ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ambirix, suspension for injection in pre-filled syringe
Hepatitis A (inactivated) and hepatitis B (rDNA) (HAB) vaccine (adsorbed).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (1 ml) contains:

Hepatitis A virus (inactivated)[1,2]	720 ELISA Units
Hepatitis B surface antigen[3,4]	20 micrograms

[1]Produced on human diploid (MRC-5) cells
[2]Adsorbed on aluminium hydroxide, hydrated 0.05 milligrams Al^{3+}
[3]Produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology
[4]Adsorbed on aluminium phosphate 0.4 milligrams Al^{3+}

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.
Ambirix is a turbid white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ambirix is indicated in non-immune children and adolescents from 1 year up to and including 15 years of age for protection against hepatitis A and hepatitis B infection.

Protection against hepatitis B infections may not be obtained until after the second dose (see section 5.1).
Therefore:
- Ambirix should be used only when there is a relatively low risk of hepatitis B infection during the vaccination course.
- It is recommended that Ambirix should be administered in settings where completion of the two-dose vaccination course can be assured.

4.2 Posology and method of administration

Posology

- Dosage

A dose of 1.0 ml is recommended for subjects from 1 year up to and including 15 years of age.

- Primary vaccination schedule

The standard primary course of vaccination consists of two doses, the first administered at the elected date and the second between 6 and 12 months after the first dose.

The recommended schedule should be adhered to. Once initiated, the primary course of vaccination should be completed with the same vaccine.

- Booster dose

In situations where a booster dose of hepatitis A and/or hepatitis B is desired, a monovalent or combined vaccine can be given. The safety and immunogenicity of Ambirix administered as a booster dose following a two dose primary course have not been evaluated.

Long-term antibody persistence data following vaccination with Ambirix are available up to 15 years after vaccination (see section 5.1).

The anti-hepatitis B surface antigen (anti-HBs) and anti-hepatitis A virus (anti-HAV) antibody titres observed following a primary vaccination course with Ambirix are in the range of what is seen following vaccination with the monovalent hepatitis A and B vaccines. General guidelines for booster vaccination can therefore be drawn from experience with the monovalent vaccines, as follows.

Hepatitis B

The need for a booster dose of hepatitis B vaccine 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 dose of hepatitis B vaccine and these should be respected.

For some categories of subjects at risk of exposure to HBV (e.g. haemodialysis or immunocompromised patients) a precautionary attitude should be considered to ensure that a protective antibody level ≥ 10 mIU/ml is maintained.

Hepatitis A

It is not yet fully established whether immunocompetent individuals who have responded to hepatitis A vaccination will require booster doses as protection in the absence of detectable antibodies may be ensured by immunological memory. Guidelines for boosting are based on the assumption that antibodies are required for protection.

Paediatric population

The safety and efficacy of Ambirix in children aged less than 1 year have not been established.
No data are available.

Method of administration

Ambirix is for intramuscular injection, usually into the deltoid muscle. However the anterolateral thigh may be used in very young subjects if preferred.

Exceptionally, the vaccine may be administered subcutaneously in patients with thrombocytopenia or bleeding disorders. However, this route of administration may result in suboptimal immune response to the vaccine (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1, or neomycin.

Hypersensitivity after previous administration of hepatitis A and/or hepatitis B vaccines.

As with other vaccines, the administration of Ambirix should be postponed in subjects suffering from acute severe febrile illness.

4.4 Special warnings and precautions for use

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

Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

It is possible that subjects may be in the incubation period of a hepatitis A or hepatitis B infection at the time of vaccination. It is not known whether Ambirix will prevent hepatitis A and hepatitis B in such cases.

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

Ambirix is not recommended for postexposure prophylaxis (e.g. needle stick injury).

If rapid protection against hepatitis B is required, the standard three-dose regimen of the combined vaccine containing 360 ELISA Units of formalin inactivated hepatitis A virus and 10 micrograms of recombinant hepatitis B surface antigen is recommended. This is because, a higher proportion of subjects are protected in the interval between the second and third dose of the three-dose combined vaccine, than after a single dose of Ambirix. This difference is no longer present after the second dose of Ambirix (see section 5.1 for seroprotection rates).

It is recommended that the two-dose regimen of Ambirix be completed prior to start of sexual activity.

The vaccine has not been tested in patients with an impaired immune system. In haemodialysis patients and persons with an impaired immune system, adequate anti-HAV and anti-HBs antibody titers may not be obtained after the primary immunisation course.

Since intradermal injection or intramuscular administration into the gluteal muscle could lead to a suboptimal response to the vaccine, these routes should be avoided. However, exceptionally Ambirix can be administered subcutaneously to subjects with thrombocytopenia or bleeding disorders since bleeding may occur following an intramuscular administration to these subjects.

Ambirix should under no circumstances be administered intravascularly.

This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

No data on concomitant administration of Ambirix with specific hepatitis A immunoglobulin or hepatitis B immunoglobulin have been generated. However, when the monovalent hepatitis A and hepatitis B vaccines were administered concomitantly with specific immunoglobulins there was no effect on seroconversion rates. Concomitant immunoglobulin administration may result in lower antibody titres.

When Ambirix was administered concomitantly with, but as a separate injection to a combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis and *Haemophilus influenzae* type b

vaccine (DTPa-IPV+Hib) or with a combined Measles-Mumps-Rubella vaccine in the second year of life, immune responses to all antigens were satisfactory (see section 5.1).

Concomitant administration of Ambirix and other vaccines than those listed above has not been studied. It is advised that Ambirix should not be administered at the same time as other vaccines unless absolutely necessary.
Concomitant vaccines should always be administered at separate injection sites and preferably into different limbs.

It may be expected that in patients receiving immunosuppressive treatment or patients with immunodeficiency, an adequate response may not be achieved.

4.6 Fertility, pregnancy and lactation

Pregnancy

Ambirix can be used during pregnancy only when clearly needed, and the possible advantages outweigh the potential risks for the foetus.

Breast-feeding

Ambirix should only be used during breast-feeding when the possible advantages outweigh the potential risks.

Fertility

No fertility data are available.

4.7 Effects on ability to drive and use machines

Ambirix has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

Clinical trials involved the administration of 2029 doses of Ambirix to 1027 subjects from 1 year up to and including 15 years of age.
In 2 comparative trials in subjects aged 1-15 years, the incidences of local and general solicited symptoms after a two-dose regimen of Ambirix was overall similar to that seen with the three-dose combined vaccine containing 360 ELISA Units of HAV and 10 µg of HBsAg.

The most commonly reported adverse reactions following Ambirix administration are pain and fatigue occurring in an approximated per dose frequency of 50% and 30% respectively.

List of adverse reactions

Local and general adverse reactions reported following primary vaccination with Ambirix were categorised by frequency.

Adverse reactions reported are listed according to the following frequency:

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

The following adverse reactions were reported during clinical trials with Ambirix.

- Clinical trial data

Metabolism and nutrition disorders
Very common: appetite lost

Psychiatric disorders
Very common: irritability

Nervous system disorders
Very common: headache
Common: drowsiness

Gastrointestinal disorders
Common: gastrointestinal symptoms

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

In addition, the following adverse reactions were reported during clinical trials with GlaxoSmithKline's other combined hepatitis A and hepatitis B vaccines (given as a 3 or 4 dose schedule).

Infections and infestations
Uncommon: upper respiratory tract infection

Blood and lymphatic system disorders
Rare: lymphadenopathy

Nervous system disorders
Uncommon: dizziness
Rare: paraesthesia

Vascular disorders
Rare: hypotension

Gastrointestinal disorders
Common: diarrhoea, nausea
Uncommon: vomiting, abdominal pain*

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

Musculoskeletal and connective tissue disorders
Uncommon: myalgia
Rare: arthralgia

General disorders and administration site conditions
Common: malaise, injection site reaction
Rare: chills, influenza like illness

* refers to adverse reactions observed in clinical trials performed with the paediatric formulation

- Post-marketing data

Because these events were reported spontaneously, it is not possible to reliably estimate their frequency.

The following adverse reactions were reported during post-marketing surveillance following vaccination with Ambirix.

Immune system disorders
Allergic reactions including anaphylactic and anaphylactoid reactions

Nervous system disorders
Syncope or vasovagal responses to injection, localised hypoaesthesia

Following widespread use of either GlaxoSmithKline's combined hepatitis A and hepatitis B vaccines or the monovalent hepatitis A and/or hepatitis B vaccines, the following adverse reactions have additionally been reported.

Infections and infestations
Meningitis

Blood and lymphatic system disorders
Thrombocytopenic purpura, thrombocytopenia

Immune system disorders
Allergic reactions including mimicking serum sickness, angioneurotic oedema

Nervous system disorders
Multiple sclerosis, encephalitis, encephalopathy, polyneuritis such as Guillain-Barré syndrome (with ascending paralysis), myelitis, convulsions, paralysis, facial palsy, neuritis, optic neuritis, neuropathy

Vascular disorders
Vasculitis

Hepatobiliary disorders
Abnormal liver function tests

Skin and subcutaneous tissue disorders
Erythema multiforme, lichen planus

Musculoskeletal and connective tissue disorders
Arthritis, muscular weakness

General disorders and administration site conditions
Immediate injection site pain, stinging and burning sensation

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Cases of overdose with GlaxoSmithKline's combined hepatitis A and hepatitis B vaccine have been reported during post-marketing surveillance. Adverse reactions reported following overdosage were similar to those reported with normal vaccine administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco therapeutic group: Vaccines, Hepatitis vaccines, ATC code J07BC20.

Mechanism of action
Ambirix confers immunity against HAV and HBV infection by inducing specific anti-HAV and anti-HBs antibodies.

Clinical studies

Immune responses post-primary vaccination

In clinical studies involving subjects from 1 year up to and including 15 years old, seropositivity rates for anti-HAV antibodies were 99.1% one month after the first dose and 100% after the second dose given at month 6 (i.e month 7). Seropositivity rates for anti-HBs antibodies were 74.2% one month after the first dose and 100% after the second dose given at month 6 (i.e. month 7). The anti-HBs seroprotection rates (titers ≥ 10 mlU/ml) at these time points were 37.4% and 98.2% respectively.

In a comparative clinical trial conducted among subjects aged from 12 years up to and including 15 years of age, 142 received two doses of Ambirix and 147 received the standard three-dose (0, 1, 6 months) of the combined HAB vaccine. The latter contained 360 ELISA Units of formalin inactivated hepatitis A virus and 10 micrograms of recombinant hepatitis B surface antigen. For the 289 subjects evaluable for immunogenicity, seroprotection rates (SP in the table below) against hepatitis B were significantly higher at months 2 and 6 with the three-dose vaccine than with Ambirix. The immune response elicited by Ambirix at month 7 (i.e. after completion of the vaccination course) was non-inferior to that to the three-dose vaccine.

Vaccine group	**Anti-HBs Month 2 SP (%)**	**Anti-HBs Month 6 SP (%)**	**Anti-HBs Month 7 SP (%)**
Ambirix	38	68.3	97.9
Combined HAB vaccine (360/10)*	85.6	98.0	100

* containing 360 ELISA Units of formalin inactivated hepatitis A virus and 10 micrograms of recombinant hepatitis B surface antigen

Immune responses obtained one month after the full vaccination course (i.e at month 7) in a comparative clinical trial in children aged 1-11 years are presented in the following table. Also shown are the results reported in the comparative study performed in 12-15 year-olds. In both studies, subjects received either a two-dose schedule of Ambirix or a three-dose regimen of the combined HAB vaccine (360/10) containing 360 ELISA Units of formalin inactivated hepatitis A virus and 10 micrograms of recombinant hepatitis B surface antigen.

Age group	**Vaccine group**	**Anti-HAV**		**Anti-HBs**	
		N	**S+ (%)**	**N**	**SP (%)**
1-5 yrs old	Ambirix	98	100	98	98
	Combined HAB vaccine (360/10)*	92	100	92	100
6-11 yrs old	Ambirix	103	100	103	99
	Combined HAB vaccine (360/10)*	96	100	96	100
12-15 yrs old	Ambirix	142	100	142	97.9

	Combined HAB vaccine (360/10)*	147	100	147	100

* containing 360 ELISA Units of formalin inactivated hepatitis A virus and 10 micrograms of recombinant hepatitis B surface antigen

Immune response post-primary vaccination using 0-12 month schedule

In a clinical study, 102 subjects aged from 12 years up to and including 15 years received the second dose of Ambirix at month 12. Seropositivity rates for anti-HAV were 99.0% and seropositivity rates for anti-HBs were 99.0% at month 13 with seroprotection rates of 97.0%.

Persistence of immune responses

The persistence of immune responses was evaluated in children up to 15 years after primary vaccination with Ambirix and is presented in the Table below.

Year after the first vaccine dose	**Age at primary vaccination**	**Schedule (Month)**	**Anti-HAV**	**Anti-HBs**
			S+ (%)	**SP (%)**
6	12-15 yrs old	0, 6	100	84.8
		0, 12	100	92.9
10	1-11 yrs old	0, 6	100	77.3
15	12-15 yrs old	0, 6	100	81.1

After 15 years in subjects aged 12-15 years at primary vaccination the anti-HAV and anti-HBs antibody concentrations were comparable between groups that had received Ambirix or a 3-dose regimen of the combined HAB vaccine (360/10). In the Ambirix group, a challenge dose of a HBV vaccine was given to a limited number of subjects (n=8) whose anti-HBs antibody concentrations decreased to < 10 mIU/ml and all mounted an anamnestic response.

Concomitant vaccinations

When the first dose of Ambirix was administered concomitantly with a booster dose of a combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis and *Haemophilus influenzae* type b vaccine (DTPa-IPV+Hib) or with the first dose of a combined Measles-Mumps-Rubella vaccine in the second year of life, immune responses to all antigens were satisfactory.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on general safety studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections

For adjuvants, see section 2.

6.2 Incompatibilities

Not applicable.

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

1 ml of suspension in a pre-filled syringe (type I glass) with a plunger stopper (butyl rubber) and with a rubber tip cap.
The tip cap and rubber plunger stopper of the pre-filled syringe are made with synthetic rubber.

Pack sizes of 1,10 and 50, with or without needles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Upon storage, a fine white deposit with a clear colourless layer above may be observed.

The vaccine should be re-suspended before use. When re-suspended, the vaccine will have a uniform hazy white appearance.

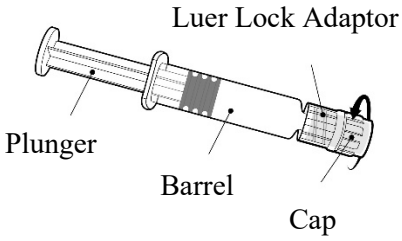
Re-suspension of the vaccine to obtain a uniform hazy white suspension

The vaccine should be re-suspended following the steps below.

1. Hold the syringe upright in a closed hand.
2. Shake the syringe by tipping it upside down and back again.
3. Repeat this action vigorously for at least 15 seconds.
4. Inspect the vaccine again:
    a. If the vaccine appears as a uniform hazy white suspension, it is ready to use – the appearance should not be clear.
    b. If the vaccine still does not appear as a uniform hazy white suspension - tip upside down and back again for at least another 15 seconds - then inspect again.

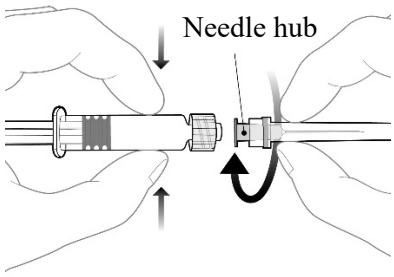
The vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, do not administer the vaccine.

Instructions for the pre-filled syringe after re-suspension



Hold the syringe by the barrel, not by the plunger.

Unscrew the syringe cap by twisting it anticlockwise.



To attach the needle, connect the hub to the Luer Lock Adaptor and rotate a quarter turn clockwise until you feel it lock.

Do not pull the syringe plunger out of the barrel. If it happens, do not administer the vaccine.

Disposal
Any unused medicinal product 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)

EU/1/02/224/001
EU/1/02/224/002
EU/1/02/224/003
EU/1/02/224/004
EU/1/02/224/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 August 2002
Date of latest renewal: 20 July 2012

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substances

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

GlaxoSmithKline Biologicals s.a.
Parc de la Noire Epine
Avenue Fleming 20
1300 Wavre
Belgium

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
1 PRE-FILLED SYRINGE WITHOUT NEEDLE
1 PRE-FILLED SYRINGE WITH 1 NEEDLE
10 PRE-FILLED SYRINGES WITHOUT NEEDLES
10 PRE-FILLED SYRINGES WITH 10 NEEDLES
50 PRE-FILLED SYRINGES WITHOUT NEEDLES

1. NAME OF THE MEDICINAL PRODUCT

Ambirix – Suspension for injection in pre-filled syringe
Hepatitis A (inactivated) and hepatitis B (rDNA) (HAB) vaccine (adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (1 ml):

Hepatitis A virus (inactivated)[1,2]	720 ELISA Units
Hepatitis B surface antigen[3,4]	20 micrograms

[1]Produced on human diploid (MRC-5) cells
[2]Adsorbed on aluminium hydroxide, hydrated 0.05 milligrams Al^{3+}
[3]Produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology
[4]Adsorbed on aluminium phosphate 0.4 milligrams Al^{3+}

3. LIST OF EXCIPIENTS

Sodium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in pre-filled syringe

1 pre-filled syringe
1 dose (1 ml)

1 pre-filled syringe + 1 needle
1 dose (1 ml)

10 pre-filled syringes
10 x 1 dose (1 ml)

10 pre-filled syringes + 10 needles
10 x 1 dose (1 ml)

50 pre-filled syringes
50 x 1 dose (1 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Intramuscular use
Shake well before use

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: 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

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/1/02/224/001 - pack of 1 without needle
EU/1/02/224/002 - pack of 1 with 1 needle
EU/1/02/224/003 - pack of 10 without needle
EU/1/02/224/004 - pack of 10 with 10 needles
EU/1/02/224/005 - pack of 50 without needle

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED SYRINGE

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

Ambirix, suspension for injection
HAB vaccine
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (1 ml)

6. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Ambirix, suspension for injection in pre-filled syringe
Hepatitis A (inactivated) and hepatitis B (rDNA) (HAB) vaccine (adsorbed)

Read all of this leaflet carefully before you/your child starts receiving this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This vaccine has been prescribed for you/your child only. Do not pass it on to others.
- If you/your child gets any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

This leaflet has been written assuming the person receiving the vaccine is reading it, but it can be given to adolescents and children so you may be reading it for your child.

What is in this leaflet

1. What Ambirix is and what it is used for

Ambirix is a vaccine used in infants, children and young people from 1 year up to and including 15 years. It is used to prevent two diseases: hepatitis A and hepatitis B.

- **Hepatitis A:** Infection with the hepatitis A virus may cause the liver to become swollen (inflamed). The virus is usually caught from food or drink that contains the virus. However, it is sometimes caught in other ways, such as by swimming in water that has sewage in it or from another infected person. The virus is found in body fluids such as faeces, serum or saliva.
  Symptoms begin 3 to 6 weeks after infection. Some people can feel sick, have a fever and aches and pains. After a few days they may be very tired, and have dark urine, pale faeces, yellowish skin or eyes (jaundice). The severity and type of symptoms can vary. Young children may not get all symptoms. Most children recover completely but the illness is usually severe enough to make children ill for about a month.

- **Hepatitis B:** Infection with the hepatitis B virus may cause the liver to become swollen (inflamed). The virus is usually caught from another infected person. It is found in body fluids such as blood, semen, vaginal secretions, or saliva (spit).
  Symptoms may not be seen for 6 weeks to 6 months after infection. Not always people who have been infected look or feel ill. Some people can feel sick, have a fever and aches and pains. However, others can become very ill. They may be very tired, and have dark urine, pale faeces, yellowish skin or eyes (jaundice). Some people may need to go into hospital.

  Most adults fully recover from the disease, but some people (particularly children) who may not have had symptoms can remain infected. They are called hepatitis B “carriers” and can still infect other people throughout their lives. Carriers are also at risk of serious liver problems, such as scarring (cirrhosis) or liver cancer.

How Ambirix works

- Ambirix helps the body to produce its own protection (antibodies) against these diseases. The vaccine does not contain live virus (see section 6 for the content of the vaccine) and therefore cannot cause hepatitis A or B infections.

- As with all vaccines, some people respond less well to a vaccine than others.

- Ambirix may not protect you from being ill if you have already caught the hepatitis A or B virus.

- Ambirix can only help to protect you against infections with hepatitis A or B viruses. It cannot protect against other infections that can affect the liver – even though these infections might have signs similar to those caused by the hepatitis A or B virus.

2. What you need to know before you receive Ambirix

Ambirix should not be given if:

- you are allergic to Ambirix, or any of the other ingredients of this vaccine (listed in section 6). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of your face or tongue
- you have previously had an allergic reaction to any vaccine against hepatitis A or hepatitis B diseases
- you have a severe infection with a high temperature. The vaccine can be given after you have recovered. A minor infection such as a cold should not be a problem, but talk to your doctor first.

Ambirix should not be given if any of the above apply. If you are not sure, talk to your doctor, nurse or pharmacist before having Ambirix.

Warnings and precautions

Talk to your doctor, nurse or pharmacist before having Ambirix if:

- you need to be fully protected against hepatitis A and B infection within the next 6 months – your doctor may recommend a different vaccine
- you have a bleeding problem or bruise easily - the injection may be given just under the skin instead of into a muscle to reduce the amount of bleeding or bruising
- you have immune system problems (such as due to an illness, treatment or dialysis) - the vaccine may not work fully. This means you may not be protected against one or both of the hepatitis A and B viruses. Your doctor will run blood tests to see whether more injections are needed to help you be better protected
- you have fainted before or during a previous injection – in case this happens again. Fainting can occur (mostly in adolescents) following, or even before, any needle injection.

If any of the above apply (or you are not sure), talk to your doctor, nurse or pharmacist before having Ambirix.

Other medicines and Ambirix

Tell your doctor if you are taking, have recently taken or might take any other medicines or vaccines. This includes medicines obtained without a prescription and herbal medicines. Ask your doctor, nurse or pharmasist if you are not sure.

If you are taking medicines that affect your body’s immune response, you can still have Ambirix if this is thought to be necessary. However, the vaccine may not work fully. This means that you may

not be protected against one or both of the hepatitis A and B viruses. Your doctor will run blood tests to see whether more injections are needed to help you be better protected.

Ambirix may need to be given at the same time as other vaccines for measles, mumps, rubella, diphtheria, tetanus, whooping cough (pertussis), poliomyelitis, *Haemophilus influenzae* type b or some types of treatments for hepatitis infections called "immunoglobulins". Your doctor will make sure that the vaccines are injected into different parts of your body.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think that you might be pregnant or are planning to have a baby, ask your doctor, nurse or pharmacist for advice before having this vaccine. Ambirix is not usually given to women who are pregnant or breast-feeding.

Driving and using machines

You may feel sleepy or dizzy after having Ambirix. If this happens, do not drive, cycle or use any tools or machines.

Ambirix contains neomycin and sodium

This vaccine contains neomycin (an antibiotic). Ambirix should not be given if you are allergic to neomycin.

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

3. How Ambirix is given

How the injection is given

- The doctor or nurse will give Ambirix as an injection into a muscle. This is usually into the upper arm.
- They will take care that Ambirix is not given into a vein.
- In very small children, the injection may be given into the thigh muscle.

How much is given

- You will normally have a total of two injections. Each is given on a separate visit.
- The injections will be given within 12 months:
  - The first injection – on a date agreed with your doctor.
  - The second injection – between 6 and 12 months after the first injection.

Your doctor will advise on the possible need for extra doses, and future booster dosing.

Missing a dose

- If you miss the second injection, talk to your doctor and arrange another visit as soon as possible.

- Make sure you finish the complete course of two injections. If not, you may not be protected against the diseases.

4. Possible side effects

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

Serious side effects

- **Tell your doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:** allergic and anaphylactic reactions - the signs can include a rash 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.

Tell your doctor straight away if you notice any of the serious side effects listed above.

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

Very common (These may occur with more than 1 in 10 doses of the vaccine): headache, loss of appetite, feeling tired or irritable, pain and redness where the injection was given.

Common (These may occur with up to 1 in 10 doses of the vaccine): fever, feeling drowsy, stomach and digestive problems, swelling where the injection was given.

Additional side effects that have been reported during clinical trials with very similar combined hepatitis A and hepatitis B vaccines, include:

Common (These may occur with up to 1 in 10 doses of the vaccine): generally feeling unwell, diarrhoea, feeling sick (nausea), reaction where the injection was given.

Uncommon (These may occur with up to 1 in 100 doses of the vaccine): feeling dizzy, stomach pain, being sick (vomiting), upper airway infections, aching muscles (myalgia).

Rare (These may occur with up to 1 in 1,000 doses of the vaccine): low blood pressure, joint pain (arthralgia), itching (pruritus), rash, pins and needles (paraesthesia), swollen glands in the neck, armpit or groin (lymphadenopathy), flu-like symptoms, such as high temperature, sore throat, runny nose, cough and chills.

Very rare (These may occur with up to 1 in 10,000 doses of the vaccine): hives (urticaria).

Please contact your doctor if you have similar side effects.

Side effects that occurred during routine use of Ambirix were as follows: fainting, loss of skin sensitivity to pain or touch (hypoaesthesia).

Additional side effects that occurred during routine use of very similar combined or individual hepatitis A and hepatitis B vaccines were as follows: multiple sclerosis, swelling of the spinal cord (myelitis), abnormal test results relating to the liver, swelling or infection of the brain (encephalitis), inflammation of some blood vessels (vasculitis), a degenerative disease of the brain (encephalopathy), swelling of the face, mouth and throat (angioneurotic oedema), severe headache with stiff neck and sensitivity to light (meningitis), a temporary inflammation of the nerves, causing pain, weakness and paralysis in the arms and legs and often progressing to the chest and face (Guillain-Barré syndrome), fits or seizures, inflammation of the nerves (neuritis), disease of the nerves of the eyes (optic neuritis), numbness or weakness of the arms and legs (neuropathy), immediate injection site pain, stinging and burning feeling, paralysis, drooping eyelid and sagging muscles on one side of the face (facial palsy), disease mainly affecting the joints with pain and swelling (arthritis), muscular weakness, purple or reddish-purple bumps on the skin (lichen planus), serious skin rashes (erythema multiforme), reduction in blood platelets, which increases risk of bleeding or bruising (thrombocytopenia), purple or red brown spots visible through the skin (thrombocytopenic purpura).

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.You can also report side effects directly via the national reporting system listed

in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ambirix

Keep this vaccine out of the sight and reach of children.
Do not use this vaccine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
Store in a refrigerator (2°C to 8 °C). Do not freeze. Freezing destroys the vaccine.
Store in the original package in order to protect from light.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ambirix contains

- The active substances are:

- Hepatitis A virus (inactivated) [1,2]	720 ELISA Units
- Hepatitis B surface antigen [3,4]	20 micrograms

[1]Produced on human diploid (MRC-5) cells
[2]Adsorbed on aluminium hydroxide, hydrated 0.05 milligrams Al^{3+}
[3]Produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology
[4]Adsorbed on aluminium phosphate, 0.4 milligrams Al^{3+}

- The other ingredients in Ambirix are: sodium chloride and water for injections.

What Ambirix looks like and contents of the pack

Ambirix is a white and slightly milky liquid.

Ambirix is available in 1-dose pre-filled syringe with or without separate needles, pack sizes of 1, 10 and 50.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

GlaxoSmithKline Biologicals s.a.
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This leaflet was last revised in

Other sources of information

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

The following information is intended for healthcare professionals only:

Upon storage, a fine white deposit with a clear colourless layer above may be observed.

The vaccine should be re-suspended before use. When re-suspended, the vaccine will have a uniform hazy white appearance.

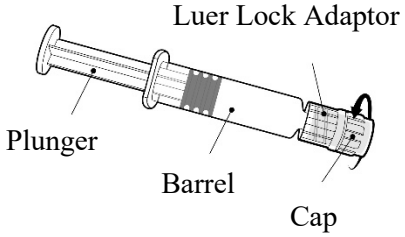
Re-suspension of the vaccine to obtain a uniform hazy white suspension

The vaccine should be re-suspended following the steps below.

1. Hold the syringe upright in a closed hand.
2. Shake the syringe by tipping it upside down and back again.
3. Repeat this action vigorously for at least 15 seconds.
4. Inspect the vaccine again:
    a. If the vaccine appears as a uniform hazy white suspension, it is ready to use – the appearance should not be clear.
    b. If the vaccine still does not appear as a uniform hazy white suspension - tip upside down and back again for at least another 15 seconds - then inspect again.

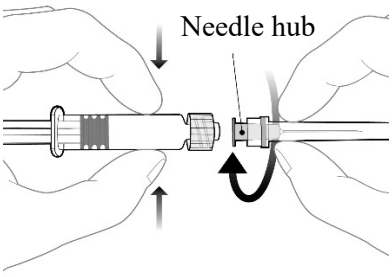
The vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, do not administer the vaccine.

<u>Instructions for the pre-filled syringe after re-suspension</u>



Hold the syringe by the barrel, not by the plunger.

Unscrew the syringe cap by twisting it anticlockwise.



To attach the needle, connect the hub to the Luer Lock Adaptor and rotate a quarter turn clockwise until you feel it lock.

Do not pull the syringe plunger out of the barrel. If it happens, do not administer the vaccine.

Disposal

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