Twinrix Adult

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

QUALITATIVE AND QUANTITATIVE COMPOSITION

Suspension for injection.

One dose (1.0 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+}

Twinrix Adult is a white, slightly milky liquid presented in a glass pre-filled syringe.

CLINICAL INFORMATION

Indications

Twinrix Adult is indicated for use in non immune adults and adolescents of 16 years of age and above who are at risk of both hepatitis A and hepatitis B infection.

Dosage and Administration

Dosage

A dose of 1.0 ml Twinrix Adult is recommended for adults and adolescents of 16 years of age and above.

Primary vaccination schedules

The standard primary course of vaccination with Twinrix Adult 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.

In exceptional circumstances in adults, when travel is anticipated within one month or more after initiating the vaccination course, but where insufficient time is available to allow the standard 0, 1, 6 month schedule to be completed, a schedule of three intramuscular injections given at 0, 7 and 21 days may be used. When this schedule is applied, a fourth dose is recommended 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

Long-term antibody persistence data following vaccination with Twinrix Adult are available for up to 20 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 ≥ 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 Adult can be given. Alternatively, subjects primed with Twinrix Adult may be administered a booster dose of either of the monovalent vaccines.

Method of administration

Twinrix Adult is for intramuscular injection, preferably in the deltoid region.
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 Adult 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.

Contraindications

Twinrix Adult 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 Adult or the monovalent hepatitis A or hepatitis B vaccines.

Warnings and Precautions

As with other vaccines, the administration of Twinrix Adult 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 Adult 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 Adult 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 and persons with an impaired immune system, adequate anti-HAV and anti-HBs antibody titres may not be obtained after the primary immunisation course and 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 Adult should under no circumstances be administered intravenously.

Interactions

No data on concomitant administration of Twinrix Adult 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.
Although the concomitant administration of Twinrix Adult and other vaccines has not specifically been studied, it is anticipated that, if different syringes and other injection sites are used, no interaction will be observed.
It may be expected that in patients receiving immunosuppressive treatment or patients with immunodeficiency, an adequate response may not be achieved.

Pregnancy and Lactation

Pregnancy
Twinrix Adult should be used during pregnancy only when clearly needed, and when the possible advantages outweigh the possible risks for the foetus.
The effect of Twinrix Adult on embryo-foetal, peri-natal and post-natal survival and development has not been prospectively evaluated in clinical trials.
The effect of Twinrix Adult 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. Twinrix Adult should therefore be used with caution in breastfeeding women.

Effects on Ability to Drive and Use Machines

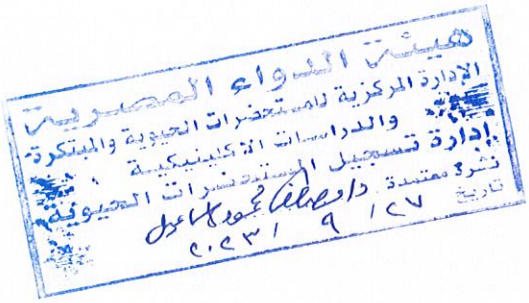
The vaccine is unlikely to produce an effect on the ability to drive and use machines.

Adverse Reactions

The safety profile presented below is based on data from more than 6,000 subjects who received either the standard 0, 1, 6 month schedule or the accelerated 0, 7, 21 days schedule.

Frequencies per dose are defined as follows:

Very common: ≥ 10%
Common: ≥ 1% and < 10%
Uncommon: ≥ 0.1% and < 1%
Rare: ≥ 0.01% and < 0.1%
Very rare: < 0.01%



- **Clinical Trial Data:**

System Organ Class	Frequency	Adverse reactions
Infections and infestations	Uncommon	Upper respiratory tract infection
Blood and lymphatic system disorders	Rare	Lymphadenopathy
Metabolism and nutrition disorders	Rare	Decreased appetite
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness
	Rare	Hypoaesthesia, paraesthesia
Vascular disorders	Rare	Hypotension
Gastrointestinal disorders	Common	Gastrointestinal symptoms (such as diarrhoea, nausea, vomiting)
Skin and subcutaneous tissue disorders	Rare	Rash, pruritus
	Very rare	Urticaria
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia
	Rare	Arthralgia
General disorders and administration site conditions	Very common	Pain and redness at the injection site, fatigue
	Common	Swelling at the injection site, injection site reaction, malaise
	Uncommon	Fever (≥ 37.5°C)
	Rare	Influenza like illness, chills

- **Post Marketing Data:**

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

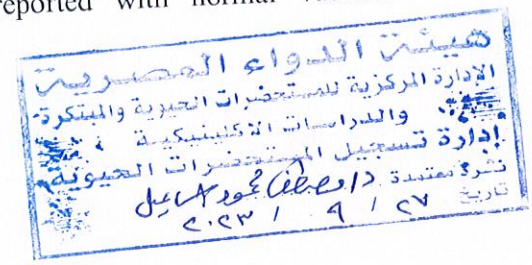
System Organ Class	Adverse reactions
Infections and infestations	Meningitis
Blood and lymphatic system disorders	Thrombocytopenia, thrombocytopenic purpura
Immune system disorders	Anaphylaxis, allergic reactions including anaphylactoid reactions and mimicking serum sickness
Nervous system disorders	Encephalitis, 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, stinging and burning sensation

In a comparative study, it was noted that the frequency of solicited adverse events following the administration of Twinrix Adult is not different from the frequency of solicited adverse events following the administration of the monovalent vaccines.

In a clinical trial where Twinrix Adult was administered at 0, 7, 21 days, solicited general symptoms were reported with the same categories of frequency as defined above. After a fourth dose given at month 12, the incidence of systemic adverse reactions was comparable to that seen after vaccination at 0, 7, 21 days.

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.



PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

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

Twinrix Adult 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 Adult, specific humoral antibodies against hepatitis A were observed in approximately 94% of the adults 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 70% of the adults after the first dose and approximately 99% after the third dose.
For use in exceptional circumstances in adults, the 0, 7 and 21 day primary schedule plus a fourth dose at month 12 results in 82% and 85% of vaccinees having seroprotective levels of anti-HBV antibodies at 1 and 5 weeks respectively following the third dose. One month after the fourth dose, all vaccinees demonstrated seroprotective levels of antibody. Seropositivity rates for anti-HAV antibodies were 100% and 99.5% at 1 and 5 weeks respectively following the third dose, and reached 100% one month after the fourth dose.

In a clinical study conducted in subjects over 40 years of age, the seropositivity rate for anti-HAV antibodies and seroprotection rate against hepatitis B following Twinrix Adult on a 0, 1, 6 month schedule were compared with the seropositivity and seroprotection rates of monovalent hepatitis A and B vaccines when administered separately.
The seroprotection rates against hepatitis B after the administration of Twinrix Adult were 92% and 57% at 7 and 48 months following the first dose respectively, versus 80% and 40% after the GlaxoSmithKline Biologicals monovalent 20 µg hepatitis B vaccine, and 71% and 27% after another licensed monovalent 10 µg hepatitis B vaccine. In all groups, anti-HBs antibody concentrations decreased as age and body mass index increased; concentrations were also lower in males compared with females.
The seropositivity rates for anti-HAV antibodies after Twinrix Adult were 97% at both 7 and 48 months following the first dose versus 99% and 94% after the GlaxoSmithKline

Biologicals monovalent hepatitis A vaccine and 99% and 96% after another licensed monovalent hepatitis A vaccine.
Subjects received an additional dose of Twinrix Adult to assess the immune memory 48 months after the first dose of the primary vaccination course with the same vaccine. One month after this dose, 95% of subjects elicited anti-HBV antibody concentration ≥ 10 mIU/ml and Geometric Mean Concentrations (GMC) increased by 179-fold (GMC of 7233.7 mIU/ml) indicative of an immune memory response.
In two long-term clinical studies conducted in adults, 20 years after the primary vaccination with Twinrix Adult the anti-HAV seropositivity rates were 100% and 96% respectively and the anti-HBs seroprotection rates were 94% and 92%, respectively (n=43).

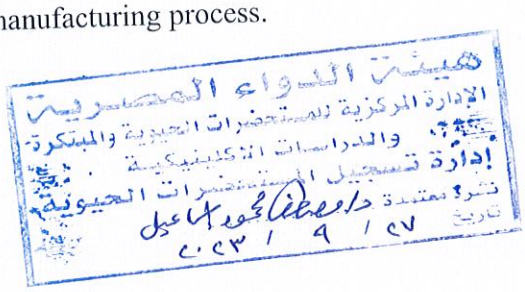
Pre-clinical Safety Data

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

PHARMACEUTICAL PARTICULARS

List of Excipients

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



Shelf Life

The expiry date is indicated on the label and packaging.

Special Precautions for Storage

Twinrix Adult 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

Nature and Contents of Container

Twinrix Adult is presented in a pre-filled syringe.
The pre-filled syringes are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.
Not all presentations are available in every country.

Incompatibilities

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

Instructions for Use/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.

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

Version number: GDS15/IPI12/ Date of issue: 26/Sep/2019

Manufacturer:
GlaxoSmithKline Biologicals s.a
89, rue de l'Institut - 1330 Rixensart
Belgium
Tel: (32) 2 656 81 11 Fax: (32) 2 656 80 00

* year of creation/update of the artwork.