

DATA SHEET

Name of Medicinal Product

TWINRIX and TWINRIX JUNIOR

Inactivated hepatitis A and recombinant DNA hepatitis B vaccine

Presentation

TWINRIX and TWINRIX JUNIOR are combined vaccines 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.

A 1.0 mL dose of TWINRIX contains not less than 720 ELISA units of inactivated HA virus, and 20 µg of recombinant HBsAg protein.

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.

The vaccine preparations also contain phenoxyethanol as a preservative.

Therapeutic indications

TWINRIX is indicated for active immunisation against hepatitis A and hepatitis B virus infection in adults.

TWINRIX is indicated in, but not limited to, the following groups of susceptible subjects at risk of acquiring hepatitis A and hepatitis B virus infection:

- Healthcare personnel
- Patients frequently receiving blood products
- Personnel and residents of institutions
- Persons at increased risk due to their sexual behaviour
- Illicit users of addictive injectable drugs
- Travellers to areas of high HAV and HBV endemicity
- Persons originating from areas of high HAV and HBV endemicity
- Organ transplant candidates
- Armed forces personnel
- Persons who may be exposed to HAV and HBV through their work or lifestyle
- Household contacts of any persons in the above groups, or of patients with acute or chronic HBV infection

TWINRIX and TWINRIX JUNIOR are indicated for active immunisation against hepatitis A and hepatitis B virus infection in infants, children and adolescents from 1 year up to and including 15 years of age at risk of, or who wish to be protected against, both infections.

Where rapid protection against hepatitis B is required in individuals 1 to 15 years, TWINRIX JUNIOR, 0.5 mL (360/10) in a three dose regimen should be used.

As hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection, it can be expected that hepatitis D will also be prevented by vaccination with TWINRIX. The vaccine will not protect against infection caused by hepatitis C or hepatitis E viruses, or other pathogens known to infect the liver.

Posology and method of administration

The vaccine is a ready-to-use suspension. It must be shaken well before use, since upon storage, the vaccine settles down as a fine white deposit with a clear colourless supernatant. After shaking the vaccine is a slightly opaque, white suspension. 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, discard the vaccine.

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

Dosage

TWINRIX and TWINRIX JUNIOR should be injected intramuscularly into the deltoid region of the upper arm in adults and older children. The antero-lateral aspect of the thigh may be used in infants. The vaccines should not be administered intramuscularly in the gluteal region or subcutaneously/intradermally since administration by these routes may result in a less than optimal antibody response.

Exceptionally, the vaccine may be administered subcutaneously in patients with thrombocytopenia or bleeding disorders (e.g. haemophiliacs).

Vaccine Schedule

In those not previously exposed to the hepatitis A or hepatitis B viruses the course is as follows:

TWINRIX, 1 mL (720/20)

Schedule (Course completed in)	Age	Total doses to complete course	Timing:
Standard (6 months)	1-15 years inclusive	2 doses	0, 6 to 12 months
Standard (6 months)	16 years and over	3 doses	0, 1 month, 6 months
Rapid (21 days + 12 months)	16 years and over	4 doses	0, 7 days, 21 days, 12 months

Rapid Schedule. 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, 21 days may be used. When this schedule is applied, a fourth dose is recommended 12 months after the first dose.

TWINRIX Junior, 0.5 mL (360/10)

In circumstances where a child is at immediate risk of exposure to hepatitis B (e.g. travellers), and did not receive a primary course of hepatitis B vaccine as an infant, TWINRIX Junior should be used as follows:

TWINRIX Junior, 0.5 mL (360/10)

Schedule (Course completed in)	Age	Total doses to complete course	Timing:
Standard (6 months)	1-15 years inclusive	3 doses	0, 1 month, 6 months

Booster dose

Long term antibody persistence data following vaccination with TWINRIX or TWINRIX JUNIOR are available up to 15 years and 10 years respectively, after vaccination. 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. The kinetics of antibody decline are also similar. 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 course has not been established. Local recommendations should be followed. For some categories of individuals 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 insured by immunological memory. Guidelines for boosting are based on the assumption that antibodies are required for protection; anti-HAV antibodies have been predicted to persist for at least 10 years.

In situations where a booster dose of both hepatitis A and Hepatitis B are desired, TWINRIX or TWINRIX JUNIOR can be given. Alternatively, subjects primed with TWINRIX or TWINRIX JUNIOR may be administered a booster dose of either of the monovalent vaccines.

Contraindications

TWINRIX and 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 Adult or the monovalent hepatitis A or hepatitis B vaccine.

Special warnings and special precautions for use

As with other vaccines, the administration of TWINRIX and 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 and 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 and TWINRIX JUNIOR 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.

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 and Twinrix Junior should under no circumstances be administered intravenously.

Interaction with other medicaments and other forms of interaction

No data on concomitant administration of TWINRIX and 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.

In one study on sixty children aged 18 months, it has been demonstrated that TWINRIX does not interfere with the response to diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis and *haemophilus influenzae* type b vaccine (DTPa-IPV/Hib) when used following DTPw-IPV as a primary series in infants. It has also been demonstrated that DTPa-IPV/Hib does not interfere with the response to TWINRIX when that response is measured after dose 2. TWINRIX was given at a different injection site to the other vaccine.

In another study on 57 children aged 12-15 months, it has been demonstrated that TWINRIX does not interfere with the response to measles, mumps and rubella vaccine. It has also been demonstrated that measles, mumps and rubella vaccine does not interfere with the response to TWINRIX when that response is measured after dose 2. TWINRIX was given at a different injection site to the other vaccine.

TWINRIX JUNIOR can be given concomitantly with Human Papillomavirus (HPV) vaccine.

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 JUNIOR alone.

Although the concomitant administration of TWINRIX and TWINRIX JUNIOR 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

TWINRIX 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 on embryo-foetal, peri-natal and post-natal survival and development has not been prospectively evaluated in clinical trials.

The effect of TWINRIX 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.

Adequate human data on use during lactation and adequate animal reproduction studies are not available. TWINRIX should therefore be used with caution in breastfeeding women.

Effects on ability to drive and use machines

The vaccines are unlikely to produce an effect on the ability to drive and use machines.

Undesirable effects

The safety profile presented below with TWINRIX 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.

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

Frequencies per dose are defined as follows:

Very common: $\geq 1/10$

Common: $\geq 1/100$ and $< 1/10$

Uncommon: $\geq 1/1000$ and $< 1/100$

Rare: $\geq 1/10000$ and $< 1/1000$

Very rare: $< 1/10000$

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 ($\geq 37.5^{\circ}\text{C}$); *Rare:* influenza like illness, chills

In a clinical trial where TWINRIX 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.

The safety profile presented below with TWINRIX JUNIOR is based on data from approximately 800 subjects:

* Refers to adverse reactions observed in clinical trials performed with TWINRIX in children and adolescents

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 ($\geq 37.5^{\circ}\text{C}$); *Very rare:* influenza like illness*, chills*

During post-marketing surveillance, the following adverse reactions have been reported with either TWINRIX or with 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, stinging and burning sensation

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.

Pharmacological properties

Pharmacodynamic properties

TWINRIX and TWINRIX JUNIOR confer immunity against HAV and HBV infection by inducing specific anti-HAV and anti-HBs antibodies.

Adults:

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.

For use in adults, the 0, 7, 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 20µg hepatitis B vaccine, and 71% and 27% after another licensed monovalent 10µg 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.

Children (1 to 15 years):

Protection against hepatitis A and hepatitis B develops within 2-4 weeks. In the clinical studies using TWINRIX Junior, 0.5 mL (360/10), 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 67% of the subjects after the first dose and 100% after the third dose.

In the clinical studies using TWINRIX, 1 mL (720/20) in a 2-dose schedule in children, specific humoral antibodies against hepatitis A were observed in approximately 99% of the subjects one month after the first dose and in 100% one month after the second dose given at month 6 (i.e. month 7). Specific humoral antibodies against hepatitis B were observed in approximately 74% of the subjects after the first dose and 100% after the second dose. The anti-HBs seroprotection rates (titres ≥ 10 IU/L) at these time points were 37.4% and 98.2% respectively.

When the second dose was administered at month 12, seropositivity rates for anti-HAV were 99.0% and seropositivity rates for anti-HBs were 99.0% at month 13 with seroprotection rates of 97.0%.

Antibody Persistence

In two long term clinical studies conducted in adults, 15 years after the primary vaccination with Twinrix Adult the anti-HAV seropositivity rates were 100% in both studies and the anti-HBs seroprotection rates were 89.3% and 92.9%, respectively (n=56). In a long term clinical trial, persistence of anti-HAV and anti-HBs antibodies has been demonstrated up to 10 years following the initiation of a primary vaccination course of TWINRIX JUNIOR, 0.5 mL (360/10) in the majority of vaccinees. After 10 years, anti-HAV seropositivity rate and anti-HBs seroprotection rate were 100% and 85% respectively. The kinetics of antibody decline of anti-HAV and anti-HBs antibodies following use of TWINRIX or TWINRIX JUNIOR were shown to be similar to those of the monovalent vaccines.

Anti-HAV and anti-HBs antibodies have been shown to persist for at least 24 months following the initiation of a 0, 6 month schedule of TWINRIX, 1 mL (720/20) in children.

Seropositivity rates were of 100% and 94.2% respectively for anti-HAV and anti-HBs antibodies at month 24. The seroprotection rate for anti-HBs at this time point was 93.3%. In this study, the immune response for both antigen components was comparable to that seen after a 3-dose regimen of TWINRIX Junior, 0.5 mL (360/10). The persistence of anti-HAV and anti-HBs antibodies at month 24 was shown to be similar following a 0, 6 month or a 0, 12 month schedule.

Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

Preclinical safety data

Not applicable.

Pharmaceutical particulars

Special precautions for storage

TWINRIX and TWINRIX JUNIOR must be stored between +2°C to +8°C. DO NOT FREEZE; freezing destroys the potency of the product. Discard the vaccine if it has been frozen.

Shelf life

The expiry date of the vaccine is indicated on the label and packaging. The shelf life of TWINRIX and TWINRIX JUNIOR is 36 months from the date of manufacture at a temperature of +2°C to +8°C.

Medicine Classification

Prescription Medicine.

Package Quantities

TWINRIX and TWINRIX JUNIOR:
Prefilled syringes in packs of 1.

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