of liver enzymes	Very rare (<1/10,000)

c. Other special population

Apnoea in very premature infants (born ≤ 28 weeks of gestation) (see section 4.4).

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2. Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

There have been reports of administration of higher than recommended doses of HBVAXPRO.
In general, the adverse event profile reported with overdose was comparable to that observed with the recommended dose of HBVAXPRO.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-infectious, ATC code: J07BC01

The vaccine induces specific humoral antibodies against hepatitis B virus surface antigen (anti-HBsAg). Development of an antibody titre against hepatitis B virus surface antigen (anti-HBsAg) equal to or greater than 10 IU/l measured 1 to 2 months after the last injection correlates with protection to hepatitis B virus infection.

In clinical trials, 96 % of 1,497 healthy infants, children, adolescents and adults given a 3 dose course of a previous formulation of Merck's recombinant hepatitis B vaccine developed a protective level of antibodies against hepatitis B virus surface antigen (≥ 10 IU/l). In two infant trials using different dosing schedules and concomitant vaccines, the proportion of infants with protective levels of antibodies were 97.5 % and 97.2 % with geometric mean titres of 214 and 297 IU/l, respectively.

The protective efficacy of a dose of hepatitis B immunoglobulin at birth followed by 3 doses of a previous formulation of Merck's recombinant hepatitis B vaccine has been demonstrated for neonates born to mothers positive for both hepatitis B virus surface antigen (HBsAg) and hepatitis B virus e antigen (HBeAg). Among 130 vaccinated infants, the estimated efficacy in prevention of chronic hepatitis B infection was 95 % as compared to the infection rate in untreated historical controls.

Although the duration of the protective effect of a previous formulation of Merck's recombinant hepatitis B vaccine in healthy vaccinees is unknown, follow-up over 5-9 years of approximately 3,000 high-risk subjects given a similar plasma-derived vaccine has revealed no cases of clinically apparent hepatitis B infection.

In addition, persistence of vaccine-induced immunologic memory for hepatitis B virus surface antigen (HBsAg) has been demonstrated through an anamnestic antibody response to a booster dose of a previous formulation of Merck's recombinant hepatitis B vaccine. As with other hepatitis B vaccines, the duration of the protective effect in healthy vaccinees is unknown at present. The need for a booster dose of HBVAXPRO is not yet defined beyond the 12 month booster dose required for the 0, 1, 2 compressed schedule.

Reduced risk of Hepatocellular Carcinoma
Hepatocellular carcinoma is a serious complication of hepatitis B virus infection. Studies have demonstrated the link between chronic hepatitis B infection and hepatocellular carcinoma and 80 % of hepatocellular carcinomas are caused by hepatitis B virus infection. Hepatitis B vaccine has been recognized as the first anti-cancer vaccine because it can prevent primary liver cancer.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Animal reproduction studies have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Borax
Water for injections

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 – 8 °C).
Do not freeze. Store in the original package in order to protect from light.

HBVAXPRO should be administered as soon as possible after being removed from refrigeration. HBVAXPRO can be administered provided total (cumulative multiple excursion) time out of refrigeration (at temperatures between 8°C and 25°C) does not exceed 72 hours. Cumulative multiple excursions between 0°C and 2°C are also permitted as long as the total time between 0°C and 2°C does not exceed 72 hours. These are not, however, recommendations for storage.

6.5 Nature and contents of container

0.5 ml of suspension in pre-filled syringe (glass) without needle with a plunger stopper (gray chlorobutyl). Pack size of 1, 10, 20, 50.
0.5 ml of suspension in pre-filled syringe (glass) with 1 separate needle with a plunger stopper (gray chlorobutyl). Pack size of 1, 10.
0.5 ml of suspension in pre-filled syringe (glass) with 2 separate needles with a plunger stopper (gray chlorobutyl). Pack size of 1, 10, 20, 50.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The vaccine should be inspected visually in order to detect any appearance of precipitate or discolouring of the content prior to administration. If these conditions exist, the product should not be administered.
Before use, the syringe should be well shaken.
Hold the syringe barrel and attach the needle by twisting in clockwise direction, until the needle fits securely on the syringe.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

MSD VACCINS
162 avenue Jean Jaurès
69007 Lyon
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/183/004
EU/1/01/183/005
EU/1/01/183/020
EU/1/01/183/021
EU/1/01/183/022
EU/1/01/183/023
EU/1/01/183/024
EU/1/01/183/025
EU/1/01/183/030
EU/1/01/183/031

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27/04/2001
Date of last renewal: 17/03/2011

10. DATE OF REVISION OF THE TEXT

13 January 2020

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