

## **SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

ENGERIX B 10 micrograms/0.5 ml  
Suspension for injection  
Hepatitis B recombinant vaccine, adsorbed

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml):

Hepatitis B virus surface antigen recombinant\* (S protein) adsorbed  
10 micrograms  
per 0.5 ml

\*produced on genetically-engineering yeast cells (*Saccharomyces cerevisiae*)

## 3. PHARMACEUTICAL FORM

Suspension for injection.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ENGERIX B is indicated for active immunisation against hepatitis B virus infection (HBV) caused by all known subtypes in **non immune** subjects of all ages. The categories within the population to be immunised are determined on the basis of official recommendations.

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

#### Dosage

20µg dose vaccine: A 20 µg dose is intended for use in adults and children older than 15 years of age.

10 µg dose vaccine: A 10 µg dose (in 0.5-ml suspension) is intended for use in children up to and including 15 years of age, including neonates. In children aged 10 to 15 years, the adult dose of 20 µg 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

#### Primary Immunisation schedule

A series of three intramuscular injections is required to achieve optimal protection.

Two primary immunisation schedules can be recommended:

An accelerated schedule, with immunisation 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.

Schedules which have more time between the second and third doses, such as immunisation at 0, 1 and 6 months, may take longer to confer protection, but will produce higher anti-HBs antibody titres. This schedule is intended for use in school children up to and including 15 years of age.

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

In exceptional circumstances in adults, where a more rapid induction of protection is required, e.g. persons travelling to areas of high endemicity and who commence a course of vaccination against hepatitis B within one month prior to departure, a schedule of three intramuscular injections given at 0, 7 and 21 days may be used. When this schedule is applied, a fourth dose is recommended 12 months after the first dose (see section 5.1 "Pharmacodynamic properties" for seroconversion rates).

#### 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 some categories of subjects or patients particularly exposed to the HBV (e.g. haemodialysis or immunocompromised patients) a precautionary attitude should be considered to ensure a protective antibody level > 10IU/l.

#### Interchangeability of hepatitis B vaccines

See 4.5. Interaction with other medicaments and other forms of interaction.

Special dosage recommendations (see Dosage)

- Dosage recommendation for neonates born of mothers who are HBV carriers:

The immunisation with ENGERIX B (10 µg) of these neonates should start at birth, and two immunisation schedules have been followed. Either the 0, 1, 2 and 12 months or the 0, 1 and 6 months schedule can be used; however, the former schedule provides a more rapid immune response. When available, hepatitis B immune globulins (HBIG) should be given simultaneously with ENGERIX B at a separate injection site as this may increase the protective efficacy.

- 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 Contra-indications**

ENGERIX B should not be administered to subjects with known hypersensitivity to any component of the vaccine, 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 special precautions for use**

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 agents such as hepatitis A, hepatitis C and hepatitis E and other pathogens known to infect the liver.

The immune response to hepatitis B vaccines is related to a number of factors, including older age, male gender, obesity, smoking habits and route of administration. In subjects who may respond less well to the administration of the hepatitis B vaccines (e.g. more than 40 years of age etc.), additional doses may be considered.

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.

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 haemodialysis patients and persons with an impaired immune system, adequate anti-HBs antibody titers may not be obtained after the primary immunisation course and such patients may therefore require administration of additional doses of vaccine. (see "Dosage recommendation for chronic haemodialysis patients.")

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.

### **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 titres provided that they are administered at separate injection sites.

ENGERIX B can be given concomitantly with BCG, DTP, DT and/or polio vaccines, if this fits conveniently in an immunisation scheme recommended by the country Health Authority.

ENGERIX B can also be administered together with measles-mumps-rubella vaccines, Haemophilus influenzae b vaccine and hepatitis A vaccine.

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 Use during 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 breastmilk is not available.

No contra-indication has been established.

#### **4.7 Effects on ability to drive and use machines**

The vaccine is unlikely to produce an effect on the ability to drive and use machines.

#### **4.8 Undesirable effects**

ENGERIX B is generally well tolerated.

The following undesirable events 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.

##### **Common**

Application site : transient soreness, erythema, induration

##### **Rare**

Body as a whole : fatigue, fever, malaise, influenza-like symptoms

Central and peripheral nervous system : dizziness, headache, paresthesia

Gastro-intestinal system : nausea, vomiting, diarrhoea, abdominal pain

Liver and biliary system : abnormal liver function tests

Musculoskeletal system : arthralgia, myalgia

Skin and appendages : rash, pruritus, urticaria

##### **Very rare**

Body as a whole : anaphylaxis, serum sickness

Cardiovascular : syncope, hypotension

Central and peripheral nervous system : paralysis, neuropathy, neuritis (including Guillain-Barré syndrome, optic neuritis and multiple sclerosis), encephalitis, encephalopathy, meningitis, convulsions

Haematological disorder : thrombocytopenia

Musculoskeletal system : arthritis

Respiratory system : bronchospasm like symptoms

Skin and appendages : angioedema, erythema multiforme

Vascular extracardiac : vasculitis

White cell and reticulo-endothelial system : lymphadenopathy

The booster dose is as well tolerated as the primary vaccination.

This medicinal product contains thiomersal (an organomercuric compound) as a preservative and therefore it is possible that sensitisation reactions may occur (see Section 4.3).

#### **4.9 Overdose**

Not applicable.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1. Pharmacodynamic properties**

ENGERIX B, hepatitis B vaccine is a sterile suspension containing the purified major surface antigen of the virus manufactured by recombinant DNA technology, adsorbed onto aluminium hydroxide.

The antigen is produced by culture of genetically-engineered yeast cells (*Saccharomyces cerevisiae*) which carry the gene which codes for the major surface antigen of the hepatitis B virus (HBV). This hepatitis B surface antigen (HBsAg) expressed in yeast cells is purified by several physico-chemical steps.

The HBsAg assembles spontaneously, in the absence of chemical treatment, into spherical particles of 20 nm in average diameter containing non-glycosylated HBsAg polypeptides and a lipid matrix consisting mainly of phospholipids. Extensive tests have demonstrated that these particles display the characteristic properties of natural HBsAg.

The vaccine is highly purified, and meets the WHO requirements for recombinant hepatitis B vaccines. No substances of human origin are used in its manufacture.

ENGERIX B induces specific humoral antibodies against HBsAg (anti-HBs antibodies). An anti-HBs antibody titre above 10 IU/l correlates with protection to HBV infection.

#### Protective efficacy

- In risk groups:

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

A 95% protective efficacy was demonstrated in neonates of HBeAg positive mothers, immunised according to the 0, 1, 2 and 12 or 0, 1 and 6 schedules without the concomitant administration of HBIG at birth. However, simultaneous administration of HBIG and vaccine at birth increased the protective efficacy to 98%.

- In healthy subjects:

When the 0, 1 and 6 month schedule is followed, □96 % of vaccinees have seroprotective levels of antibody 7 months after the first dose.

When the 0, 1, 2 and 12 month schedule is followed, 15 % and 89% of vaccinees have seroprotective levels of antibody one month after first dose and one month after the third dose respectively. One month after the fourth dose 95.8 % of vaccinees achieved seroprotective levels of antibody.

For use in exceptional circumstances, the 0, 7 and 21 day primary schedule plus a fourth dose at month 12 results in 65.2 % and 76% of vaccinees having seroprotective levels of antibody within 1 and 5

weeks respectively following the third dose. One month after the fourth dose 98.6 % of vaccinees achieved seroprotective levels of antibody.

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 oxide hydrated, thiomersal, polysorbate 20, sodium chloride, disodium phosphate dihydrate, sodium dihydrogen phosphate, water for injections.

## **6.2 Incompatibilities**

ENGERIX B should not be mixed with other vaccines.

## **6.3 Shelf-life**

3 years.

## **6.4 Special precautions for storage**

The vaccine should be stored at +2 °C to +8 °C.  
Do not freeze; discard if vaccine has been frozen.

## **6.5 Nature and content of container**

0.5 ml suspension in vial (type I glass) with stopper (butyl). Pack of 1, 10, 25, 50, 100.  
Disposal syringe(s) may be supplied.

## **6.6 Instructions for use and handling, and disposal (if appropriate)**

The content, upon storage 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.

# **7. MARKETING AUTHORISATION HOLDER**

# **8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS**

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10. DATE OF REVISION OF THE TEXT**

## 1. NAME OF THE MEDICINAL PRODUCT

ENGERIX B 10 micrograms/0.5 ml  
Suspension for injection in pre-filled syringe  
Hepatitis B recombinant vaccine, adsorbed

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml):

Hepatitis B virus surface antigen recombinant (S protein)* adsorbed	10 micrograms per 0.5 ml
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\* produced on genetically-engineered yeast cells (*Saccharomyces cerevisiae*)

## 3. PHARMACEUTICAL FORM

Suspension for injection in pre-filled syringe.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ENGERIX B is indicated for active immunisation against hepatitis B virus infection (HBV) caused by all known subtypes in non immune subjects of all ages. The categories within the population to be immunised are determined on the basis of official recommendations.

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

#### Dosage

20µg dose vaccine: A 20 µg dose is intended for use in adults and children older than 15 years of age.

10 µg dose vaccine: A 10 µg dose (in 0.5-ml suspension) is intended for use in children up to and including 15 years of age, including neonates. In children aged 10 to 15 years, the adult dose of 20 µg 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.

#### Primary Immunisation schedule

A series of three intramuscular injections is required to achieve optimal protection.

Two primary immunisation schedules can be recommended:

An accelerated schedule, with immunisation 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.

Schedules which have more time between the second and third doses, such as immunisation at 0, 1 and 6 months, may take longer to confer protection, but will produce higher anti-HBs antibody titres. This schedule is intended for use in school children up to and including 15 years of age.

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

In exceptional circumstances in adults, where a more rapid induction of protection is required, e.g. persons travelling to areas of high endemicity and who commence a course of vaccination against hepatitis B within one month prior to departure, a schedule of three intramuscular injections given at 0, 7 and 21 days may be used. When this schedule is applied, a fourth dose is recommended 12 months after the first dose (see section 5.1 "Pharmacodynamic properties" for seroconversion rates).

#### 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 some categories of subjects or patients particularly exposed to the HBV (e.g. haemodialysis or immunocompromised patients) a precautionary attitude should be considered to ensure a protective antibody level > 10IU/l.

#### Interchangeability of hepatitis B vaccines

See 4.5. Interaction with other medicaments and other forms of interaction.

Special dosage recommendations (see Dosage)

- Dosage recommendation for neonates born of mothers who are HBV carriers:

The immunisation with ENGERIX B (10 µg) of these neonates should start at birth, and two immunisation schedules have been followed. Either the 0, 1 and 2 months or the 0, 1 and 6 months schedule can be used; however, the former schedule provides a more rapid immune response. When available, hepatitis B immune globulins (HBIG) should be given simultaneously with ENGERIX B at a separate injection site as this may increase the protective efficacy.

- 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 Contra-indications**

ENGERIX B should not be administered to subjects with known hypersensitivity to any component of the vaccine, 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 special precautions for use**

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 agents such as hepatitis A, hepatitis C and hepatitis E and other pathogens known to infect the liver.

The immune response to hepatitis B vaccines is related to a number of factors, including older age, male gender, obesity, smoking habits and route of administration. In subjects who may respond less well to the administration of the hepatitis B vaccines (e.g. more than 40 years of age etc.), additional doses may be considered.

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.

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 haemodialysis patients and persons with an impaired immune system, adequate anti-HBs antibody titers may not be obtained after the primary immunisation course and such patients may therefore require administration of additional doses of vaccine. (see "Dosage recommendation for chronic haemodialysis patients.")

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.

### **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 titres provided that they are administered at separate injection sites.

ENGERIX B can be given concomitantly with BCG, DTP, DT and/or polio vaccines, if this fits conveniently in an immunisation scheme recommended by the country Health Authority.

ENGERIX B can also be administered together with measles-mumps-rubella vaccines, Haemophilus influenzae b vaccine and hepatitis A vaccine.

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 Use during 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 breastmilk is not available.

No contra-indication has been established.

#### **4.7 Effects on ability to drive and use machines**

The vaccine is unlikely to produce an effect on the ability to drive and use machines.

#### **4.8 Undesirable effects**

ENGERIX B is generally well tolerated.

The following undesirable events 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.

##### **Common**

Application site : transient soreness, erythema, induration

##### **Rare**

Body as a whole : fatigue, fever, malaise, influenza-like symptoms

Central and peripheral nervous system : dizziness, headache, paresthesia

Gastro-intestinal system : nausea, vomiting, diarrhoea, abdominal pain

Liver and biliary system : abnormal liver function tests

Musculoskeletal system : arthralgia, myalgia

Skin and appendages : rash, pruritus, urticaria

##### **Very rare**

Body as a whole : anaphylaxis, serum sickness

Cardiovascular : syncope, hypotension

Central and peripheral nervous system : paralysis, neuropathy, neuritis (including Guillain-Barré syndrome, optic neuritis and multiple sclerosis), encephalitis, encephalopathy, meningitis, convulsions  
Haematological disorder : thrombocytopenia  
Musculoskeletal system : arthritis  
Respiratory system : bronchospasm like symptoms  
Skin and appendages : angioedema, erythema multiforme  
Vascular extracardiac : vasculitis  
White cell and reticulo-endothelial system : lymphadenopathy

The booster dose is as well tolerated as the primary vaccination.

This medicinal product contains thiomersal (an organomercuric compound) as a preservative and therefore, it is possible that sensitisation reactions may occur (see Section 4.3).

#### **4.9 Overdose**

Not applicable.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1. Pharmacodynamic properties**

ENGERIX B, hepatitis B vaccine is a sterile suspension containing the purified major surface antigen of the virus manufactured by recombinant DNA technology, adsorbed onto aluminium hydroxide.

The antigen is produced by culture of genetically-engineered yeast cells (*Saccharomyces cerevisiae*) which carry the gene which codes for the major surface antigen of the hepatitis B virus (HBV). This hepatitis B surface antigen (HBsAg) expressed in yeast cells is purified by several physico-chemical steps.

The HBsAg assembles spontaneously, in the absence of chemical treatment, into spherical particles of 20 nm in average diameter containing non-glycosylated HBsAg polypeptides and a lipid matrix consisting mainly of phospholipids. Extensive tests have demonstrated that these particles display the characteristic properties of natural HBsAg.

The vaccine is highly purified, and meets the WHO requirements for recombinant hepatitis B vaccines. No substances of human origin are used in its manufacture.

ENGERIX B induces specific humoral antibodies against HBsAg (anti-HBs antibodies). An anti-HBs antibody titre above 10 IU/l correlates with protection to HBV infection.

#### Protective efficacy

- In risk groups:

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

A 95% protective efficacy was demonstrated in neonates of HBeAg positive mothers, immunised according to the 0, 1, 2 and 12 or 0, 1 and 6 schedules without the concomitant administration of HBIG at birth. However, simultaneous administration of HBIG and vaccine at birth increased the protective efficacy to 98%.

- In healthy subjects:

When the 0, 1 and 6 month schedule is followed,  $\geq 96$  % of vaccinees have seroprotective levels of antibody 7 months after the first dose.

When the 0, 1, 2 and 12 month schedule is followed, 15 % and 89% of vaccinees have seroprotective levels of antibody one month after first dose and one month after the third dose respectively. One month after the fourth dose 95.8 % of vaccinees achieved seroprotective levels of antibody.

For use in exceptional circumstances, the 0, 7 and 21 day primary schedule plus a fourth dose at month 12 results in 65.2 % and 76% of vaccinees having seroprotective levels of antibody within 1 and 5 weeks respectively following the third dose. One month after the fourth dose 98.6 % of vaccinees achieved seroprotective levels of antibody.

#### 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 oxide hydrated, thiomersal, polysorbate 20, sodium chloride, disodium phosphate dihydrate, sodium dihydrogen phosphate, water for injections.

### **6.2 Incompatibilities**

ENGERIX B should not be mixed with other vaccines.

### **6.3 Shelf-life**

3 years.

### **6.4 Special precautions for storage**

The vaccine should be stored at +2 °C to +8 °C. Do not freeze; discard if vaccine has been frozen.

### **6.5 Nature and content of container**

0.5 ml suspension in pre-filled syringe (type I glass). Pack of 1, 10, 25, 50.

### **6.6 Instructions for use and handling, and disposal (if appropriate)**

The content, upon storage 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.

**7. MARKETING AUTHORISATION HOLDER**

**8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS**

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

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## 1. NAME OF THE MEDICINAL PRODUCT

ENGERIX B 20 micrograms/1 ml  
Suspension for injection in pre-filled syringe  
Hepatitis B recombinant vaccine, adsorbed

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (1 ml):

Hepatitis B virus surface antigen recombinant (S protein)\* adsorbed

20 micrograms  
per 1 ml

\* produced on genetically-engineered yeast cells (*Saccharomyces cerevisiae*)

## 3. PHARMACEUTICAL FORM

Suspension for injection in pre-filled syringe.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ENGERIX B is indicated for active immunisation against hepatitis B virus infection (HBV) caused by all known subtypes in non immune subjects of all ages. The categories within the population to be immunised are determined on the basis of official recommendations.

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

#### Dosage

20 µg dose vaccine: A 20 µg dose is intended for use in adults and children older than 15 years of age.

10 µg dose vaccine: A 10 µg dose (in 0.5-ml suspension) is intended for use in children up to and including 15 years of age, including neonates. In children aged 10 to 15 years, the adult dose of 20 µg 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

#### Primary Immunisation schedule

A series of three intramuscular injections is required to achieve optimal protection.

Two primary immunisation schedules can be recommended:

An accelerated schedule, with immunisation 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.

Schedules which have more time between the second and third doses, such as immunisation at 0, 1 and 6 months, may take longer to confer protection, but will produce higher anti-HBs antibody titres. This schedule is intended for use in school children up to and including 15 years of age.

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

In exceptional circumstances in adults, where a more rapid induction of protection is required, e.g. persons travelling to areas of high endemicity and who commence a course of vaccination against hepatitis B within one month prior to departure, a schedule of three intramuscular injections given at 0, 7 and 21 days may be used. When this schedule is applied, a fourth dose is recommended 12 months after the first dose (see section 5.1 "Pharmacodynamic properties" for seroconversion rates).

#### 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 some categories of subjects or patients particularly exposed to the HBV (e.g. haemodialysis or immunocompromised patients) a precautionary attitude should be considered to ensure a protective antibody level > 10IU/l.

#### Interchangeability of hepatitis B vaccines

See 4.5. Interaction with other medicaments and other forms of interaction.

Special dosage recommendations (see Dosage)

- Dosage recommendation for neonates born of mothers who are HBV carriers:

The immunisation with ENGERIX B (10 µg) of these neonates should start at birth, and two immunisation schedules have been followed. Either the 0, 1 and 2 months or the 0, 1 and 6 months schedule can be used; however, the former schedule provides a more rapid immune response. When available, hepatitis B immune globulins (HBIG) should be given simultaneously with ENGERIX B at a separate injection site as this may increase the protective efficacy.

- 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 Contra-indications**

ENGERIX B should not be administered to subjects with known hypersensitivity to any component of the vaccine, 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 special precautions for use**

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 agents such as hepatitis A, hepatitis C and hepatitis E and other pathogens known to infect the liver.

The immune response to hepatitis B vaccines is related to a number of factors, including older age, male gender, obesity, smoking habits and route of administration. In subjects who may respond less well to the administration of the hepatitis B vaccines (e.g. more than 40 years of age etc.), additional doses may be considered.

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.

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 haemodialysis patients and persons with an impaired immune system, adequate anti-HBs antibody titers may not be obtained after the primary immunisation course and such patients may therefore require administration of additional doses of vaccine. (see "Dosage recommendation for chronic haemodialysis patients.")

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.

### **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 titres provided that they are administered at separate injection sites.

ENGERIX B can be given concomitantly with BCG, DTP, DT and/or polio vaccines, if this fits conveniently in an immunisation scheme recommended by the country Health Authority.

ENGERIX B can also be administered together with measles-mumps-rubella vaccines, Haemophilus influenzae b vaccine and hepatitis A vaccine.

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 Use during 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 breastmilk is not available.

No contra-indication has been established.

#### **4.7 Effects on ability to drive and use machines**

The vaccine is unlikely to produce an effect on the ability to drive and use machines.

#### **4.8 Undesirable effects**

ENGERIX B is generally well tolerated.

The following undesirable events 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.

##### **Common**

Application site : transient soreness, erythema, induration

##### **Rare**

Body as a whole : fatigue, fever, malaise, influenza-like symptoms

Central and peripheral nervous system : dizziness, headache, paresthesia

Gastro-intestinal system : nausea, vomiting, diarrhoea, abdominal pain

Liver and biliary system : abnormal liver function tests

Musculoskeletal system : arthralgia, myalgia

Skin and appendages : rash, pruritus, urticaria

##### **Very rare**

Body as a whole : anaphylaxis, serum sickness

Cardiovascular : syncope, hypotension

Central and peripheral nervous system : paralysis, neuropathy, neuritis (including Guillain-Barré syndrome, optic neuritis and multiple sclerosis), encephalitis, encephalopathy, meningitis, convulsions

Haematological disorder : thrombocytopenia

Musculoskeletal system : arthritis  
Respiratory system : bronchospasm like symptoms  
Skin and appendages : angioedema, erythema multiforme  
Vascular extracardiac : vasculitis  
White cell and reticulo-endothelial system : lymphadenopathy

The booster dose is as well tolerated as the primary vaccination.

This medicinal product contains thiomersal (an organomercuric compound) as a preservative and therefore, it is possible that sensitisation reactions may occur (see Section 4.3).

#### **4.9 Overdose**

Not applicable.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1. Pharmacodynamic properties**

ENGERIX B, hepatitis B vaccine is a sterile suspension containing the purified major surface antigen of the virus manufactured by recombinant DNA technology, adsorbed onto aluminium hydroxide.

The antigen is produced by culture of genetically-engineered yeast cells (*Saccharomyces cerevisiae*) which carry the gene which codes for the major surface antigen of the hepatitis B virus (HBV). This hepatitis B surface antigen (HBsAg) expressed in yeast cells is purified by several physico-chemical steps.

The HBsAg assembles spontaneously, in the absence of chemical treatment, into spherical particles of 20 nm in average diameter containing non-glycosylated HBsAg polypeptides and a lipid matrix consisting mainly of phospholipids. Extensive tests have demonstrated that these particles display the characteristic properties of natural HBsAg.

The vaccine is highly purified, and meets the WHO requirements for recombinant hepatitis B vaccines. No substances of human origin are used in its manufacture.

ENGERIX B induces specific humoral antibodies against HBsAg (anti-HBs antibodies). An anti-HBs antibody titre above 10 IU/l correlates with protection to HBV infection.

#### Protective efficacy

##### - In risk groups:

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

A 95% protective efficacy was demonstrated in neonates of HBeAg positive mothers, immunised according to the 0, 1, 2 and 12 or 0, 1 and 6 schedules without the concomitant administration of HBIG at birth. However, simultaneous administration of HBIG and vaccine at birth increased the protective efficacy to 98%.

##### - In healthy subjects:

When the 0, 1 and 6 month schedule is followed,  $\geq 96\%$  of vaccinees have seroprotective levels of antibody 7 months after the first dose.

When the 0, 1, 2 and 12 month schedule is followed, 15 % and 89% of vaccinees have seroprotective levels of antibody one month after first dose and one month after the third dose respectively. One month after the fourth dose 95.8 % of vaccinees achieved seroprotective levels of antibody.

For use in exceptional circumstances, the 0, 7 and 21 day primary schedule plus a fourth dose at month 12 results in 65.2 % and 76% of vaccinees having seroprotective levels of antibody within 1 and 5 weeks respectively following the third dose. One month after the fourth dose 98.6 % of vaccinees achieved seroprotective levels of antibody.

#### 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 oxide hydrated, thiomersal, polysorbate 20, sodium chloride, disodium phosphate dihydrate, sodium dihydrogen phosphate, water for injections.

### **6.2 Incompatibilities**

ENGERIX B should not be mixed with other vaccines.

### **6.3 Shelf-life**

3 years.

### **6.4 Special precautions for storage**

The vaccine should be stored at +2 °C to +8 °C. Do not freeze; discard if vaccine has been frozen.

### **6.5 Nature and content of container**

1 ml suspension in pre-filled syringe (type I glass). Pack of 1, 10, 25.

### **6.6 Instructions for use and handling, and disposal (if appropriate)**

The content, upon storage 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.

- 7. MARKETING AUTHORISATION HOLDER**
- 8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS**
- 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
- 10. DATE OF REVISION OF THE TEXT**

## 1. NAME OF THE MEDICINAL PRODUCT

ENGERIX B 20 micrograms/1 ml  
Suspension for injection  
Hepatitis B recombinant vaccine, adsorbed

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (1 ml):

Hepatitis B virus surface antigen recombinant (S protein)\* adsorbed  
20 micrograms  
per 1 ml

\* produced on genetically-engineered yeast cells (*Saccharomyces cerevisiae*)

## 3. PHARMACEUTICAL FORM

Suspension for injection

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ENGERIX B is indicated for active immunisation against hepatitis B virus infection (HBV) caused by all known subtypes in non immune subjects of all ages. The categories within the population to be immunised are determined on the basis of official recommendations.

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

#### Dosage

20 µg dose vaccine: A 20 µg dose is intended for use in adults and children older than 15 years of age.

10 µg dose vaccine: A 10 µg dose (in 0.5-ml suspension) is intended for use in children up to and including 15 years of age, including neonates. In children aged 10 to 15 years, the adult dose of 20 µg 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

#### Primary Immunisation schedule

A series of three intramuscular injections is required to achieve optimal protection.

Two primary immunisation schedules can be recommended:

An accelerated schedule, with immunisation 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.

Schedules which have more time between the second and third doses, such as immunisation at 0, 1 and 6 months, may take longer to confer protection, but will produce higher anti-HBs antibody titres. This schedule is intended for use in school children up to and including 15 years of age.

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

In exceptional circumstances in adults, where a more rapid induction of protection is required, e.g. persons travelling to areas of high endemicity and who commence a course of vaccination against hepatitis B within one month prior to departure, a schedule of three intramuscular injections given at 0, 7 and 21 days may be used. When this schedule is applied, a fourth dose is recommended 12 months after the first dose (see section 5.1 "Pharmacodynamic properties" for seroconversion rates).

#### 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 some categories of subjects or patients particularly exposed to the HBV (e.g. haemodialysis or immunocompromised patients) a precautionary attitude should be considered to ensure a protective antibody level > 10IU/l.

#### Interchangeability of hepatitis B vaccines

See 4.5. Interaction with other medicaments and other forms of interaction.

Special dosage recommendations (see Dosage)

- Dosage recommendation for neonates born of mothers who are HBV carriers:

The immunisation with ENGERIX B (10 µg) of these neonates should start at birth, and two immunisation schedules have been followed. Either the 0, 1 and 2 months or the 0, 1 and 6 months schedule can be used; however, the former schedule provides a more rapid immune response. When available, hepatitis B immune globulins (HBIG) should be given simultaneously with ENGERIX B at a separate injection site as this may increase the protective efficacy.

- 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 Contra-indications**

ENGERIX B should not be administered to subjects with known hypersensitivity to any component of the vaccine, 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 special precautions for use**

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 agents such as hepatitis A, hepatitis C and hepatitis E and other pathogens known to infect the liver.

The immune response to hepatitis B vaccines is related to a number of factors, including older age, male gender, obesity, smoking habits and route of administration. In subjects who may respond less well to the administration of the hepatitis B vaccines (e.g. more than 40 years of age etc.), additional doses may be considered.

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.

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 haemodialysis patients and persons with an impaired immune system, adequate anti-HBs antibody titers may not be obtained after the primary immunisation course and such patients may therefore require administration of additional doses of vaccine. (see "Dosage recommendation for chronic haemodialysis patients.")

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.

### **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 titres provided that they are administered at separate injection sites.

ENGERIX B can be given concomitantly with BCG, DTP, DT and/or polio vaccines, if this fits conveniently in an immunisation scheme recommended by the country Health Authority.

ENGERIX B can also be administered together with measles-mumps-rubella vaccines, Haemophilus influenzae b vaccine and hepatitis A vaccine.

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 Use during 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 breastmilk is not available.

No contra-indication has been established.

#### **4.7 Effects on ability to drive and use machines**

The vaccine is unlikely to produce an effect on the ability to drive and use machines.

#### **4.8 Undesirable effects**

ENGERIX B is generally well tolerated.

The following undesirable events 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.

##### **Common**

Application site : transient soreness, erythema, induration

##### **Rare**

Body as a whole : fatigue, fever, malaise, influenza-like symptoms

Central and peripheral nervous system : dizziness, headache, paresthesia

Gastro-intestinal system : nausea, vomiting, diarrhoea, abdominal pain

Liver and biliary system : abnormal liver function tests

Musculoskeletal system : arthralgia, myalgia

Skin and appendages : rash, pruritus, urticaria

##### **Very rare**

Body as a whole : anaphylaxis, serum sickness

Cardiovascular : syncope, hypotension

Central and peripheral nervous system : paralysis, neuropathy, neuritis (including Guillain-Barré syndrome, optic neuritis and multiple sclerosis), encephalitis, encephalopathy, meningitis, convulsions

Haematological disorder : thrombocytopenia

Musculoskeletal system : arthritis  
Respiratory system : bronchospasm like symptoms  
Skin and appendages : angioedema, erythema multiforme  
Vascular extracardiac : vasculitis  
White cell and reticulo-endothelial system : lymphadenopathy

The booster dose is as well tolerated as the primary vaccination.

This medicinal product contains thiomersal (an organomercuric compound) as a preservative and therefore, it is possible that sensitisation reactions may occur (see Section 4.3).

#### **4.9 Overdose**

Not applicable.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1. Pharmacodynamic properties**

ENGERIX B, hepatitis B vaccine is a sterile suspension containing the purified major surface antigen of the virus manufactured by recombinant DNA technology, adsorbed onto aluminium hydroxide.

The antigen is produced by culture of genetically-engineered yeast cells (*Saccharomyces cerevisiae*) which carry the gene which codes for the major surface antigen of the hepatitis B virus (HBV). This hepatitis B surface antigen (HBsAg) expressed in yeast cells is purified by several physico-chemical steps.

The HBsAg assembles spontaneously, in the absence of chemical treatment, into spherical particles of 20 nm in average diameter containing non-glycosylated HBsAg polypeptides and a lipid matrix consisting mainly of phospholipids. Extensive tests have demonstrated that these particles display the characteristic properties of natural HBsAg.

The vaccine is highly purified, and meets the WHO requirements for recombinant hepatitis B vaccines. No substances of human origin are used in its manufacture.

ENGERIX B induces specific humoral antibodies against HBsAg (anti-HBs antibodies). An anti-HBs antibody titre above 10 IU/l correlates with protection to HBV infection.

#### Protective efficacy

##### **- In risk groups:**

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

A 95% protective efficacy was demonstrated in neonates of HBeAg positive mothers, immunised according to the 0, 1, 2 and 12 or 0, 1 and 6 schedules without the concomitant administration of HBIG at birth. However, simultaneous administration of HBIG and vaccine at birth increased the protective efficacy to 98%.

##### **- In healthy subjects:**

When the 0, 1 and 6 month schedule is followed,  $\geq 96\%$  of vaccinees have seroprotective levels of antibody 7 months after the first dose.

When the 0, 1, 2 and 12 month schedule is followed, 15 % and 89% of vaccinees have seroprotective levels of antibody one month after first dose and one month after the third dose respectively. One month after the fourth dose 95.8 % of vaccinees achieved seroprotective levels of antibody.

For use in exceptional circumstances, the 0, 7 and 21 day primary schedule plus a fourth dose at month 12 results in 65.2 % and 76% of vaccinees having seroprotective levels of antibody within 1 and 5 weeks respectively following the third dose. One month after the fourth dose 98.6 % of vaccinees achieved seroprotective levels of antibody.

#### 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 oxide hydrated, thiomersal, polysorbate 20, sodium chloride, disodium phosphate dihydrate, sodium dihydrogen phosphate, water for injections.

### **6.2 Incompatibilities**

ENGERIX B should not be mixed with other vaccines.

### **6.3 Shelf-life**

3 years.

### **6.4 Special precautions for storage**

The vaccine should be stored at +2 °C to +8 °C. Do not freeze; discard if vaccine has been frozen.

### **6.5 Nature and content of container**

1 ml suspension in vial (type I glass) with stopper (butyl). Pack of 1, 3, 10, 25, 100.  
Disposal syringe(s) may be supplied.

### **6.6 Instructions for use and handling, and disposal (if appropriate)**

The content, upon storage 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.

**7. MARKETING AUTHORISATION HOLDER**

**8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS**

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10. DATE OF REVISION OF THE TEXT**

## 1. NAME OF THE MEDICINAL PRODUCT

ENGERIX B 20 micrograms/1 ml  
Suspension for injection, multidose  
Hepatitis B recombinant vaccine, adsorbed

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

10 doses (10 x 1 ml)

Hepatitis B virus surface antigen recombinant (S protein)\* adsorbed

20 micrograms  
per 1 ml

\* produced on genetically-engineered yeast cells (*Saccharomyces cerevisiae*)

## 3. PHARMACEUTICAL FORM

Suspension for injection.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ENGERIX B is indicated for active immunisation against hepatitis B virus infection (HBV) caused by all known subtypes in non immune subjects of all ages. The categories within the population to be immunised are determined on the basis of official recommendations.

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

#### Dosage

20 µg dose vaccine: A 20 µg dose is intended for use in adults and children older than 15 years of age.

10 µg dose vaccine: A 10 µg dose (in 0.5-ml suspension) is intended for use in children up to and including 15 years of age, including neonates. In children aged 10 to 15 years, the adult dose of 20 µg 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

#### Primary Immunisation schedule

A series of three intramuscular injections is required to achieve optimal protection.

Two primary immunisation schedules can be recommended:

An accelerated schedule, with immunisation 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.

Schedules which have more time between the second and third doses, such as immunisation at 0, 1 and 6 months, may take longer to confer protection, but will produce higher anti-HBs antibody titres. This schedule is intended for use in school children up to and including 15 years of age.

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

In exceptional circumstances in adults, where a more rapid induction of protection is required, e.g. persons travelling to areas of high endemicity and who commence a course of vaccination against hepatitis B within one month prior to departure, a schedule of three intramuscular injections given at 0, 7 and 21 days may be used. When this schedule is applied, a fourth dose is recommended 12 months after the first dose (see section 5.1 "Pharmacodynamic properties" for seroconversion rates).

#### 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 some categories of subjects or patients particularly exposed to the HBV (e.g. haemodialysis or immunocompromised patients) a precautionary attitude should be considered to ensure a protective antibody level > 10IU/l.

#### Interchangeability of hepatitis B vaccines

See 4.5. Interaction with other medicaments and other forms of interaction.

#### Special dosage recommendations (see Dosage)

- Dosage recommendation for neonates born of mothers who are HBV carriers:

The immunisation with ENGERIX B (10 µg) of these neonates should start at birth, and two immunisation schedules have been followed. Either the 0, 1 and 2 months or the 0, 1 and 6 months schedule can be used; however, the former schedule provides a more rapid immune response. When available, hepatitis B immune globulins (HBIG) should be given simultaneously with ENGERIX B at a separate injection site as this may increase the protective efficacy.

- 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 Contra-indications**

ENGERIX B should not be administered to subjects with known hypersensitivity to any component of the vaccine, 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 special precautions for use**

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 agents such as hepatitis A, hepatitis C and hepatitis E and other pathogens known to infect the liver.

The immune response to hepatitis B vaccines is related to a number of factors, including older age, male gender, obesity, smoking habits and route of administration. In subjects who may respond less well to the administration of the hepatitis B vaccines (e.g. more than 40 years of age etc.), additional doses may be considered.

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.

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 haemodialysis patients and persons with an impaired immune system, adequate anti-HBs antibody titers may not be obtained after the primary immunisation course and such patients may therefore require administration of additional doses of vaccine. (see "Dosage recommendation for chronic haemodialysis patients.")

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.

### **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 titres provided that they are administered at separate injection sites.

ENGERIX B can be given concomitantly with BCG, DTP, DT and/or polio vaccines, if this fits conveniently in an immunisation scheme recommended by the country Health Authority.

ENGERIX B can also be administered together with measles-mumps-rubella vaccines, Haemophilus influenzae b vaccine and hepatitis A vaccine.

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 Use during 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 breastmilk is not available.

No contra-indication has been established.

#### **4.7 Effects on ability to drive and use machines**

The vaccine is unlikely to produce an effect on the ability to drive and use machines.

#### **4.8 Undesirable effects**

ENGERIX B is generally well tolerated.

The following undesirable events 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.

##### **Common**

Application site : transient soreness, erythema, induration

##### **Rare**

Body as a whole : fatigue, fever, malaise, influenza-like symptoms

Central and peripheral nervous system : dizziness, headache, paresthesia

Gastro-intestinal system : nausea, vomiting, diarrhoea, abdominal pain

Liver and biliary system : abnormal liver function tests

Musculoskeletal system : arthralgia, myalgia

Skin and appendages : rash, pruritus, urticaria

##### **Very rare**

Body as a whole : anaphylaxis, serum sickness

Cardiovascular : syncope, hypotension

Central and peripheral nervous system : paralysis, neuropathy, neuritis (including Guillain-Barré syndrome, optic neuritis and multiple sclerosis), encephalitis, encephalopathy, meningitis, convulsions

Haematological disorder : thrombocytopenia

Musculoskeletal system : arthritis  
Respiratory system : bronchospasm like symptoms  
Skin and appendages : angioedema, erythema multiforme  
Vascular extracardiac : vasculitis  
White cell and reticulo-endothelial system : lymphadenopathy

The booster dose is as well tolerated as the primary vaccination.

This medicinal product contains thiomersal (an organomercuric compound) as a preservative and therefore, it is possible that sensitisation reactions may occur (see Section 4.3).

#### **4.9 Overdose**

Not applicable.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1. Pharmacodynamic properties**

ENGERIX B, hepatitis B vaccine is a sterile suspension containing the purified major surface antigen of the virus manufactured by recombinant DNA technology, adsorbed onto aluminium hydroxide.

The antigen is produced by culture of genetically-engineered yeast cells (*Saccharomyces cerevisiae*) which carry the gene which codes for the major surface antigen of the hepatitis B virus (HBV). This hepatitis B surface antigen (HBsAg) expressed in yeast cells is purified by several physico-chemical steps.

The HBsAg assembles spontaneously, in the absence of chemical treatment, into spherical particles of 20 nm in average diameter containing non-glycosylated HBsAg polypeptides and a lipid matrix consisting mainly of phospholipids. Extensive tests have demonstrated that these particles display the characteristic properties of natural HBsAg.

The vaccine is highly purified, and meets the WHO requirements for recombinant hepatitis B vaccines. No substances of human origin are used in its manufacture.

ENGERIX B induces specific humoral antibodies against HBsAg (anti-HBs antibodies). An anti-HBs antibody titre above 10 IU/l correlates with protection to HBV infection.

#### Protective efficacy

##### **- In risk groups:**

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

A 95% protective efficacy was demonstrated in neonates of HBeAg positive mothers, immunised according to the 0, 1, 2 and 12 or 0, 1 and 6 schedules without the concomitant administration of HBIG at birth. However, simultaneous administration of HBIG and vaccine at birth increased the protective efficacy to 98%.

##### **- In healthy subjects:**

When the 0, 1 and 6 month schedule is followed,  $\geq 96$  % of vaccinees have seroprotective levels of antibody 7 months after the first dose.

When the 0, 1, 2 and 12 month schedule is followed, 15 % and 89% of vaccinees have seroprotective levels of antibody one month after first dose and one month after the third dose respectively. One month after the fourth dose 95.8 % of vaccinees achieved seroprotective levels of antibody.

For use in exceptional circumstances, the 0, 7 and 21 day primary schedule plus a fourth dose at month 12 results in 65.2 % and 76% of vaccinees having seroprotective levels of antibody within 1 and 5 weeks respectively following the third dose. One month after the fourth dose 98.6 % of vaccinees achieved seroprotective levels of antibody.

#### 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 oxide hydrated, thiomersal, polysorbate 20, sodium chloride, disodium phosphate dihydrate, sodium dihydrogen phosphate, water for injections.

### **6.2 Incompatibilities**

ENGERIX B should not be mixed with other vaccines.

### **6.3 Shelf-life**

3 years.

### **6.4 Special precautions for storage**

The vaccine should be stored at +2 °C to +8 °C. Partially used vials must be used the same day. Do not freeze; discard if vaccine has been frozen.

### **6.5 Nature and content of container**

10 ml suspension in vial (type I glass) with stopper (butyl). Pack of 1, 50.

### **6.6 Instructions for use and handling, and disposal (if appropriate)**

The content, upon storage 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.

When using a multidose vial, each dose should be taken with a sterile needle and syringe. As with other vaccines, a dose of vaccine should be withdrawn under strict aseptic conditions and precautions taken to avoid contamination of the contents.

**7.    MARKETING AUTHORISATION HOLDER**

**8.    NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL    PRODUCTS**

**9.    DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10.   DATE OF REVISION OF THE TEXT**

## 1. NAME OF THE MEDICINAL PRODUCT

ENGERIX B 10 micrograms/0.5 ml  
Suspension for injection, multidose  
Hepatitis B recombinant vaccine, adsorbed

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

5 doses (5 x 0.5 ml):

Hepatitis B virus surface antigen recombinant (S protein)\* adsorbed

10 micrograms  
per 0.5 ml

\* produced on genetically-engineered yeast cells (*Saccharomyces cerevisiae*)

## 3. PHARMACEUTICAL FORM

Suspension for injection.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ENGERIX B is indicated for active immunisation against hepatitis B virus infection (HBV) caused by all known subtypes in non immune subjects of all ages. The categories within the population to be immunised are determined on the basis of official recommendations.

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

#### Dosage

20µg dose vaccine: A 20 µg dose is intended for use in adults and children older than 15 years of age.

10 µg dose vaccine: A 10 µg dose (in 0.5-ml suspension) is intended for use in children up to and including 15 years of age, including neonates. In children aged 10 to 15 years, the adult dose of 20 µg 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

#### Primary Immunisation schedule

A series of three intramuscular injections is required to achieve optimal protection.

Two primary immunisation schedules can be recommended:

An accelerated schedule, with immunisation 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.

Schedules which have more time between the second and third doses, such as immunisation at 0, 1 and 6 months, may take longer to confer protection, but will produce higher anti-HBs antibody titres. This schedule is intended for use in school children up to and including 15 years of age.

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

In exceptional circumstances in adults, where a more rapid induction of protection is required, e.g. persons travelling to areas of high endemicity and who commence a course of vaccination against hepatitis B within one month prior to departure, a schedule of three intramuscular injections given at 0, 7 and 21 days may be used. When this schedule is applied, a fourth dose is recommended 12 months after the first dose (see section 5.1 "Pharmacodynamic properties" for seroconversion rates).

#### 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 some categories of subjects or patients particularly exposed to the HBV (e.g. haemodialysis or immunocompromised patients) a precautionary attitude should be considered to ensure a protective antibody level > 10IU/l.

#### Interchangeability of hepatitis B vaccines

See 4.5. Interaction with other medicaments and other forms of interaction.

Special dosage recommendations (see Dosage)

- Dosage recommendation for neonates born of mothers who are HBV carriers:

The immunisation with ENGERIX B (10 µg) of these neonates should start at birth, and two immunisation schedules have been followed. Either the 0, 1 and 2 months or the 0, 1 and 6 months schedule can be used; however, the former schedule provides a more rapid immune response. When available, hepatitis B immune globulins (HBIG) should be given simultaneously with ENGERIX B at a separate injection site as this may increase the protective efficacy.

- 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 Contra-indications**

ENGERIX B should not be administered to subjects with known hypersensitivity to any component of the vaccine, 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 special precautions for use**

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 agents such as hepatitis A, hepatitis C and hepatitis E and other pathogens known to infect the liver.

The immune response to hepatitis B vaccines is related to a number of factors, including older age, male gender, obesity, smoking habits and route of administration. In subjects who may respond less well to the administration of the hepatitis B vaccines (e.g. more than 40 years of age etc.), additional doses may be considered.

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.

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 haemodialysis patients and persons with an impaired immune system, adequate anti-HBs antibody titers may not be obtained after the primary immunisation course and such patients may therefore require administration of additional doses of vaccine. (see "Dosage recommendation for chronic haemodialysis patients.")

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.

### **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 titres provided that they are administered at separate injection sites.

ENGERIX B can be given concomitantly with BCG, DTP, DT and/or polio vaccines, if this fits conveniently in an immunisation scheme recommended by the country Health Authority.

ENGERIX B can also be administered together with measles-mumps-rubella vaccines, Haemophilus influenzae b vaccine and hepatitis A vaccine.

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 Use during 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 breastmilk is not available.

No contra-indication has been established.

#### **4.7 Effects on ability to drive and use machines**

The vaccine is unlikely to produce an effect on the ability to drive and use machines.

#### **4.8 Undesirable effects**

ENGERIX B is generally well tolerated.

The following undesirable events 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.

##### **Common**

Application site : transient soreness, erythema, induration

##### **Rare**

Body as a whole : fatigue, fever, malaise, influenza-like symptoms

Central and peripheral nervous system : dizziness, headache, paresthesia

Gastro-intestinal system : nausea, vomiting, diarrhoea, abdominal pain

Liver and biliary system : abnormal liver function tests

Musculoskeletal system : arthralgia, myalgia

Skin and appendages : rash, pruritus, urticaria

##### **Very rare**

Body as a whole : anaphylaxis, serum sickness

Cardiovascular : syncope, hypotension

Central and peripheral nervous system : paralysis, neuropathy, neuritis (including Guillain-Barré syndrome, optic neuritis and multiple sclerosis), encephalitis, encephalopathy, meningitis, convulsions

Haematological disorder : thrombocytopenia

Musculoskeletal system : arthritis  
Respiratory system : bronchospasm like symptoms  
Skin and appendages : angioedema, erythema multiforme  
Vascular extracardiac : vasculitis  
White cell and reticulo-endothelial system : lymphadenopathy

The booster dose is as well tolerated as the primary vaccination.

This medicinal product contains thiomersal (an organomercuric compound) as a preservative and therefore, it is possible that sensitisation reactions may occur (see Section 4.3).

#### **4.9 Overdose**

Not applicable.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1. Pharmacodynamic properties**

ENGERIX B, hepatitis B vaccine is a sterile suspension containing the purified major surface antigen of the virus manufactured by recombinant DNA technology, adsorbed onto aluminium hydroxide.

The antigen is produced by culture of genetically-engineered yeast cells (*Saccharomyces cerevisiae*) which carry the gene which codes for the major surface antigen of the hepatitis B virus (HBV). This hepatitis B surface antigen (HBsAg) expressed in yeast cells is purified by several physico-chemical steps.

The HBsAg assembles spontaneously, in the absence of chemical treatment, into spherical particles of 20 nm in average diameter containing non-glycosylated HBsAg polypeptides and a lipid matrix consisting mainly of phospholipids. Extensive tests have demonstrated that these particles display the characteristic properties of natural HBsAg.

The vaccine is highly purified, and meets the WHO requirements for recombinant hepatitis B vaccines. No substances of human origin are used in its manufacture.

ENGERIX B induces specific humoral antibodies against HBsAg (anti-HBs antibodies). An anti-HBs antibody titre above 10 IU/l correlates with protection to HBV infection.

#### Protective efficacy

##### **- In risk groups:**

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

A 95% protective efficacy was demonstrated in neonates of HBeAg positive mothers, immunised according to the 0, 1, 2 and 12 or 0, 1 and 6 schedules without the concomitant administration of HBIG at birth. However, simultaneous administration of HBIG and vaccine at birth increased the protective efficacy to 98%.

##### **- In healthy subjects:**

When the 0, 1 and 6 month schedule is followed,  $\geq 96\%$  of vaccinees have seroprotective levels of antibody 7 months after the first dose.

When the 0, 1, 2 and 12 month schedule is followed, 15 % and 89% of vaccinees have seroprotective levels of antibody one month after first dose and one month after the third dose respectively. One month after the fourth dose 95.8 % of vaccinees achieved seroprotective levels of antibody.

For use in exceptional circumstances, the 0, 7 and 21 day primary schedule plus a fourth dose at month 12 results in 65.2 % and 76% of vaccinees having seroprotective levels of antibody within 1 and 5 weeks respectively following the third dose. One month after the fourth dose 98.6 % of vaccinees achieved seroprotective levels of antibody.

#### 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 oxide hydrated, thiomersal, polysorbate 20, sodium chloride, disodium phosphate dihydrate, sodium dihydrogen phosphate, water for injections.

### **6.2 Incompatibilities**

ENGERIX B should not be mixed with other vaccines.

### **6.3 Shelf-life**

3 years.

### **6.4 Special precautions for storage**

The vaccine should be stored at +2 °C to +8 °C. Partially used vials must be used the same day. Do not freeze; discard if vaccine has been frozen.

### **6.5 Nature and content of container**

2.5 ml suspension in vial (type I glass) with stopper (butyl). Pack of 1, 50.

### **6.6 Instructions for use and handling, and disposal (if appropriate)**

The content, upon storage 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.

When using a multidose vial, each dose should be taken with a sterile needle and syringe. As with other vaccines, a dose of vaccine should be withdrawn under strict aseptic conditions and precautions taken to avoid contamination of the contents.

**7. MARKETING AUTHORISATION HOLDER**

**8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS**

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10. DATE OF REVISION OF THE TEXT**

## 1. NAME OF THE MEDICINAL PRODUCT

ENGERIX B 10 micrograms/0.5 ml  
Suspension for injection, multidose  
Hepatitis B recombinant vaccine, adsorbed

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

10 doses (10 x 0.5 ml):

Hepatitis B virus surface antigen recombinant (S protein)* adsorbed	10 micrograms per 0.5 ml
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\* produced on genetically-engineered yeast cells (*Saccharomyces cerevisiae*)

## 3. PHARMACEUTICAL FORM

Suspension for injection.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ENGERIX B is indicated for active immunisation against hepatitis B virus infection (HBV) caused by all known subtypes in non immune subjects of all ages. The categories within the population to be immunised are determined on the basis of official recommendations.

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

#### Dosage

20µg dose vaccine: A 20 µg dose is intended for use in adults and children older than 15 years of age.

10 µg dose vaccine: A 10 µg dose (in 0.5-ml suspension) is intended for use in children up to and including 15 years of age, including neonates. In children aged 10 to 15 years, the adult dose of 20 µg 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

#### Primary Immunisation schedule

A series of three intramuscular injections is required to achieve optimal protection.

Two primary immunisation schedules can be recommended:

An accelerated schedule, with immunisation 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.

Schedules which have more time between the second and third doses, such as immunisation at 0, 1 and 6 months, may take longer to confer protection, but will produce higher anti-HBs antibody titres. This schedule is intended for use in school children up to and including 15 years of age.

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

In exceptional circumstances in adults, where a more rapid induction of protection is required, e.g. persons travelling to areas of high endemicity and who commence a course of vaccination against hepatitis B within one month prior to departure, a schedule of three intramuscular injections given at 0, 7 and 21 days may be used. When this schedule is applied, a fourth dose is recommended 12 months after the first dose (see section 5.1 "Pharmacodynamic properties" for seroconversion rates).

#### 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 some categories of subjects or patients particularly exposed to the HBV (e.g. haemodialysis or immunocompromised patients) a precautionary attitude should be considered to ensure a protective antibody level > 10IU/l.

#### Interchangeability of hepatitis B vaccines

See 4.5. Interaction with other medicaments and other forms of interaction.

Special dosage recommendations (see Dosage)

- Dosage recommendation for neonates born of mothers who are HBV carriers:

The immunisation with ENGERIX B (10 µg) of these neonates should start at birth, and two immunisation schedules have been followed. Either the 0, 1 and 2 months or the 0, 1 and 6 months schedule can be used; however, the former schedule provides a more rapid immune response. When available, hepatitis B immune globulins (HBIG) should be given simultaneously with ENGERIX B at a separate injection site as this may increase the protective efficacy.

- 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 Contra-indications**

ENGERIX B should not be administered to subjects with known hypersensitivity to any component of the vaccine, 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 special precautions for use**

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 agents such as hepatitis A, hepatitis C and hepatitis E and other pathogens known to infect the liver.

The immune response to hepatitis B vaccines is related to a number of factors, including older age, male gender, obesity, smoking habits and route of administration. In subjects who may respond less well to the administration of the hepatitis B vaccines (e.g. more than 40 years of age etc.), additional doses may be considered.

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.

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 haemodialysis patients and persons with an impaired immune system, adequate anti-HBs antibody titers may not be obtained after the primary immunisation course and such patients may therefore require administration of additional doses of vaccine. (see "Dosage recommendation for chronic haemodialysis patients.")

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.

### **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 titres provided that they are administered at separate injection sites.

ENGERIX B can be given concomitantly with BCG, DTP, DT and/or polio vaccines, if this fits conveniently in an immunisation scheme recommended by the country Health Authority.

ENGERIX B can also be administered together with measles-mumps-rubella vaccines, Haemophilus influenzae b vaccine and hepatitis A vaccine.

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 Use during 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 breastmilk is not available.

No contra-indication has been established.

#### **4.7 Effects on ability to drive and use machines**

The vaccine is unlikely to produce an effect on the ability to drive and use machines.

#### **4.8 Undesirable effects**

ENGERIX B is generally well tolerated.

The following undesirable events 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.

##### **Common**

Application site : transient soreness, erythema, induration

##### **Rare**

Body as a whole : fatigue, fever, malaise, influenza-like symptoms

Central and peripheral nervous system : dizziness, headache, paresthesia

Gastro-intestinal system : nausea, vomiting, diarrhoea, abdominal pain

Liver and biliary system : abnormal liver function tests

Musculoskeletal system : arthralgia, myalgia

Skin and appendages : rash, pruritus, urticaria

##### **Very rare**

Body as a whole : anaphylaxis, serum sickness

Cardiovascular : syncope, hypotension

Central and peripheral nervous system : paralysis, neuropathy, neuritis (including Guillain-Barré syndrome, optic neuritis and multiple sclerosis), encephalitis, encephalopathy, meningitis, convulsions

Haematological disorder : thrombocytopenia

Musculoskeletal system : arthritis  
Respiratory system : bronchospasm like symptoms  
Skin and appendages : angioedema, erythema multiforme  
Vascular extracardiac : vasculitis  
White cell and reticulo-endothelial system : lymphadenopathy

The booster dose is as well tolerated as the primary vaccination.

This medicinal product contains thiomersal (an organomercuric compound) as a preservative and therefore, it is possible that sensitisation reactions may occur (see Section 4.3).

#### **4.9 Overdose**

Not applicable.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1. Pharmacodynamic properties**

ENGERIX B, hepatitis B vaccine is a sterile suspension containing the purified major surface antigen of the virus manufactured by recombinant DNA technology, adsorbed onto aluminium hydroxide.

The antigen is produced by culture of genetically-engineered yeast cells (*Saccharomyces cerevisiae*) which carry the gene which codes for the major surface antigen of the hepatitis B virus (HBV). This hepatitis B surface antigen (HBsAg) expressed in yeast cells is purified by several physico-chemical steps.

The HBsAg assembles spontaneously, in the absence of chemical treatment, into spherical particles of 20 nm in average diameter containing non-glycosylated HBsAg polypeptides and a lipid matrix consisting mainly of phospholipids. Extensive tests have demonstrated that these particles display the characteristic properties of natural HBsAg.

The vaccine is highly purified, and meets the WHO requirements for recombinant hepatitis B vaccines. No substances of human origin are used in its manufacture.

ENGERIX B induces specific humoral antibodies against HBsAg (anti-HBs antibodies). An anti-HBs antibody titre above 10 IU/l correlates with protection to HBV infection.

#### Protective efficacy

##### **- In risk groups:**

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

A 95% protective efficacy was demonstrated in neonates of HBeAg positive mothers, immunised according to the 0, 1, 2 and 12 or 0, 1 and 6 schedules without the concomitant administration of HBIG at birth. However, simultaneous administration of HBIG and vaccine at birth increased the protective efficacy to 98%.

##### **- In healthy subjects:**

When the 0, 1 and 6 month schedule is followed,  $\geq 96\%$  of vaccinees have seroprotective levels of antibody 7 months after the first dose.

When the 0, 1, 2 and 12 month schedule is followed, 15 % and 89% of vaccinees have seroprotective levels of antibody one month after first dose and one month after the third dose respectively. One month after the fourth dose 95.8 % of vaccinees achieved seroprotective levels of antibody.

For use in exceptional circumstances, the 0, 7 and 21 day primary schedule plus a fourth dose at month 12 results in 65.2 % and 76% of vaccinees having seroprotective levels of antibody within 1 and 5 weeks respectively following the third dose. One month after the fourth dose 98.6 % of vaccinees achieved seroprotective levels of antibody.

#### 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 oxide hydrated, thiomersal, polysorbate 20, sodium chloride, disodium phosphate dihydrate, sodium dihydrogen phosphate, water for injections.

### **6.2 Incompatibilities**

ENGERIX B should not be mixed with other vaccines.

### **6.3 Shelf-life**

3 years.

### **6.4 Special precautions for storage**

The vaccine should be stored at +2 °C to +8 °C. Partially used vials must be used the same day. Do not freeze; discard if vaccine has been frozen.

### **6.5 Nature and content of container**

5 ml suspension in vial (type I glass) with stopper (butyl). Pack of 1, 50.

### **6.6 Instructions for use and handling, and disposal (if appropriate)**

The content, upon storage 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.

When using a multidose vial, each dose should be taken with a sterile needle and syringe. As with other vaccines, a dose of vaccine should be withdrawn under strict aseptic conditions and precautions taken to avoid contamination of the contents.

**7. MARKETING AUTHORISATION HOLDER**

**8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS**

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10. DATE OF REVISION OF THE TEXT**