

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Twinrix Paediatric, suspension for injection
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 |

¹Produced on human diploid (MRC-5) cells

²Adsorbed on aluminium hydroxide, hydrated

0.025 milligrams Al³⁺

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

⁴Adsorbed on aluminium phosphate

0.2 milligrams Al³⁺

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.

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.

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 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: $< 1/10,000$

| 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 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* |
| 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 MRC₅ 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 10 years in children aged 12-15 years and up to 5 years in children aged 1-11

years.

At 10 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 85% had anti-HBs antibody ≥ 10 mIU/ml.

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.

The kinetics of decline of anti-HAV and anti-HBs antibodies were shown to be similar to those of the monovalent vaccines.

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

24 September 2018

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