

## 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) <sup>1,2</sup>	360 ELISA Units
Hepatitis B surface antigen <sup>3,4</sup>	10 micrograms

<sup>1</sup>Produced on human diploid (MRC-5) cells

<sup>2</sup>Adsorbed on aluminium hydroxide, hydrated 0.025 milligrams Al<sup>3+</sup>

<sup>3</sup>Produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology

<sup>4</sup>Adsorbed on aluminium phosphate 0.2 milligrams Al<sup>3+</sup>

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  $\geq 10\text{IU/l}$ .

### 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.

#### 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  $\geq 10$  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 Paediatric 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:  $\geq 1/10$   
 Common:  $\geq 1/100$  to  $< 1/10$   
 Uncommon:  $\geq 1/1,000$  to  $< 1/100$   
 Rare:  $\geq 1/10,000$  to  $< 1/1,000$   
 Very rare:  $< 1/10,000$

<b>System Organ Class</b>	<b>Frequency</b>	<b>Adverse reactions</b>
<b>Clinical trials</b>		
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 site conditions	Very common	Pain and redness at the injection site
	Common	Swelling at the injection site, injection site reaction (such as bruising), fatigue,

		malaise, fever ( $\geq 37.5^{\circ}\text{C}$ )
	Rare	Influenza like illness*, chills*
<b>Post-marketing surveillance</b>		
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<sub>5</sub> 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  $\geq 15$  mIU/ml anti-HAV antibody and 97% had anti-HBs antibody  $\geq 10$  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  $\geq 15$  mIU/ml anti-HAV antibody and 81.8% had anti-HBs antibody  $\geq 10$  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 (rubber butyl).  
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.

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>.