ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fendrix suspension for injection.
Hepatitis B (rDNA) vaccine (adjuvanted, adsorbed).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) of Fendrix contains:

Hepatitis B surface antigen [1, 2, 3]	20 micrograms

[1]adjuvanted by AS04C containing:

- 3-*O*-desacyl-4'- monophosphoryl lipid A (MPL) [2]	50 micrograms

[2]adsorbed on aluminium phosphate (0.5 milligrams Al^{3+} in total)

[3]produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology.

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Suspension for injection.

Turbid white suspension. Upon storage, a fine white deposit with a clear colourless supernatant can be observed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fendrix is indicated for active immunisation against hepatitis B virus infection (HBV) caused by all known subtypes for patients with renal insufficiency (including pre-haemodialysis and haemodialysis patients), from the age of 15 years onwards.

4.2 Posology and method of administration

Posology

Primary Immunisation schedule:

A four dose schedule, with immunisations at the elected date, 1 month, 2 months and 6 months from the date of the first dose is recommended.

Once initiated, the primary course of vaccination at 0, 1, 2 and 6 months should be completed with Fendrix, and not with other commercially available HBV vaccine.

Booster dose:

As pre-haemodialysis and haemodialysis patients are particularly exposed to HBV and have a higher risk to become chronically infected, a precautionary attitude should be considered i.e. giving a booster dose in order to ensure a protective antibody level as defined by national recommendations and guidelines.

Fendrix can be used as a booster dose after a primary vaccination course with either Fendrix or any other commercial recombinant hepatitis B vaccine.

Special dosage recommendation for known or presumed exposure to HBV:

Data on concomitant administration of Fendrix with specific hepatitis B immunoglobulin (HBIg) have not been generated. However, in circumstances where exposure to HBV has recently occurred (e.g. stick with contaminated needle) and where simultaneous administration of Fendrix and a standard dose of HBIg is necessary, these should be given at separate injection sites.

Method of administration

Fendrix should be injected intramuscularly in the deltoid region.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Hypersensitivity after previous administration of other hepatitis B vaccines.

Subjects suffering from acute severe febrile illness. The presence of a minor infection such as a cold, is not a contraindication for immunisation.

4.4 Special warnings and special precautions for use

Because of the long incubation period of hepatitis B, it is possible that patients could have been infected before 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 or other pathogens known to infect the liver.

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

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

Since intramuscular administration into the gluteal muscle could lead to a suboptimal response to the vaccine, this route should be avoided.

Fendrix should under no circumstances be administered intradermally or 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 Hepatitis B vaccination should thus be considered on a casebycase basis by the physician.

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

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

No data on the concomitant administration of Fendrix and other vaccines or with specific hepatitis B immunoglobulin have been generated. If concomitant administration of specific hepatitis B immunoglobulin and Fendrix is required, these should be given at different injection sites. As no data are available for the concomitant administration of this particular vaccine with other vaccines, an interval of 2 to 3 weeks should be respected.

4.6 Pregnancy and lactation

No clinical data on use during pregnancies are available with Fendrix.
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

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

Adequate human data on use during lactation are not available. In a reproductive toxicity study in animals which included post-natal follow-up until weaning (see 5.3), no effect on the development of the pups was observed. Vaccination should only be performed if the risk-benefit ratio at individual level outweighs possible risks for the infant.

4.7 Effects on the ability to drive and use machines

Fendrix has a minor or moderate influence on the ability to drive and use machine.

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

4.8 Undesirable effects

- Clinical trials involving the administration of 2476 doses of Fendrix to 82 pre-haemodialysis and haemodialysis patients and to 713 healthy subjects ≥ 15 years of age allowed to document the reactogenicity of the vaccine.

Pre-haemodialysis and haemodialysis patients

The reactogenicity profile of Fendrix in a total of 82 pre-haemodialysis and haemodialysis patients was generally comparable to that seen in healthy subjects.

Adverse reactions reported in a clinical trial following primary vaccination with Fendrix and considered as being related or possibly related to vaccination have been categorised by frequency.

Frequencies are reported as:
Very common: >1/10
Common: >1/100, <1/10
Uncommon: >1/1000, <1/100
Rare: >1/10 000, <1/1000
Very rare: <1/10 000, including isolated reports

Nervous system disorders:
Very common: headache

Gastrointestinal disorders:
Common: gastrointestinal disorder

General disorders and administration site conditions
Very common: pain, fatigue
Common: fever, redness, injection site swelling

Unsolicited symptoms considered to be at least possibly related to vaccination were uncommonly reported and consisted of rigors, other injection site reaction and maculo-papular rash.

Healthy subjects

The reactogenicity profile of Fendrix in healthy subjects was generally comparable to that seen in pre-haemodialysis and haemodialysis patients.

In a large double-blind randomised comparative study, healthy subjects were enrolled to receive a three dose primary course of Fendrix (N= 713) or a commercially available hepatitis B vaccine (N= 238) at 0, 1, 2 months. Fendrix was generally well tolerated. The most common adverse events reported were local reactions at the injection site.
Vaccination with Fendrix induced more transient local symptoms as compared to the comparator vaccine, with pain at the injection site being the most frequently reported solicited local symptom. However, solicited general symptoms were observed with similar frequencies in both groups.

Adverse reactions reported in a clinical trial following primary vaccination with Fendrix and considered as being at least possibly related to vaccination have been categorised by frequency.

Infections and infestations:
Rare: viral infection

Metabolism and nutrition disorders:
Rare: thirst

Psychiatric disorders:
Rare: nervousness

Nervous system disorders:
Common: headache
Rare: vertigo

Gastrointestinal disorders:
Common: gastrointestinal disorder

Muskuloskeletal and connective tissue disorders:
Rare: back pain, tendinitis

General disorders and administration site conditions
Very common: fatigue, pain, redness, injection site swelling
Common: fever
Uncommon: other injection site reaction
Rare: allergy, asthenia, hot flushes, rigors

No increase in the incidence or severity of these undesirable events was seen with subsequent doses of the primary vaccination schedule.

No increase in the reactogenicity was observed after the booster vaccination with respect to the primary vaccination.

Allergic reactions, including anaphylactoid reactions, may occur very rarely.

- Experience with hepatitis B vaccine:

Following widespread use of hepatitis B vaccines, in very rare cases, syncope, paralysis, neuropathy, neuritis (including Guillain-Barré syndrome, optic neuritis and multiple sclerosis), encephalitis, encephalopathy, meningitis and convulsions have been reported. The causal relationship to the vaccine has not been established.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Hepatitis vaccines, ATC code J07BC01.

Fendrix induces specific humoral antibodies against HBsAg (anti-HBs antibodies). An anti-HBs antibody titre ≥ 10 mIU/ml correlates with protection to HBV infection.

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

Immunological data

In pre-haemodialysis and haemodialysis patients:
In a comparative clinical study in 165 pre-haemodialysis and haemodialysis patients (15 years and above), protective levels of specific humoral antibodies (anti-HBs titres ≥ 10 mIU/ml) were observed in 74.4% of Fendrix recipients (N = 82) one month after the third dose (i.e at month 3), as compared to 52.4% of patients in the control group who received a double dose of a commercially available hepatitis B vaccine (N = 83) for this population.

At month 3, Geometric Mean Titres (GMT) were 223.0 mIU/ml and 50.1 mIU/ml in the Fendrix and control groups respectively, with 41.0% and 15.9% of subjects with anti-HBs antibody titres ≥100 mIU/ml respectively.

After completion of a four dose primary course (i.e at month 7), 90.9% of Fendrix recipients were seroprotected (≥ 10 mIU/ml) against hepatitis B, in comparison with 84.4% in a control group who received the commercially available hepatitis B vaccine.

At month 7, GMTs were 3559.2 mIU/ml and 933.0 mIU/ml in the Fendrix and control groups who received the commercially available hepatitis B vaccine respectively, with 83.1% and 67.5% of subjects with anti-HBs antibody titres ≥100 mIU/ml respectively.

Antibody persistence

In pre-haemodialysis and haemodialysis patients:
Anti-HBs antibodies have been shown to persist for at least 36 months following a 0, 1, 2, 6 month primary course of Fendrix in pre-haemodialysis and haemodialysis patients. At month 36, 80.4% of these patients retained protective antibody levels (anti-HBs titres ≥ 10mIU/ml), as compared to 51.3% of patients who received a commercially available hepatitis B vaccine.

At month 36, GMTs were 154.1 mIU/ml and 111.9 mIU/ml in the Fendrix and control groups respectively, with 58.7% and 38.5% of subjects with anti-HBs antibody titres ≥100 mIU/ml respectively.

5.2 Pharmacokinetic properties

Pharmacokinetic properties of Fendrix or MPL alone has not been studied in humans.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional animal studies consisting of acute and repeated dose toxicity, cardiovascular and respiratory safety pharmacology and reproductive toxicity including pregnancy and peri and postnatal development of the pups till weaning.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections

For adjuvants, see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

0.5 ml of suspension in pre-filled syringe (type I glass) with a plunger stopper (rubber butyl) with or without separate needle in a pack size of 1, or without needles in a pack size of 10.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Upon storage, a fine white deposit with a clear colourless supernatant can be observed.

Before administration, the vaccine should be well shaken to obtain a slightly opaque, white suspension.

The vaccine should be visually inspected both before and after re-suspension for any foreign particulate matter and/or change in physical appearance. The vaccine must not be used if any change in the appearance of the vaccine has taken place.

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE ANDMANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

GlaxoSmithKline Biologicals S.A.
89, rue de l'Institut – 1330 Rixensart
Belgium

Name and address of the manufacturer responsible for batch release

GlaxoSmithKline Biologicals S.A.
89, rue de l'Institut – 1330 Rixensart
Belgium

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

Official batch release: in accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING
PACK SIZE OF 1 SYRINGE WITH A SEPARATE NEEDLE

1. NAME OF THE MEDICINAL PRODUCT

Fendrix suspension for injection
Hepatitis B (rDNA) vaccine (adjuvanted, adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml):

Hepatitis B surface antigen[1, 2, 3] 20 µg

[1]adjuvanted by AS04C containing:
- 3-*O*-desacyl-4'- monophosphoryl lipid A (MPL)[2] 50 µg

[2]adsorbed on aluminium phosphate (0.5 mg Al^{3+} in total)

[3]produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology.

3. LIST OF EXCIPIENTS

Sodium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
Pre-filled syringe
Separate needle
1 dose (0.5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Shake before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/0299/001

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING
PACK SIZE OF 1 SYRINGE WITHOUT NEEDLE

1. NAME OF THE MEDICINAL PRODUCT

Fendrix suspension for injection
Hepatitis B (rDNA) vaccine (adjuvanted, adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml):

Hepatitis B surface antigen[1, 2, 3] 20 µg

[1]adjuvanted by AS04C containing:
- 3-*O*-desacyl-4'- monophosphoryl lipid A (MPL) [2] 50 µg

[2]adsorbed on aluminium phosphate (0.5 mg Al^{3+} in total)

[3]produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology.

3. LIST OF EXCIPIENTS

Sodium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
Pre-filled syringe
1 dose (0.5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Shake before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/0299/002

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING
PACK SIZE OF 10 SYRINGES WITHOUT NEEDLES

1. NAME OF THE MEDICINAL PRODUCT

Fendrix suspension for injection
Hepatitis B (rDNA) vaccine (adjuvanted, adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml):

Hepatitis B surface antigen[1, 2, 3] 20 µg

[1]adjuvanted by AS04C containing:
- 3-*O*-desacyl-4'- monophosphoryl lipid A (MPL)[2] 50 µg

[2]adsorbed on aluminium phosphate (0.5 mg Al^{3+} in total)

[3]produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology.

3. LIST OF EXCIPIENTS

Sodium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
Pre-filled syringe
10 x 1 dose
1 dose (0.5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Shake before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/0299/003

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PACK SIZE OF 1 SYRINGE WITH A SEPARATE NEEDLE
PACK SIZE OF 1 SYRINGE WITHOUT NEEDLE
PACK SIZE OF 10 SYRINGES WITHOUT NEEDLES

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

Fendrix suspension for injection
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 ml)

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Read all of this leaflet carefully before you start receiving this vaccine.
- Keep this leaflet until you have finished the complete vaccination course. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This vaccine has been prescribed for you and must not be passed on to others

In this leaflet:

1. What Fendrix is and what it is used for
2. Before you receive Fendrix
3. How Fendrix is given
4. Possible side effects
5. Storing Fendrix
6. Further information

Fendrix – 0.5 ml – Suspension for injection
Hepatitis B (rDNA) vaccine (adjuvanted, adsorbed).

The active substance contained in 1 dose (0.5 ml) of Fendrix is:

Hepatitis B surface antigen [1, 2, 3]	20 micrograms

[1]adjuvanted by AS04C containing:

- 3-*O*-desacyl-4'- monophosphoryl lipid A (MPL) [2]	50 micrograms

[2]adsorbed on aluminium phosphate (0.5 milligrams Al^{3+} in total)

[3]produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology.

The other ingredients in the vaccine are: sodium chloride, water for injections.

Marketing authorisation holder and Manufacturer: GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart
Belgium

1. WHAT FENDRIX IS AND WHAT IT IS USED FOR

Fendrix is presented as a suspension for injection in a pre-filled syringe (0.5 ml) with a plunger stopper (rubber butyl) with or without separate needle in a pack size of 1, or without needles in a pack size of 10. The suspension is white and milky.

Fendrix is a vaccine which prevents hepatitis B disease in patients with renal insufficiency (including pre-haemodialysis and haemodialysis patients) from the age of 15 years onwards. The vaccine works by causing the body to produce its own protection (antibodies) against the disease. MPL is included in this vaccine as an adjuvant and aluminium phosphate as an adsorbent. These substances are included in Fendrix to accelerate, improve and prolong the protective effect of the vaccine.

Hepatitis B disease is caused by the hepatitis B virus. It causes the liver to become swollen (inflamed). The virus is found in body fluids such as blood, semen, vaginal secretions, or saliva (spit) of infected people. Symptoms may not be seen for 6 weeks to 6 months after infection. Sometimes people who have been infected do not look or feel ill. Others have mild flu-like symptoms, but some

people can become very ill. They may be extremely tired, and have dark urine, pale faces, yellowish skin and/or eyes (jaundice), and other symptoms possibly requiring hospitalisation.

Most adults fully recover from the disease. But some people, who may not even have had symptoms can remain infected. They are called hepatitis B virus carriers. Hepatitis B virus carriers can infect others throughout their lives. Hepatitis B virus carriers are at risk of serious liver disease, such as cirrhosis (liver scarring) and liver cancer.

As with all vaccines, Fendrix cannot completely prevent infections with hepatitis B virus, even after you have received the complete primary course of four doses.

Also, if you have already been infected with hepatitis B virus prior to receiving Fendrix, but you are not yet feeling unwell, Fendrix may not be able to prevent you from becoming ill.

Fendrix can only help to protect you against infection with hepatitis B virus. It cannot protect you against other infections that can affect the liver and that can cause symptoms similar to those of hepatitis B virus infection.

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

Vaccination is the best way to protect against this disease. None of the components in the vaccine are infectious.

2. BEFORE YOU RECEIVE FENDRIX

In the following cases, Fendrix should not be given to you. You must tell your doctor:

- if you have previously had any allergic reaction to Fendrix, or any ingredient contained in this vaccine. The active substances and other ingredients in Fendrix are listed at the beginning of the leaflet. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue;
- if you have previously had an allergic reaction to any vaccine against hepatitis B disease;
- if you have a severe infection with a high temperature. In these cases, the vaccination will be postponed until you have recovered. A minor infection such as a cold should not be a problem, but talk to your doctor first.

Take special care with Fendrix
Thiomersal is present (in trace amounts) in this product, and it is possible that you may experience an allergic reaction.
Tell your doctor if you have any known allergies.
Tell your doctor if you have experienced any health problems after previous administration of a vaccine.

Taking other medicines
Tell your doctor if you have recently had or expect to shortly have any other vaccinations. An interval of at least 2 to 3 weeks between Fendrix and any other vaccine is recommended.
If Fendrix is to be given at the same time as specific hepatitis B immunoglobulins, these should be given at different injection sites.
Your doctor will be able to advise you."

Pregnancy
Tell your doctor if you are or think you may be pregnant.

Breast-feeding
Tell your doctor if you are breast-feeding.

Driving and using machines
Take special care while driving and using machines as Fendrix may give you headache or make you feel tired.

3. HOW FENDRIX IS GIVEN

If you are a patient with renal insufficiency, you will receive a total of four injections. These will be given within a time period of 6 months.
Each injection is given on a separate visit.
The first dose will be given on an agreed date with your doctor and the remaining three doses will be given one month, two months, and six months after the first dose.

- First dose: at an elected date
- Second dose: 1 month later
- Third dose: 2 months after the first dose
- Fourth dose: 6 months after the first dose

Once you have received the first injection of Fendrix, the subsequent injections need to be of the same vaccine. The doctor or nurse will inform you when you should come back for the subsequent injections.

Your doctor will advise you on the possible need for extra doses, and future booster doses. Fendrix can be used as a booster dose after a primary vaccination course with either a commercial recombinant hepatitis B vaccine or Fendrix.

If you miss a scheduled injection, talk to your doctor and arrange another visit.

Make sure you finish the complete vaccination course of four injections. If not, you may not be fully protected against the disease.

The doctor or nurse will give Fendrix as an injection into the muscle, usually in your upper arm. They will take care that Fendrix is not given into a blood vessel and into the skin.

4. POSSIBLE SIDE EFFECTS

Like all vaccines, Fendrix can have side effects.

Side effects that occurred during a clinical trial with Fendrix in pre-haemodialysis and haemodialysis patients were as follows:

- **Very common** (more than 1 per 10 doses of vaccine):
  - Pain or discomfort at the injection site
  - Fatigue
  - Headache

- **Common** (less than 1 per 10 but more than 1 per 100 doses of vaccine):
  - Redness, swelling at the injection site
  - Fever
  - Stomach and digestive complaints

- **Uncommon** (less than 1 per 100 but more than 1 per 1,000 doses of vaccine):
  - Chills
  - Other injection site reaction

- Red raised skin rash

Healthy subjects were also included in clinical studies.Side effects observed with Fendrix were generally comparable to those seen in pre-haemodialysis and haemodialysis patients. In addition, the following effects were rarely observed:

♦ **Rare** (less than 1 per 1,000 but more than 1 per 10,000 doses of vaccine):
- Allergy, unusual tiredness, hot flushes,
- Dizziness
- Thirst
- Back pain, swelling of the tendons
- Nervousness
- Viral infection

If these events continue or become severe, tell your doctor.

Allergic reactions, including anaphylactoid reactions, may occur very rarely (less than 1 per 10,000 doses of vaccine). These may be local or widespread rashes that may be itchy or blistering, swelling of the eyes and face, difficulty in breathing or swallowing, a sudden drop in blood pressure and loss of consciousness. Such reactions may occur before leaving the doctor's surgery. However, you should seek immediate treatment in any event.

Additional side effects that have been reported very rarely (less than 1 per 10,000 doses of vaccine) in the days or weeks after vaccination with hepatitis B vaccines, include fits, faints, disease of the nerves of the eye, multiple sclerosis, loss of sensation in, or of the ability to move some parts of the body, severe headache with stiff neck, disruption of the normal brain functions.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING FENDRIX

Store in a refrigerator (2°C - 8°C).
Store in the original package in order to protect from light.
Do not freeze. Freezing destroys the vaccine.
Keep out of the reach and sight of children.

Do not use after the expiry date stated on the pack. The date for last use corresponds to the last day of the month mentioned.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation holder.

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The following information is intended for medical or healthcare professionals only:

Upon storage, a fine white deposit with a clear colourless supernatant can be observed.

Before administration, the vaccine should be well shaken to obtain a slightly opaque, white suspension.

The vaccine should be visually inspected both before and after re-suspension for any foreign particulate matter and/or change in physical appearance. The vaccine must not be used if any change in the appearance of the vaccine has taken place.

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

Fendrix should not be given to subjects with hypersensitivity to the active substance or to any of the excipients.

Fendrix should not be given to subjects with hypersensitivity after previous administration of other hepatitis B vaccines.

Fendrix should not be given to subjects suffering from acute severe febrile illness. The presence of a minor infection such as a cold, is not a contraindication for immunisation.

Fendrix should be injected intramuscularly in the deltoid region.

Since intramuscular administration into the gluteal muscle could lead to a suboptimal response to the vaccine, this route should be avoided.

Fendrix should under no circumstances be administered intradermally or intravenously.

As pre-haemodialysis and haemodialysis patients are particularly exposed to HBV and have a higher risk to become chronically infected, a precautionary attitude should be considered i.e. giving a booster

dose in order to ensure a protective antibody level as defined by national recommendations and guidelines.

Appropriate medical treatment should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine.