1. name of the Medicinal Product

Twinrix Adult ▼

Combined inactivated hepatitis A (720 ELISA units) and rDNA hepatitis B (20 mcg) vaccine.

2. Qualitative And Quantitative Composition

Twinrix Adult 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 on to 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.

A 1.0 ml dose of vaccine contains not less than 720 ELISA Units of inactivated HA virus and 20 mcg of recombinant HBsAg protein.

3. Pharmaceutical Form

Suspension for injection.

4. Clinical Particulars

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

- Dosage

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

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

It is not yet fully established whether immunocompetent individuals who have responded to hepatitis A and/or B vaccination(s) will require booster doses as protection in the absence of detectable antibodies may be ensured by immunological memory.

Long-term antibody persistence data following vaccination with Twinrix Adult are not currently available. However, 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. These guidelines are based on the assumption that a minimal antibody level is required for protection; protective levels (10 mIU/ml) of anti-HBs will persist in the majority of subjects for five years, with anti-HAV predicted to persist for at least 10 years.

Booster vaccination with the combined vaccine can be recommended five years after initiation of the primary course. If the monovalent vaccines are used as boosters, they can be administered five years after initiation of the primary course for hepatitis B and 10 years after initiation of the primary course for hepatitis A.

Antibody levels of subjects at risk can be assessed at regular intervals and appropriate boosters administered when titres fall below minimal levels.

Method of administration

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

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 Contra-indications

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

4.4 Special warnings and special precautions for use

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.

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 Adult 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 Adult should under no circumstances be administered intravascularly.

4.5 Interactions with other medicinal products and other forms of interaction

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

4.6 Use during pregnancy and lactation

Pregnancy

The effect of Twinrix Adult on foetal development has not been assessed. However, as with all inactivated vaccines, one does not expect harm to the foetus. Twinrix Adult should be used during pregnancy only when there is a clear risk of hepatitis A and hepatitis B.

Lactation

The effect on breast fed infants of the administration of Twinrix Adult to their mothers has not been evaluated in clinical studies. Twinrix Adult should therefore be used with caution in breast feeding women.

4.7 Effects on the 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

In controlled clinical studies, signs and symptoms were actively monitored in all subjects for four days following the administration of the vaccine. A checklist was used for this purpose. The vaccinees were also requested to report any clinical events occurring during the study period. The most common reactions were those at the site of injection. They included transient pain, redness and swelling. Systemic adverse events seen were fever, headache, malaise, fatigue, nausea and vomiting. These events were transient, only rarely reported and were considered by the subjects as mild.

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.

Following widespread use of the monovalent hepatitis A and/or hepatitis B vaccines, the following undesirable events have been reported in temporal association in the days or weeks after vaccination. In many instances, a causal relationship has not been established.

abdominal pain, abnormal liver function tests, rash, pruritus, urticaria.

Very rarely reported : allergic reactions mimicking serum sickness, vasculitis, syncope, hypotension, lymphadenopathy, cases of peripheral and/or central neurological disorders, and may include multiple sclerosis, optic neuritis, myelitis, Bells palsy, polyneuritis such as Guillain-Barré syndrome (with ascending paralysis), meningitis, encephalitis, encephalopathy, thrombocytopenic purpura, erythema exsudativum multiforme.

4.9 Overdose

No information available.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hepatitis vaccines, ATC code JO7BC.

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 two to four weeks. In the clinical studies, 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 seven). Specific humoral antibodies against hepatitis B were observed in 70% of the adults after the first dose and approximately 99% after the third dose. Based on experience with the monovalent vaccines, it is expected that in most vaccinees the antibodies will persist for at least four to five years after the primary vaccination course. To establish long-term protection, booster vaccination with either the monovalent vaccines or the combination vaccine is indicated. (See Section 4.2**.**)**.**

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Not applicable.

Aluminium hydroxide, aluminium phosphate, aminoacids for injection, formaldehyde, neomycin sulphate, 2-phenoxyethanol, polysorbate 20, sodium chloride, residual tris and phosphate buffer and water for injection.

6.2 Incompatibilities

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

6.3 Shelf-life

The expiry date of the vaccine is indicated on the label and packaging.

Shelf-life is **36** months when stored at +2°C to +8°C.

6.4 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.

6.5 Nature and contents of container

Twinrix Adult is presented in a glass prefilled syringe.
The prefilled syringes are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.

The content upon storage may present a fine white deposit with a clear colourless supernatant. Once shaken, the vaccine is slightly opaque.

6.6 Instructions for use, handling and disposal (if appropriate)

The vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. Before use of Twinrix Adult, the vaccine should be well shaken to obtain a slightly opaque, white suspension. Discard if the content appears otherwise.

7. Marketing Authorisation Holder

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Telex: 63251 SB BIO B

8. Marketing Authorisation Number

EU/1/96 /020/001 pack of 1 prefilled syringe and EU 1/96/020/002 packs 10 prefilled syringes are held by SmithKline Beecham Biologicals S.A., Rixensart, Belgium.

9. Date of First Authorisation/Renewal of the Authorisation

20 September 1996

10. Date of Revision of the Text

12 January 1999

LEGAL CATEGORY: POM.

Any queries should be addressed to the Medical Information Department at the address below.

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