

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Twinrix Adult, suspension for injection in pre-filled syringe
Hepatitis A (inactivated) and hepatitis B (rDNA) (HAB) vaccine (adsorbed).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (1 ml) contains:

| | |
|--|-----------------|
| Hepatitis A virus (inactivated) ^{1,2} | 720 ELISA Units |
| Hepatitis B surface antigen ^{3,4} | 20 micrograms |

¹Produced on human diploid (MRC-5) cells

²Adsorbed on aluminium hydroxide, hydrated 0.05 milligrams Al³⁺

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

⁴Adsorbed on aluminium phosphate 0.4 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 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.

- Primary vaccination schedule

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 up to 20 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.

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 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.

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 Adult 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 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 postexposure 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.

Obesity (defined as BMI ≥ 30 kg/m²) has been observed to reduce the immune response to hepatitis A vaccines. A number of factors have been observed to reduce the immune response to hepatitis B vaccines. These factors include older age, male gender, obesity, smoking, route of administration, and some chronic underlying diseases. Consideration should be given to serological testing of those subjects who may be at risk of not achieving seroprotection following a complete course of Twinrix Adult. Additional doses may need to be considered for persons who do not respond or have a sub-optimal response to a course of vaccinations.

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.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

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 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

The effect of Twinrix Adult 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 Adult 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 Adult 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 Adult is excreted in human breast milk. The excretion of Twinrix Adult in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Twinrix Adult should be made taking into account the benefit of breast-feeding to the child and the benefit of Twinrix Adult therapy to the woman.

4.7 Effects on ability to drive and use machines

Twinrix Adult 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 a pooled analysis of events per dose from more than 6,000 subjects who received either the standard 0, 1, 6 month schedule (n=5,683) or the accelerated 0, 7, 21 days schedule (n=320). The most commonly reported adverse reactions following Twinrix Adult administration with the standard 0, 1, 6 month schedule are pain and redness occurring in a per dose frequency of 37.6% and 17.0% respectively.

In the two clinical trials in which Twinrix Adult was administered at 0, 7, 21 days, overall solicited general and local symptoms were reported with the same categories of frequency as defined below. After a fourth dose given at month 12, the incidence of systemic and local adverse reactions was comparable to that seen after vaccination at 0, 7, 21 days.

In comparative studies, 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.

Tabulated list of adverse reactions

Frequencies are reported as:

| | |
|--------------|-------------------------|
| Very common: | ≥ 1/10 |
| Common: | ≥ 1/100 to < 1/10 |
| Uncommon: | ≥ 1/1,000 to < 1/100 |
| Rare: | ≥ 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 | Rare | Decreased appetite |
| Nervous system disorders | Very common | Headache |
| | Uncommon | Dizziness |
| | Rare | Hypoaesthesia, paraesthesia |
| Vascular disorders | Rare | Hypotension |
| Gastrointestinal disorders | Common | Gastrointestinal symptoms, diarrhoea, nausea |
| | Uncommon | Vomiting, abdominal pain* |
| 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 reactions (such as haematoma, pruritus and bruising), malaise |
| | Uncommon | Fever (≥ 37.5°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 paediatric 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 HPRAs Pharmacovigilance, Website: www.hpra.ie.

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 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 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 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, 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.

The 0, 7 and 21 day primary schedule plus a fourth dose at month 12 is for use in exceptional circumstances in adults. In a clinical trial where Twinrix Adult was administered according to this schedule, 82% and 85% of vaccinees had seroprotective levels of anti-HBV antibodies at 1 and 5 weeks respectively following the third dose (i.e. at months 1 and 2 after the initial dose). The seroprotection rate against hepatitis B increased to 95.1% by three months after the first dose.

Seropositivity rates for anti-HAV antibodies were 100%, 99.5% and 100% at months 1, 2 and 3 after the initial dose. One month after the fourth dose, all vaccinees demonstrated seroprotective levels of anti-HBs antibodies and were seropositive for anti-HAV antibodies.

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 of Twinrix Adult following a 0, 1, 6 months schedule were compared with the seropositivity and seroprotection rates of monovalent hepatitis A and B vaccines when administered in opposite arms.

The seroprotection rate against hepatitis B after the administration of Twinrix Adult was 92% and 56% at 7 and 48 months respectively, versus 80% and 43% after the GlaxoSmithKline Biologicals monovalent 20µg hepatitis B vaccine, and 71% and 31% after another licensed monovalent 10µg hepatitis B vaccine. Anti-HBs antibody concentrations decreased as age and body mass index increased; they were also lower in male than in female subjects.

The seropositivity rate for anti-HAV antibodies after Twinrix Adult was 97% at both 7 and 48 months versus 99% and 93% after the GlaxoSmithKline Biologicals monovalent hepatitis A vaccine and 99% and 97% after another licensed monovalent hepatitis A vaccine.

Subjects received an additional dose of the same vaccine(s) 48 months after the first dose of the primary vaccination course. One month after this dose, 95% of the subjects vaccinated with Twinrix Adult achieved seroprotective levels of anti-HBV antibodies (≥ 10 mIU/ml).

In two long-term clinical studies conducted in adults aged 17 years to 43 years, respectively 18 and 25 subjects had evaluable tests 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.

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

1 ml of suspension in a pre-filled syringe (type I glass) with a plunger stopper (rubber butyl).
Pack sizes of 1, 10 and 25 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/1/96/020/001
EU/1/96/020/002

EU/1/96/020/003
EU/1/96/020/007
EU/1/96/020/008
EU/1/96/020/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 1996
Date of latest renewal: 28 August 2006

10. DATE OF REVISION OF THE TEXT

26/03/2020

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