1. NAME OF THE MEDICINAL PRODUCT

Twinrix Junior

Inactivated hepatitis A and rDNA hepatitis B vaccine (adsorbed)
Suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Twinrix Junior 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.
A 0.5 ml dose of Twinrix Junior contains not less than 360 ELISA Units of inactivated HA virus and 10 µg of recombinant HBsAg protein.

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

3. PHARMACEUTICAL FORM

Suspension for injection

4. Clinical particulars

4.1 Therapeutic indications

Twinrix Junior is indicated for use in non-immune infants, children and adolescents aged 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

Dosage

A dose of 0.5 ml Twinrix Junior is recommended for infants, children and adolescents aged from 1 year up to and including 15 years of age.

Primary vaccination schedule

The standard primary course of vaccination with Twinrix Junior 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

Long-term antibody persistence data following vaccination with Twinrix Junior are available for up to 15 years after vaccination (See section "*Pharmacodynamics*"). 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.

- 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 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 Junior can be given. Alternatively, subjects primed with Twinrix Junior may be administered a booster dose of either of the monovalent vaccines.

Method of administration

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

Since intradermal injection or intramuscular administration into the gluteal muscle could

lead to a suboptimal response to the vaccine, these routes should be avoided. Exceptionally, Twinrix Junior can be administered subcutaneously to subjects with thrombocytopenia or bleeding disorders since bleeding may occur following an intramuscular administration to these subjects. However, this route of administration may result in suboptimal immune response to the vaccine.

4.3 Contraindications

Twinrix Junior should not be administered to subjects with known hypersensitivity to any constituent of the vaccine, or to subjects having shown signs of hypersensitivity after previous administration of Twinrix Junior or the monovalent hepatitis A or hepatitis B vaccines.

4.4 Special warnings and precautions for use

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

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. 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 Twinrix Junior 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.

Twinrix Junior is not recommended for post-exposure 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 therefore require administration of additional doses of vaccine.

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.

Twinrix Junior 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 Junior 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 Junior can be given concomitantly with Human Papillomavirus (HPV) vaccine. Administration of Twinrix Junior 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 Junior with Cervarix has been specifically studied. It is advised that vaccines other than Cervarix should not be administered at the same time as Twinrix Junior.
It may be expected that in patients receiving immunosuppressive treatment or patients with immunodeficiency, an adequate response may not be achieved.

4.6 Pregnancy and Lactation

Pregnancy

Twinrix Junior should be used during pregnancy only when clearly needed, and when the possible advantages outweigh the possible risks to the foetus. The effect of Twinrix Junior on embryo-foetal, peri-natal and post-natal survival and development has not been prospectively evaluated in clinical trials.
The effect of Twinrix Junior on embryo-foetal, peri-natal and post-natal survival and development has been assessed in rats. Such animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development.

Lactation

Adequate human data on use during lactation and adequate animal reproduction studies are not available.

4.7 Effects on ability to drive and use machines

The vaccine is unlikely to produce an effect on the ability to drive and use machines.

4.8 Undesirable effects

The safety profile presented below is based on data from approximately 800 subjects.

Adverse reactions reported are listed according to the following frequency:
Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1000 to < 1/100
Rare: ≥ 1/10000 to <1/1000
Very rare: < 1/10000

- **Clinical Trial Data:**

System Organ Class	Frequency	Adverse reactions
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	Dizziness
	Very rare	Paraesthesia*, hypoaesthesia*
Vascular disorders	Very rare	Hypotension*
Gastrointestinal disorders	Common	Gastrointestinal symptoms (such as nausea, diarrhoea*, vomiting)
Skin and subcutaneous tissue disorders	Uncommon	Rash
	Rare	Urticaria
	Very rare	Pruritus*
Musculoskeletal and connective tissue disorders	Very rare	Myalgia*, 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, fatigue, malaise, fever (≥37.5°C)
	Very rare	Influenza like illness*, chills*

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

- **Post Marketing Data:**

These adverse reactions have been reported with either Twinrix or with GlaxoSmithKline monovalent hepatitis A or B vaccines.

System Organ Class	Adverse reactions
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	Encephalopathy, encephalitis, 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, stinging and burning sensation

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

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

Twinrix Junior confers immunity against HAV and HBV infection by inducing specific anti-HAV and anti-HBs antibodies.
Protection against hepatitis A and hepatitis B develops within 2-4 weeks. In the clinical studies for Twinrix Junior, 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 a long-term clinical trial, persistence of anti-HAV and anti-HBs antibodies has been demonstrated up to 15 years following the initiation of a primary vaccination course of Twinrix Junior. After 15 years, anti-HAV seropositivity rate and anti-HBs seroprotection rate were 100% and 81.8% respectively.
A challenge dose of a HBV vaccine was given to a limited number of subjects (n=11) whose anti-HBs antibody concentrations decreased to < 10 mIU/ml and 90.9% mounted an anamnestic response.

Non-Clinical Information

Pre-clinical data reveal no special hazard for humans based on general safety studies (See section *Pregnancy and Lactation*).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride and water for injections. Aminoacids for injection, formaldehyde, neomycin sulphate and polysorbate 20 are present as residual from the manufacturing process.

6.2 Incompatibilities

Twinrix Junior should not be mixed with other vaccines in the same syringe.

6.3 Shelf life

The expiry date is indicated on the label and packaging.

6.4 Special precautions for storage

Twinrix Junior should be stored at +2 °C to +8 °C.
Do not freeze; discard if the vaccine has been frozen.
The storage conditions are detailed on the packaging

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

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 not made with natural rubber latex.

6.6 Special precautions for disposal <and other handling>

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

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

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

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

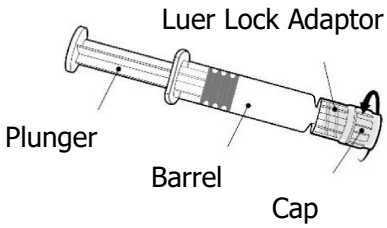
1. Hold the syringe upright in a closed hand.
2. Shake the syringe by tipping it upside down and back again.
3. Repeat this action vigorously for at least 15 seconds.
4. Inspect the vaccine again:

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

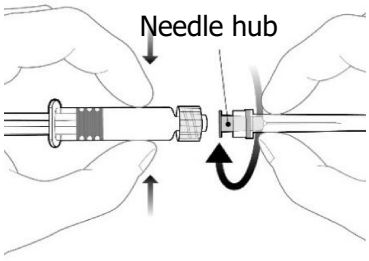
administer the vaccine.

Instructions for the pre-filled syringe



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

7. <MANUFACTURER>

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

Tel: (32) 2 656 81 11

Version number: GDS13/IPI11