For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

ENGERIX® B

Hepatitis B Vaccine (rDNA) IP (Genetically Engineered)

1. NAME OF THE MEDICINAL PRODUCT

Hepatitis B Vaccine (rDNA) IP (Genetically Engineered)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ENGERIX B 20 mcg/1 ml (Adult)

1 dose (1 ml) contains :

Equivalent to 20 mcg purified HBV surface antigen produced in *Saccharomyces cerevisiae*;

Hydrated Aluminium Oxide IP equiv to 0.5 mg Aluminium

ENGERIX B 10 mcg/0.5 ml (Paediatric)

1 dose (0.5 ml) contains:

Equivalent to 10 mcg purified HBV surface antigen produced in *Saccharomyces cerevisiae*;

Hydrated Aluminium Oxide IP equiv to 0.25 mg Aluminium

For the full list of excipients, see *section 6.1 List of excipients*

3. PHARMACEUTICAL FORM

Suspension for injection
The suspension is turbid white.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ENGERIX B is indicated for active immunization against Hepatitis B Virus infection (HBV) caused by all known subtypes in subjects of all ages considered at risk of exposure to HBV. It can be expected that hepatitis D will also be prevented by immunization with *ENGERIX B* as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

Immunization against hepatitis B is expected in the long term to reduce not only the incidence of this disease but also its chronic complication such as chronic active hepatitis B and hepatitis B associated cirrhosis.

In areas of **low prevalence** of hepatitis B, immunization is particularly recommended for those belonging to groups identified at increased risk of infection (see below), however, universal immunization of all infants and adolescents will contribute to the control of hepatitis B on a population basis.

In areas of **intermediate and high prevalence** of hepatitis B, with most of the population at risk of acquiring the HBV the best strategy is to provide universal immunization of neonates, infants, children and adolescents as well as adults belonging to groups at increased risk of infection.

The WHO, the US Immunisation Practices Advisory Committee (ACIP) and the American Academy of Paediatrics advocate that the vaccination of new-borns and/or the vaccination of adolescents is the optimal strategy for the control of hepatitis B in all countries.

Groups identified at increased risk of infection:

- **Health Care Personnel.**
- **Patients frequently receiving blood products.**
- **Personnel and residents of institutions.**
- **Persons at increased risk due to their sexual behaviour.**
- **Illicit users of addictive injectable drugs.**
- **Travellers to areas with a high endemicity of HBV**
- **Infants born of mothers who are HBV carriers.**
- **Persons originating from areas with a high endemicity of HBV.**
- **Patients with sickle-cell anemia.**
- **Patients who are candidates for organ transplantation.**
- **Household contacts of any of the above groups and of patients with acute or chronic HBV infection.**
- **Subjects with chronic liver disease (CLD) or at risk of developing CLD (e.g. Hepatitis C virus carriers, persons who abuse alcohol).**

Others: Police personnel, fire brigade personnel, armed forces personnel and anybody who through their work or personal lifestyle may be exposed to HBV.

4.2. Posology and method of administration

Posology

A 20 µg dose vaccine:

A 20 µg dose (in 1.0 ml suspension) is intended for use in subjects 20 years of age and older.

A 10 µg dose vaccine:

A 10 µg dose (in 0.5 ml suspension) is intended for use in neonates, infants, children and adolescents upto and including the age of 19 years. In children and adolescents aged 10-19 years, the adult dose of 20µg can be employed if low compliance is anticipated since a higher percentage of vaccinees with protective antibody levels ($\geq$ 10 IU/L) is obtained after two injections at this dosage.

IMMUNIZATION SCHEDULE

Primary Immunisation

A series of three intramuscular injections is required to achieve optimal protection. Two primary immunization schedules can be recommended.

- Schedules which have more time between the second and third doses, such as immunization at 0,1 and 6 months, may take longer to confer protection, but will produce higher antiHBs antibody

titres after three doses. This schedule is intended for use in children and adolescents upto and including 19 years of age with a 10µg dose of *ENGERIX B.*

- An accelerated schedule, with immunization at 0,1 and 2 months, will confer protection more quickly and is expected to provide better patient compliance. A fourth dose should be administered at 12 months. In infants this schedule will allow for simultaneous administration of hepatitis B with other childhood vaccines.

These immunization schedules may be adjusted to accommodate local immunization practices with regard to recommended age of administration of other childhood vaccines.

Booster dose

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

For haemodialysis and other immunocompromised patients, booster doses are recommended in order to ensure an antibody level of > 10 IU/L.

Booster data are available. The booster dose is as well tolerated as the primary vaccination course.

SPECIAL DOSAGE RECOMMENDATIONS

Dosage recommendation for neonates born of mothers who are HBV carriers

The immunisation with *ENGERIX B* (10µg) of these neonates should start at birth, using either the 0, 1 and 2 months or the 0, 1 and 6 months immunization schedule; however, the former schedule provides a more rapid immune response. (For the additional administration of HBIg and the vaccine simultaneously at birth see *Pharmacodynamic properties***).**

Dosage recommendation for known or presumed exposure to HBV

In circumstances where exposure to HBV has recently occurred (eg. needlestick with contaminated needle) the first dose of *ENGERIX B* can be administered simultaneously with HBIg which however must be given at a separate injection site. The accelerated immunisation schedule should be advised.

Dosage recommendation for chronic haemodialysis patients

The primary immunisation schedule for chronic haemodialysis patients is four doses of 40 µg at elected date, 1 month, 2 months and 6 months from the date of the first dose. The immunisation schedule should be adapted in order to ensure that the anti-HBs antibody titre remains above the accepted protective level of 10 IU/L.

Method of administration

ENGERIX B should be injected intramuscularly in the deltoid region in adults and children or in the anterolateral thigh in neonates, infants and young children.

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

4.3. Contraindications

ENGERIX B should not be administered to subjects with known hypersensitivity to the active substances or to any of the excipients listed in *section 6.1 List of excipients*, or to subjects having shown signs of hypersensitivity after previous *ENGERIX B* administration.

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

4.4. Special warnings and precautions for use

Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents 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 from faints.

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

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

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

A number of factors have been observed to reduce the immune response to hepatitis B vaccines. These factors include older age, male gender, obesity, smoking, route of administration, and some chronic underlying diseases. Consideration should be given to serological testing of those subjects who may be at risk of not achieving seroprotection following a complete course of *ENGERIX B.* Additional doses may need to be considered for persons who do not respond or have a sub-optimal response to a course of vaccinations.

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 HB vaccination should thus be considered on a case by case basis by the physician. In HIV infected patients, as also in patients with renal insufficiency including patients undergoing haemodialysis and persons with an impaired immune system, adequate anti-HBs antibody concentrations may not be obtained after the primary immunisation course and such patients may therefore require administration of additional doses of vaccine.

ENGERIX B should not be administered in the buttock or intradermally since this may result in a lower immune response.

ENGERIX B should under no circumstances be administered intravenously.

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.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunization series to very premature infants (born $\leq$ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity.

As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Multidose vials:

Thiomersal (an organomercuric compound) has been used in the manufacturing process of this medicinal product and residues of it are present in the final product. Therefore, sensitisation reactions may occur.

4.5. Interaction with other medicinal products and other forms of interaction

The simultaneous administration of *ENGERIX B* and a standard dose of HBIg does not result in lower anti-HBs antibody concentrations provided that they are administered at separate injection sites.

ENGERIX B 20 mcg/1 ml can be given concomitantly with BCG hepatitis A, polio, measles, mumps, rubella, diphtheria and tetanus vaccines.

ENGERIX B 10 mcg/0.5 ml can be given concomitantly with *Haemophilus influenzae* b, BCG, hepatitis A, polio, measles, mumps, rubella, diphtheria, tetanus and pertussis vaccines.

ENGERIX B can be given concomitantly with Human Papillomavirus (HPV) vaccine.

Administration of *ENGERIX B* at the same time as Cervarix (HPV vaccine) has shown no clinically relevant interference in the antibody response to the HPV antigens. Anti-HBs geometric mean antibody concentrations were lower on co-administration, but the clinical significance of this observation is not known since the seroprotection rates remain unaffected. The proportion of subjects reaching anti-HBs ≥ 10mIU/ml was 97.9% for concomitant vaccination and 100% for *ENGERIX B* alone.

Different injectable vaccines should always be administered at different injection sites.

ENGERIX B may be used to complete a primary immunisation course started either with plasma-derived or with other genetically-engineered hepatitis B vaccines, or, if it is desired to administer a booster dose, it may be administered to subjects who have previously received a primary immunisation course with plasma-derived or with other genetically-engineered hepatitis B vaccines.

4.6. Pregnancy and lactation

Pregnancy

The effect of the HBsAg on foetal development has not been assessed.

However, as with all inactivated viral vaccines one does not expect harm for the foetus. *ENGERIX B* should be used during pregnancy only when clearly needed, and the possible advantages outweigh the possible risks for the foetus.

Lactation

The effect on breastfed infants of the administration of *ENGERIX B* to their mothers has not been evaluated in clinical studies, as information concerning the excretion into the breast milk is not available.

No contra-indication has been established.

Fertility

ENGERIX B has not been evaluated in fertility studies.

4.7. Effects on ability to drive and use machines

Some of the effects mentioned under *section 4.8 Undesirable Effects* may affect the ability to drive or operate machinery.

4.8. Undesirable effects

The following undesirable effects have been reported following the use of the thiomersal containing formulations as well as the thiomersal free formulation.

Clinical trials

In one clinical study conducted with the thiomersal free formulation, the incidence of pain, redness, swelling, drowsiness, irritability, loss of appetite and fever was comparable to the incidence observed in the clinical studies conducted with thiomersal containing vaccine formulations - *ENGERIX B JUNIOR*

In one clinical study conducted with the thiomersal free formulation, the incidence of pain, redness, swelling, fatigue, gastro-enteritis, headache and fever was comparable to the incidence observed in the clinical studies conducted with thiomersal containing vaccine formulations – *ENGERIX B ADULT*

The safety profile presented below is based on data from 5329 subjects followed in 23 studies.

Frequencies per dose are defined as follows:

Very common: (≥1/10)
Common: (≥1/100 to <1/10)
Uncommon: (≥1/1,000 to <1/100)
Rare: (≥1/10,000 to<1/1,000)
Very rare: (<1/10,000)

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

<u>Blood and lymphatic system disorders</u>:
Rare: lymphadenopathy

<u>Nervous system disorders</u>:
Common: drowsiness, headache*
(*For *ENGERIX B JUNIOR* 10 micrograms/0.5 ml, headache is reported under ‘very common’ category of undesirable effects.)
Uncommon: dizziness
Rare: paraesthesia

Gastrointestinal disorders:
Common: gastrointestinal symptoms (such as nausea, vomiting, diarrhoea, abdominal pain)

Skin and subcutaneous tissue disorders:
Rare: urticaria, pruritus, rash

Musculoskeletal and connective tissue disorders:
Uncommon: myalgia
Rare: arthralgia

Metabolism and nutrition disorders
Common: appetite lost

General disorders and administration site conditions
Very common: pain and redness at injection site, fatigue
Common: fever (≥37.5°C), malaise, swelling at injection site, injection site reaction (such as induration)
Uncommon: influenza-like illness

Psychiatric disorders:
Very common: irritability

In a comparative trial in subjects from 11 years up to and including 15 years of age, the incidence of local and general solicited symptoms reported after a two-dose regimen of *ENGERIX B* (20 µg/1 ml) was similar overall to that reported after the standard three-dose regimen of *ENGERIX B JUNIOR* (10 µg/0.5 ml).

Post-marketing surveillance

Blood and lymphatic system disorders
Thrombocytopenia

Nervous system disorders
Encephalitis, encephalopathy, convulsions, paralysis, neuritis (including Guillain-Barré syndrome, optic neuritis and multiple sclerosis), neuropathy, hypoaesthesia

Respiratory thoracic and mediastinal disorders:
Apnoea in very premature infants (≤ 28 weeks of gestation) (see *section 4.4 Special warnings and precautions for use*)

Skin and subcutaneous tissue disorders
Erythema multiforme, angioneurotic oedema, lichen planus

Musculoskeletal and connective tissue disorders
Arthritis, muscular weakness

Infections and infestations
Meningitis

Vascular disorders
Vasculitis, hypotension

Immune system disorders
Anaphylaxis, allergic reactions including anaphylactoid reactions and mimicking serum sickness

4.9. Overdose

Cases of overdose have 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: Hepatitis B vaccine, ATC code: J07BC01

ENGERIX B induces specific humoral antibodies against HBsAg (anti-HBs antibodies). Anti-HBs antibody concentrations ≥ 10 IU/l correlate with protection to HBV infection.

ENGERIX B 10 micrograms/0.5 ml

Protective efficacy

- At risk groups:
In field studies, a protective efficacy between 95% and 100% was demonstrated in neonates, children and adults at risk.

In healthy subjects in high risk area, one month after the last vaccine dose, a 95% protective efficacy (serum anti HBs IgG ≥ 10 mIU/ml) was demonstrated in neonates of HBeAg positive mothers, immunised according to the 0, 1, 2 and 12 month or 0, 1 and 6 month schedules without concomitant administration of hepatitis B immunoglobulin (HBIg) at birth. However, simultaneous administration of HBIg and vaccine at birth increased the protective efficacy to 98%.

Neonates born to mothers who were hepatitis B virus carriers (HBsAg positive with or without HBeAg) and who did not receive HBIg at birth received a challenge dose of *ENGERIX B* twenty years after primary vaccination (3-dose or 4-dose schedules).

The seroprotection rate before and after the challenge dose has been evaluated:

Seroprotection rate	**N**	**n**	**%**	**95% CI**	
				LL	**UL**
Pre-challenge	72	39	54.2	42.0	66.0
Post-challenge	75	74	98.7	92.8	100

N = number of subjects with available results
n = number of subjects with concentration equal to or above 10mIU/ml
% = percentage of subjects with concentration equal to or above 10mIU/ml
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = at the time of administration of the challenge dose / POST = one month after challenge dose

The anamnestic response according to the pre-challenge serostatus was also evaluated:

	Anamnestic response

				95% CI	
Pre-challenge status	**N**	**n**	**%**	**LL**	**UL**
Subjects < 10 mIU/ml	33	31	93.9	79.8	99.3
Subjects ≥ 10 mIU/ml	39	39	100	91.0	100
Total	72	70	97.2	90.3	99.7

Stratification based on last available time point prior to booster dose:

- subjects <10 mIU/ml = subjects with antibody concentration <10 mIU/ml prior to the challenge dose
- subjects ≥10 mIU/ml = subjects with antibody concentration ≥10 mIU/ml prior to the challenge dose

Anamnestic response is defined as:

- anti-HBs antibody concentrations ≥ 10 mIU/ml in subjects who were seronegative before the challenge dose, or
- an increase in anti-HBs antibody concentrations by at least 4-fold in subjects who were seropositive before the challenge dose.

N = number of subjects with both pre- and post-vaccination results available
n = number of responders
% = percentage of responders
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit

- <u>In healthy subjects up to and including 15 years of age:</u>

The Table below summarizes seroprotection rates (i.e. percentages of subjects with anti-HBs antibody concentrations ≥ 10 IU/l) obtained in clinical studies with the different schedules mentioned in *Posology*:

Population	**Schedule**	**Seroprotection rate**
Healthy subjects up to and including 15 years of age	0, 1, 6 months	at month 7: ≥ 96 %
	0, 1, 2 – 12 months	at month 1: 15 % at month 3: 89 % at month 13: 95.8 %

The data in the above Table were generated with thiomersal containing vaccines. Two additional clinical studies conducted with the current formulation of *ENGERIX B*, which does not contain thiomersal, among healthy infants and adults, elicit similar seroprotection rates as compared to former thiomersal containing formulations of *ENGERIX B.*

<u>- In healthy subjects from 11 years up to and including 15 years of age:</u>

Seroprotection rates (i.e. percentages of subjects with anti-HBs antibody concentrations ≥ 10 IU/l) obtained in a comparative study with the two different dosages and schedules licensed in subjects from 11 years up to and including 15 years of age were evaluated up to 66 months after the first dose of the primary vaccination and are presented in the Table below (ATP cohort for efficacy):

Vaccination schedule	Months after the first vaccine dose						
	2	6	7	30	42	54	66
	% of seroprotection						
ENGERIX B JUNIOR (10µg/0.5 ml) (0, 1, 6 months)	55.8	87.6	98.2*	96.9	92.5	94.7	91.4
ENGERIX B (20µg/1 ml) (0, 6 months)	11.3	26.4	96.7*	87.1	83.7	84.4	79.5

*At month 7, 97.3% and 88.8% of subjects aged 11 to 15 years vaccinated with *ENGERIX B JUNIOR* (10 µg/0.5 ml) (0, 1, 6 months schedule) or *ENGERIX B* (20 µg/1 ml) (0, 6 months schedule) respectively developed anti-HBs antibody concentrations ≥ 100 mIU/ml. Geometric Mean Concentrations (GMC) were 7238 mIU/ml and 2739 mIU/ml respectively.

All subjects in both vaccine groups (N=74) received a challenge dose 72 to 78 months after primary vaccination. One month later, all subjects mounted an anamnestic response with a GMC increase of 108 and 95 fold from the pre-to the post challenge time points in the 2-dose and 3-dose priming schedule respectively and were shown to be seroprotected. These data suggest that immune memory was induced in all subjects who responded to primary vaccination, even among those who had lost seroprotection at Month 66.

- Rechallenge of healthy subjects in a low prevalence area (Germany):

Seroprotection rates before and after a challenge dose have been evaluated in subjects aged 12 to 13 years who were vaccinated with 3 doses of *ENGERIX B* during the first two years of life:

Seroprotection rate	N	n	%	95% CI	
				LL	UL
Pre-challenge	279	181	64.9	59.0	70.5
Post-challenge	276	271	98.2	95.8	99.4

N = number of subjects with available results
n = number of subjects with concentration equal to or above 10mIU/ml
% = percentage of subjects with concentration equal to or above 10mIU/ml
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = prior to the challenge dose / POST= one month after challenge dose

Anamnestic response has been evaluated according to pre-challenge serostatus in subjects aged 12 to 13 years who were vaccinated with 3 doses of *ENGERIX B* during the first two years of life:

	Anamnestic response				
				95% CI	
Pre-challenge status	N	n	%	LL	UL
Subjects < 10 mIU/ml	96	92	95.8	89.7	98.9
Subjects ≥ 10 mIU/ml	175	175	100	97.9	100
Total	271	267	98.5	96.3	99.6

Stratification based on last available time point prior to booster dose:

- subjects <10 mIU/ml = subjects with antibody concentration <10 mIU/ml prior to the challenge dose
- subjects ≥10 mIU/ml = subjects with antibody concentration ≥10 mIU/ml prior to the challenge dose

Anamnestic response is defined as:
- anti-HBs antibody concentrations ≥ 10 mIU/ml in subjects who were seronegative before the challenge dose, or
- an increase in anti-HBs antibody concentrations by at least 4-fold in subjects who were seropositive before the challenge dose.

N = number of subjects with both pre- and post-vaccination results available
n = number of responders
% = percentage of responders
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit

Reduction in the incidence of hepatocellular carcinoma in children:

A clear link has been demonstrated between hepatitis B infection and the occurrence of hepatocellular carcinoma (HCC). The prevention of hepatitis B by vaccination results in a reduction of the incidence of HCC, as has been observed in Taiwan in children aged 6-14 years.

ENGERIX B 20 micrograms/1 ml

Protective efficacy

In field studies, a protective efficacy between 95% and 100% was demonstrated in neonates, children and adults at risk.

- Subjects 16 years of age and above:

The table below summarizes seroprotection rates (i.e. percentages of subjects with anti-HBs antibody concentrations ≥ 10 IU/l) obtained in clinical studies with *ENGERIX B* (20µg/1ml), given according to the different schedules mentioned *Section 4.2 Posology and method of administration:*

Population	Schedule	Seroprotection rate
Healthy subjects 16 years of age and above	0, 1, 6 months 0, 1, 2 – 12 months	at month 7: ≥ 96 % at month 1: 15 % at month 3: 89 % at month 13: 95.8 %
Healthy subjects 18 years of age and above	0, 7, 21 days – 12 months	at day 28: 65.2 % at month 2: 76 % at month 13: 98.6 %
Patients with renal insufficiency including patients undergoing haemodialysis 16 years of age and above	0, 1, 2, 6 months (2 x 20 µg)	at month 3: 55.4 % at month 7: 87.1 %

The data in the table were generated with thiomersal containing vaccines. Two additional clinical studies conducted with the current formulation of *ENGERIX B*, which contains no thiomersal, among healthy infants and adults, elicit similar seroprotection rates as compared to former thiomersal containing formulations of *ENGERIX B.*

- Healthy subjects from 11 years up to and including 15 years of age:

The seroprotection rates with the two different dosages and schedules licensed in subjects from 11 years up to and including 15 years of age were evaluated up to 66 months after the first dose of the primary vaccination and are presented in the Table below (ATP cohort for efficacy):

	Months after the first vaccine dose:						
Vaccination schedule	**2**	**6**	**7**	**30**	**42**	**54**	**66**
	% of seroprotection						
ENGERIX B JUNIOR (10µg/0.5 ml) (0, 1, 6 months)	55.8	87.6	98.2*	96.9	92.5	94.7	91.4
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*At month 7, 97.3% and 88.8% of subjects aged 11 to 15 years vaccinated with *ENGERIX B JUNIOR* (10 µg/0.5 ml) (0, 1, 6 months schedule) or *ENGERIX B* (20 µg/1 ml) (0, 6 months schedule) respectively developed anti-HBs antibody concentrations ≥ 100 mIU/ml. Geometric Mean Concentrations (GMC) were 7238 mIU/ml and 2739 mIU/ml respectively.

All subjects in both vaccine groups (N=74) received a challenge dose 72 to 78 months after primary vaccination. One month later, all subjects mounted an anamnestic response with a GMC increase of 108 and 95 fold from the pre to the post challenge time points in the 2-dose and 3-dose priming schedule respectively and were shown to be seroprotected. These data suggest that immune memory was induced in all subjects who responded to primary vaccination, even among those who had lost seroprotection at Month 66.

Reduction in the incidence of hepatocellular carcinoma in children:

A clear link has been demonstrated between hepatitis B infection and the occurrence of hepatocellular carcinoma (HCC). The prevention of hepatitis B by vaccination results in a reduction of the incidence of HCC, as has been observed in Taiwan in children aged 6-14 years.

5.2. Pharmacokinetic properties

Not applicable.

5.3. Preclinical safety data

The preclinical safety data satisfy the requirements of the WHO.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Aluminium hydroxide, sodium chloride, Disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, Polysorbate 20 (as a residual from the manufacturing process), water for injections.

Multidose presentations contain 2 phenoxyethanol as preservative.

The vaccine is formulated without thiomersal as a preservative.

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

The expiry date is indicated on the label and packaging.

6.4. Special Precautions for Storage

Store in a refrigerator (2°C - 8°C).
Do not freeze; discard if vaccine has been frozen

Keep out of reach of children.

Additional information on the stability

The following experimental data give an indication of the stability of the vaccine and are not recommendations for storage (see under *Section 6.6 Special Precautions for disposal and other handling).*

ENGERIX B has been kept in a refrigerator at $+2^0$C to $+8^0$C for 48 months without significant loss of potency.

ENGERIX B has been kept at 37^0C for 1 month and 45^0C for 1 week without loss of its potency.

6.5. Nature and contents of container

1 ml Monodose preparation in Vials (Adult)
0.5 ml Monodose preparation in Vials (Paediatric)
10 ml Multidose preparation in Vials

ENGERIX B is presented in a glass vial / pre-filled syringe. The vials are made of neutral glass type 1, which conforms to European Pharmacopoeia requirements.

Not all pack presentations may be marketed in India.

6.6. Special precautions for disposal and other handling

Upon storage, the content may present a fine white deposit with a clear colourless supernatant. Once shaken the vaccine is slightly opaque.

The vaccine should be inspected visually for any foreign particulate matter and/or coloration prior to administration. Discard if the content appears otherwise.

The entire contents of a mono-dose container must be withdrawn and should be used immediately.

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Pharmaceuticals Limited,
Registered office:
Dr. Annie Besant Road, Worli
Mumbai 400 030, India

8. MARKETING AUTHORISATION NUMBER(S)

Not applicable

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 23rd January, 1987

Manufactured by:	**Imported , Labelled/ Packed by:**	**For further information please contact:**
GlaxoSmithKline Biologicals s.a. Rue de l'Institut, 89 B-1330 Rixensart, Belgium.	GlaxoSmithKline Asia Pvt. Ltd., Plot No. A-10/1, Additional M.I.D.C., Ambad-Pathardi Block, Nashik - 422010, India	GlaxoSmithKline Pharmaceuticals Limited, Registered office: Dr. Annie Besant Road, Worli Mumbai 400 030, India

ENGERIX is a registered trademark of the GlaxoSmithKline group of companies

Version: ENG/PI/IN/2015/01 dated 4 March 2015

Adapted from ENGERIX B JUNIOR SPC dated 6 August 2014 and ENGERIX B ADULT SPC dated 13 August 2012 (aligned to GDS 12 in line with changes approved in the SPC)