ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) contains:

Hepatitis A virus (inactivated)[1,2]	360 ELISA Units
Hepatitis B surface antigen[3,4]	10 micrograms

[1]Produced on human diploid (MRC-5) cells
[2]Adsorbed on aluminium hydroxide, hydrated 0.025 milligrams Al^{3+}
[3]Produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology
[4]Adsorbed on aluminium phosphate 0.2 milligrams Al^{3+}

The vaccine may contain traces of neomycin which is used during the manufacturing process (see section 4.3).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.
Turbid white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Twinrix Paediatric is indicated for use in non immune infants, children and adolescents from 1 year up to and including 15 years who are at risk of both hepatitis A and hepatitis B infection.

4.2 Posology and method of administration

Posology

- Dosage

The dose of 0.5 ml (360 ELISA Units HA/10 µg HBsAg) is recommended for infants, children and adolescents from 1 year up to and including 15 years of age.

- Primary vaccination schedule

The standard primary course of vaccination with Twinrix Paediatric consists of three doses, the first administered at the elected date, the second one month later and the third six 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 Twinrix Paediatric administered as a booster

dose following a three-dose primary course have not been evaluated.

Long-term antibody persistence data following vaccination with Twinrix Paediatric are available up to 15 years after vaccination (see section 5.1).
The anti-HBs and anti-HAV antibody titres observed following a primary vaccination course with the combined vaccine are in the range of what is seen following vaccination with the monovalent 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 or patients exposed to HBV (e.g. haemodialysis or immunocompromised patients) a precautionary attitude should be considered to ensure a protective antibody level ≥ 10IU/l.

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.

In situations where a booster dose of both hepatitis A and hepatitis B are desired, Twinrix Paediatric can be given. Alternatively, subjects primed with Twinrix Paediatric may be administered a booster dose of either of the monovalent vaccines.

Method of administration

Twinrix Paediatric is for intramuscular injection, preferably in the deltoid region in adolescents and children or in the anterolateral thigh in infants.

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.

The administration of Twinrix Paediatric should be postponed in subjects suffering from acute severe febrile illness.

4.4 Special warnings and precautions for use

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

It is possible that subjects may be in the incubation period of a HA or HB infection at the time of

vaccination. It is not known whether Twinrix Paediatric will prevent HA and HB 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.

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

The vaccine has not been tested in patients with impaired immunity. In haemodialysis patients, patients receiving immunosuppressive treatment or patients with an impaired immune system, the anticipated immune response may not be achieved after the primary immunisation course. Such patients may require additional doses of vaccine; nevertheless immunocompromised patients may fail to demonstrate an adequate response.

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

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 Twinrix Paediatric can be administered subcutaneously to subjects with thrombocytopenia or bleeding disorders since bleeding may occur following an intramuscular administration to these subjects (see section 4.2).

Twinrix Paediatric 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 Twinrix Paediatric 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, no influence on seroconversion was observed although it may result in lower antibody titres.

Twinrix Paediatric can be given concomitantly with Human Papillomavirus (HPV) vaccine. Administration of Twinrix Paediatric at the same time as Cervarix (HPV vaccine) has shown no clinically relevant interference in the antibody response to the HPV and hepatitis A antigens. Anti-HBs geometric mean antibody concentrations were lower on co-administration, but the clinical significance of this observation is not known since the seroprotection rates remain unaffected. The proportion of subjects reaching anti-HBs ≥ 10 mIU/ml was 98.3% for concomitant vaccination and 100% for Twinrix alone.

Only the concomitant administration of Twinrix Paediatric with Cervarix has been specifically studied. It is advised that vaccines other than Cervarix should not be administered at the same time as Twinrix Paediatric.

4.6 Fertility, pregnancy and lactation

Pregnancy

The effect of Twinrix Paediatrict on embryo-fetal, peri-natal and post-natal survival and development has been assessed in rats. This study did not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/fetal development, parturition or post-natal development.

The effect of Twinrix Paediatric on embryo-fetal, peri-natal and post-natal survival and development has not been prospectively evaluated in clinical trials.

Data on outcomes of a limited number of pregnancies in vaccinated women do not indicate any adverse effects of Twinrix Paediatric on pregnancy or on the health of the fetus/newborn child. While it is not expected that recombinant hepatitis B virus surface antigen would have adverse effects on pregnancies or the fetus it is recommended that vaccination should be delayed until after delivery unless there is an urgent need to protect the mother against hepatitis B infection.

Breast-feeding

It is unknown whether Twinrix Paediatric is excreted in human breast milk. The excretion of Twinrix Paediatric in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Twinrix Paediatric should be made taking into account the benefit of breast-feeding to the child and the benefit of Twinrix Paediatric therapy to the woman.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The safety profile presented below is based on data from approximately 800 subjects. The most commonly reported adverse reactions following Twinrix Paediatric administration are pain and redness occurring in a per dose frequency of 28.5% and 11.5% respectively.

Tabulated list of adverse reactions

Frequencies are reported as:
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

System Organ Class	Frequency	Adverse reactions
Clinical trials		
Infections and infestations	Uncommon	Upper respiratory tract infection*
Blood and lymphatic system disorders	Rare	Lymphadenopathy
Metabolism and nutrition disorders	Common	Appetite lost
Psychiatric disorders	Common	Irritability
Nervous system disorders	Common	Drowsiness, headache
	Rare	Hypoaesthesia*, paraesthesia*, dizziness
Vascular disorders	Rare	Hypotension*
Gastrointestinal disorders	Common	Gastrointestinal symptoms, nausea
	Uncommon	Diarrhoea, vomiting, abdominal pain
Skin and subcutaneous tissue disorders	Uncommon	Rash
	Rare	Urticaria, pruritus*
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia*
	Rare	Arthralgia*
General disorders and administration	Very common	Pain and redness at the injection site

site conditions	Common	Swelling at the injection site, injection site reaction (such as bruising), fatigue, malaise, fever (≥ 37.5°C)
	Rare	Influenza like illness*, chills*
Post-marketing surveillance		
The following adverse reactions have been reported with either Twinrix or with GlaxoSmithKline monovalent hepatitis A or B vaccines:		
Infections and infestations	Meningitis	
Blood and lymphatic system disorders	Thrombocytopenia, thrombocytopenic purpura	
Immune system disorders	Anaphylaxis, allergic reactions including anaphylactoid reactions and mimicking serum sickness	
Nervous system disorders	Encephalitis, encephalopathy, neuritis, neuropathy, paralysis, convulsions	
Vascular disorders	Vasculitis	
Skin and subcutaneous tissue disorders	Angioneurotic oedema, lichen planus, erythema multiforme	
Musculoskeletal and connective tissue disorders	Arthritis, muscular weakness	
General disorders and administration site conditions	Immediate injection site pain	
Following widespread use of the monovalent hepatitis A and/or hepatitis B vaccines, the following undesirable events have additionally been reported in temporal association with vaccination:		
Nervous system disorders	Multiple sclerosis, myelitis, facial palsy, polyneuritis such as Guillain-Barré syndrome (with ascending paralysis), optic neuritis	
General disorders and administration site conditions	Stinging and burning sensation	
Investigations	Abnormal liver function tests	

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

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 have been reported during post-marketing surveillance. Adverse events reported following overdosage were similar to those reported with normal vaccine administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Twinrix Paediatric is a combined vaccine formulated by pooling bulk preparations of the purified, inactivated hepatitis A (HA) virus and purified hepatitis B surface antigen (HBsAg), separately adsorbed onto aluminium hydroxide and aluminium phosphate.
The HA virus is propagated in MRC_5 human diploid cells. HBsAg is produced by culture, in a selective medium, of genetically engineered yeast cells.
Twinrix Paediatric confers immunity against HAV and HBV infection by inducing specific anti-HA and anti-HBs antibodies.

Protection against hepatitis A and hepatitis B develops within 2-4 weeks. In the clinical studies, specific humoral antibodies against hepatitis A were observed in approximately 89% of the subjects one month after the first dose and in 100% one month after the third dose (i.e. month 7). Specific humoral antibodies against hepatitis B were observed in approximately 67% of the subjects after the first dose and 100% after the third dose.

In two long-term clinical trials, persistence of anti-HAV and anti-HBs antibodies has been demonstrated up to 5 years in children aged 1-11 years and up to 15 years in children aged 12-15 years.
At 5 years following initiation of a 0, 1, 6 month schedule of Twinrix Paediatric in children aged 1-11 years all subjects followed up retained ≥15 mIU/ml anti-HAV antibody and 97% had anti-HBs antibody ≥10 mIU/ml.

At 15 years following the initiation of a 0, 1, 6 month schedule of Twinrix Paediatric in children aged 12-15 years, all subjects followed up retained ≥15 mIU/ml anti-HAV antibody and 81.8% had anti-HBs antibody ≥10 mIU/ml. A challenge dose of a HBV vaccine was given to a limited number of subjects (n=11) whose anti-HBs antibody concentrations had decreased to <10 mIU/ml and 10 of the 11 subjects (90.9%) mounted an anamnestic response.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

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

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 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.

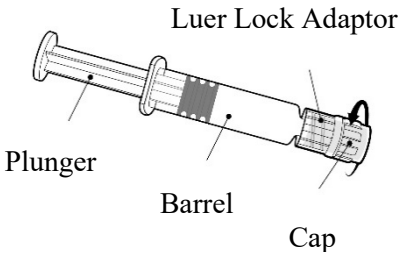
Re-suspension of the vaccine to obtain a uniform hazy white suspension

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.

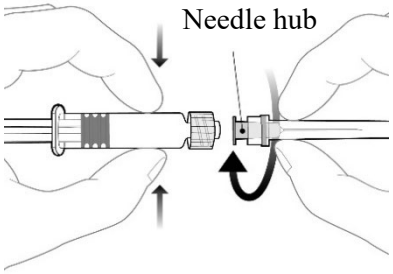
The vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, do not administer the vaccine.

<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.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/029/001
EU/1/97/029/002
EU/1/97/029/006
EU/1/97/029/007
EU/1/97/029/008
EU/1/97/029/009
EU/1/97/029/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 February 1997
Date of latest renewal: 28 August 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal 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 MANUFATURER 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, 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
10 PRE-FILLED SYRINGES WITHOUT NEEDLE
50 PRE-FILLED SYRINGES WITHOUT NEEDLE
1 PRE-FILLED SYRINGE WITH 1 NEEDLE
10 PRE-FILLED SYRINGES WITH 10 NEEDLES
1 PRE-FILLED SYRINGE WITH 2 NEEDLES
10 PRE-FILLED SYRINGES WITH 20 NEEDLES

1. NAME OF THE MEDICINAL PRODUCT

Twinrix Paediatric – 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 (0.5 ml):

Hepatitis A virus (inactivated)[1,2]	360 ELISA Units
Hepatitis B surface antigen[3,4]	10 micrograms

[1]Produced on human diploid (MRC-5) cells

[2]Adsorbed on aluminium hydroxide, hydrated	0.025 milligrams Al^{3+}

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

[4]Adsorbed on aluminium phosphate	0.2 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 (0.5 ml)

10 pre-filled syringes
10 x 1 dose (0.5 ml)

50 pre-filled syringes
50 x 1 dose (0.5 ml)

1 pre-filled syringe + 1 needle
1 dose (0.5 ml)

10 pre-filled syringes + 10 needles
10 x 1 dose (0.5 ml)

1 pre-filled syringe + 2 needles
1 dose (0.5 ml)

10 pre-filled syringes + 20 needles
10 x 1 dose (0.5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Intramuscular use
Shake 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/1/97/029/001 – pack of 1 without needle

EU/1/97/029/002 – pack of 10 without needle
EU/1/97/029/008 – pack of 50 without needle
EU/1/97/029/006 – pack of 1 with 1 needle

EU/1/97/029/007 – pack of 10 with 10 needles
EU/1/97/029/009 – pack of 1 with 2 needles
EU/1/97/029/010 – pack of 10 with 20 needles

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

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

Twinrix Paediatric, suspension for injection
HAB vaccine
I.M.

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)

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Twinrix Paediatric, 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 start/ 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 or your pharmacist.
- This vaccine has been prescribed for you/ your child only. Do not pass it on to others.
- If you get / your child gets any side effects, talk to your doctor 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 Twinrix Paediatric is and what it is used for
2. What you need to know before you receive Twinrix Paediatric
3. How Twinrix Paediatric is given
4. Possible side effects
5. How to store Twinrix Paediatric
6. Contents of the pack and other information

1. What Twinrix Paediatric is and what it is used for

Twinrix Paediatric is a vaccine used in infants, children and adolescents from 1 year up to and including 15 years to prevent two diseases: hepatitis A and hepatitis B. The vaccine works by causing the body to produce its own protection (antibodies) against these diseases.

- **Hepatitis A:** Hepatitis A is an infectious disease, which can affect the liver. This disease is caused by the hepatitis A virus. The hepatitis A virus can be passed from person to person in food and drink, or by swimming in water contaminated by sewage. Symptoms of hepatitis A begin 3 to 6 weeks after coming into contact with the virus. These consist of nausea (feeling sick), fever and aches and pains. After a few days the whites of eyes and skin may become yellowish (jaundice). The severity and type of symptoms can vary. Young children may not develop jaundice. Most people recover completely but the illness is usually severe enough to keep people off work for about a month.

- **Hepatitis B:** Hepatitis B 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.

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

2. What you need to know before you receive Twinrix Paediatric

Twinrix Paediatric should not be given if
- you are allergic to:
  - the active substances, or any of the ingredients of this medicine (listed in section 6).
  - neomycin.

  Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.
- you have previously had an allergic reaction to any vaccine against hepatitis A and hepatitis B

diseases.
- you have a severe infection with a high temperature (over 38°C). A minor infection such as a cold should not be a problem, but talk to your doctor first.

Warnings and precautions
Talk to you doctor or pharmacist before you receive Twinrix Paediatric if:
- you have experienced any health problems after previous administration of a vaccine.
- you have a poor immune system due to illness or drug treatment.
- you have a bleeding problem or bruise/ bruises easily.

Fainting can occur (mostly in adolescents) following, or even before, any needle injection. Therefore tell the doctor or nurse if you fainted with a previous injection.

Other medicines and Twinrix Paediatric
Twinrix Paediatric can be given with a Human Papillomavirus (HPV) vaccine at a separate injection site (another part of your body, e.g. the other arm) during the same visit.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think that you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this vaccine.
It is not known if Twinrix Paediatric passes into breast milk, however the vaccine is not expected to cause problems in breast-fed babies.

Twinrix Paediatric contains neomycin and sodium
Please tell your doctor if you have had an allergic reaction to neomycin (antibiotic).
This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How Twinrix Paediatric is given

You will receive a total of three injections over 6 months. Each injection is given on a separate visit. The first dose will be given on an elected date. The remaining two doses will be given one month, and six months after the first dose.

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

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

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

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

The doctor will give Twinrix Paediatric as an injection into your upper arm muscle or into the thigh muscle of your child.

The vaccine should never be given into a vein.

If you have any further questions on the use of this vaccine, ask your doctor or pharmacist.

4. Possible side effects

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

Side effects that may occur are the following:

Side effects occured during clinical studies or routine use of the vaccine or with individual hepatitis A and hepatitis B vaccines or with the adult formulation of Twinrix.

Very common (these may occur with more than 1 in 10 doses of the vaccine): pain and redness at the injection site.

Common (these may occur with up to 1 in 10 doses of the vaccine): drowsiness, headache, nausea, loss of appetite, swelling or bruising at the injection site, generally feeling unwell, tiredness, fever equal to or greater than 37.5°C, irritability.

Uncommon (these may occur with up to 1 in 100 doses of the vaccine): diarrhoea, vomiting, stomach pain, rash, aching muscles, upper respiratory tract infection.

Rare (these may occur with up to 1 in 1,000 doses of the vaccine): swollen glands in the neck armpit or groin (lymphadenopathy), dizziness, loss of skin sensitivity to pain or touch (hypoaesthesia), feeling of pins and needles (paraesthesia), hives, itching, joint pain, low blood pressure, 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): reduction in blood platelets, which increases risk of bleeding or bruising (thrombocytopenia), purple or red brown spots visible through the skin (thrombocytopenic purpura), swelling or infection of the brain (encephalitis), degenerative disease of the brain (encephalopathy), inflammation of nerves (neuritis), numbness or weakness of the arms and legs (neuropathy), paralysis, fits or seizures, swelling of the face, mouth or throat (angioneurotic oedema), purple or reddish-purple bumps on the skin (lichen planus), serious skin rashes (erythema multiforme), joint swelling, muscular weakness, infection around the brain which may give severe headache with stiff neck and sensitivity to light (meningitis), inflammation of some blood vessels (vasculitis), abnormal laboratory liver test results, multiple sclerosis, swelling of the spinal cord (myelitis), drooping eyelid and sagging muscles on one side of the face (facial palsy), a temporary inflammation of the nerves, causing pain, weakness and paralysis in the extremities and often progressing to the chest and face (Guillain-Barré syndrome), a disease of the nerves of the eye (optic neuritis), immediate injection site pain, stinging and burning feeling.
Serious allergic reactions (anaphylaxis, anaphylactoid reactions and mimicking serum sickness) may also occur very rarely (with up to 1 in 10,000 doses of the vaccine).
Signs of serious allergic reactions may be 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, if you get any of these symptoms you should contact a doctor urgently.

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 Twinrix Paediatric

Keep this medicine out of the sight and reach of children.

Do not use this medicine 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 - 8°C).
Store in the original package in order to protect from light.
Do not freeze. Freezing destroys the vaccine.

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 Twinrix Paediatric contains

- The active substances are:

Hepatitis A virus (inactivated)[1,2]	360 ELISA Units
Hepatitis B surface antigen[3,4]	10 micrograms

[1]Produced on human diploid (MRC-5) cells
[2]Adsorbed on aluminium hydroxide, hydrated 0.025 milligrams Al^{3+}
[3]Produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology
[4]Adsorbed on aluminium phosphate 0.2 milligrams Al^{3+}

- The other ingredients in Twinrix Paediatric are: sodium chloride, water for injections.

What Twinrix Paediatric looks like and contents of the pack

Suspension for injection in pre-filled syringe.

Twinrix Paediatric is a white, slightly milky liquid.

Twinrix Paediatric 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

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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.

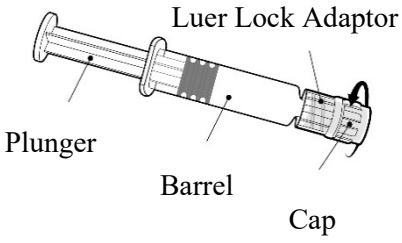
Re-suspension of the vaccine to obtain a uniform hazy white suspension

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.

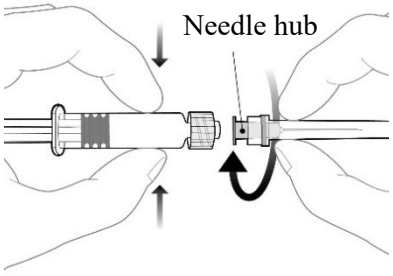
The vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, do not administer the vaccine.

<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.