

TWINRIX® (720/20) and TWINRIX® JUNIOR (360/10) PRODUCT INFORMATION

(Combined Hepatitis A and Hepatitis B vaccine)

DESCRIPTION

TWINRIX is a non-infectious combination vaccine containing hepatitis A virus antigen and hepatitis B surface antigen (rys). TWINRIX is a sterile suspension.

Each 1 mL dose of TWINRIX contains 720 ELISA units of hepatitis A virus antigen and 20 micrograms of hepatitis B surface antigen (rys). The viral antigens are adsorbed on 0.45mg aluminium in the form of aluminium phosphate and aluminium hydroxide and suspended in a normal saline solution.

Each 0.5 mL dose of TWINRIX Junior contains 360 ELISA units of hepatitis A virus antigen and 10 micrograms of hepatitis B surface antigen (rys). The viral antigens are adsorbed on 0.225mg aluminium in the form of aluminium phosphate and aluminium hydroxide and suspended in a normal saline solution.

The vaccine preparation also contains 2-phenoxyethanol as a preservative, amino acid supplement, neomycin sulphate (<20ng/mL), polysorbate 20 and residual amounts of phosphate buffer and trometamol. Residual formaldehyde in the vaccine is not more than 0.01%.

TWINRIX is formulated using the HM 175 strain of hepatitis A grown in human cell culture (MRC5), and inactivated with formaldehyde. The hepatitis B surface antigen (rys) component is produced by culturing genetically-engineered *Saccharomyces cerevisiae* yeast cells (Baker's yeast), which carry the relevant gene of an adw subtype, of the surface antigen of the hepatitis B virus. Both the hepatitis A virus antigen and hepatitis B surface antigen (rys) are purified by several physico-chemical steps, and formulated as separate antigen suspensions adsorbed onto aluminium salts. TWINRIX is produced by pooling bulk preparations of the purified antigens. The bulk hepatitis A virus antigen and hepatitis B surface antigen (rys) preparations are identical to those used in the manufacture of the currently licensed monovalent hepatitis A (Havrix) and hepatitis B (Engerix-B) vaccines. Standardised fermentation and purification procedures ensure batch to batch consistency. The vaccines are free of association with human blood or blood products.

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

TWINRIX meets the World Health Organization requirements for the manufacture of biological substances.

CLINICAL PHARMACOLOGY

TWINRIX induces the production of specific anti-HAV and anti-HBs antibodies, which confer immunity against HAV and HBV infection.

Adults – Standard schedule

The immunogenicity of TWINRIX (720/20) has been investigated using a 0, 1 and 6 month vaccination schedule in randomised clinical studies involving over 700 adult volunteers.

Specific humoral antibodies (seropositivity) against HAV were elicited in:

- 97-100% of vaccinees one month after the second dose
- 100% of vaccinees one month after the third dose.

Seropositivity was defined as anti-HAV antibody titres ≥ 33 IU/L.

Seroprotective levels of anti-HBs antibodies (titers ≥ 10 IU/L) were elicited in:

- 83.9% of vaccinees one month after the second dose
- 99.3% of vaccinees one month after the third dose.

An anti-HBs antibody titre above 10 IU/L correlates with protection against hepatitis B infection.

Adults- Rapid Schedule

The immunogenicity of TWINRIX (720/20) has also been investigated using a 0, 7, 21 day primary schedule plus a fourth dose at month 12 in a randomised clinical study involving over 400 adult volunteers, of whom 239 received TWINRIX (720/20).

Specific humoral antibodies (seropositivity) against HAV were elicited in:

- 100% of vaccinees one week after the third dose
- 99.5% of vaccinees five weeks after the third dose
- 100% of vaccinees one month after the fourth dose.

Seroprotective levels of anti-HBs antibodies (titers ≥ 10 IU/L) were elicited in:

- 82% of vaccinees one week after the third dose
- 85% of vaccinees five weeks after the third dose
- 100% of vaccinees one month after the fourth dose.

Children

The immunogenicity of TWINRIX (720/20) has been investigated using a 0 and 6 month vaccination schedule in randomised clinical studies involving 451 subjects aged 1 to 15 years old.

Specific humoral antibodies (seropositivity) against HAV were elicited in:

- 99.1% of vaccinees one month after the first dose
- 100% of vaccinees one month after the second dose.

Seroprotective levels of anti-HBs antibodies (titers ≥ 10 IU/L) were elicited in:

- 37.4% of vaccinees one month after the first dose
- 70.5% of vaccinees 6 months after the first dose
- 98.2% of vaccinees one month after the second dose.

In a clinical study involving 117 subjects who received the second dose at month 12, specific humoral antibodies (seropositivity) against HAV were elicited in 99.0% of vaccinees one month after the second dose, and seroprotective levels of anti-HBs were induced in 97.0% of subjects.

The immunogenicity of TWINRIX Junior (360/10) has been investigated using a 0, 1 and 6 month vaccination schedule in randomised clinical studies involving 168 children: 54 subjects aged 1 to 6 years and 114 subjects aged 6 to 15 years.

Specific humoral antibodies (seropositivity) against HAV were elicited in:

- 100% of vaccinees one month after the second dose
- 100% of vaccinees one month after the third dose.

Seroprotective levels of anti-HBs antibodies (titers ≥ 10 IU/L) were elicited in:

- 86.2% to 94.6% of vaccinees one month after the second dose
- 100% of vaccinees one month after the third dose.

In a comparative study in children and adolescents, TWINRIX (720/20) following a 0 and 6 month schedule was proven to be non-inferior for both hepatitis A and B antibody responses to TWINRIX Junior (360/10) following a 0, 1 and 6 month schedule. However, seroprotection rates for hepatitis B at month 2 after two doses of TWINRIX Junior (given one month apart) were higher (85.6%) than after a single dose of TWINRIX (38.0%).

Antibody Persistence

In two long term clinical studies conducted in healthy adults, persistence of anti-HAV and anti-HBs antibodies have been demonstrated up to 5 years following the initiation of a 0, 1, 6 month primary vaccination schedule of TWINRIX (720/20) in 100% and at least 97% of vaccinees, respectively. In a long term clinical study using TWINRIX Junior (360/10), persistence of anti-HAV and anti-HBs antibodies have been demonstrated up to 4 years following the initiation of a 0, 1, 6 month primary

vaccination schedule of TWINRIX Junior (360/10) in 100% of vaccinees. For both vaccines, the anti-HAV and anti-HBs antibody titres are in the range seen following vaccination with the monovalent hepatitis A (Havrix) and hepatitis B (Engerix-B) vaccines. The kinetics of antibody decline are also similar.

In a clinical study conducted in subjects over 40 years of age, the seroprotection rate against hepatitis B of Twinrix Adult following a 0, 1, 6 months schedule were compared with the seroprotection rates of monovalent hepatitis B vaccines.

The seroprotection rate against hepatitis B after the administration of bivalent Twinrix Adult was 91.7% and 87.5% at 7 and 12 months respectively, compared to the 79.7% and 73.8% after administration of monovalent hepatitis B vaccine 20 µg. Administration of another licensed monovalent hepatitis B vaccine 10 µg showed 71.0% and 56.4% seroprotection at 7 and 12 months respectively.

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 (720/20) in children. Specific humoral antibodies (seropositivity) against HAV were elicited in 100% of vaccinees at month 24, and anti-HBs seroprotective levels were present in 93.3% of subjects. In this study, the immune response for both antigen components was comparable to that seen after a 3-dose regimen of TWINRIX Junior (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 of TWINRIX (720/20) in children.

Hepatitis D

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.

INDICATIONS

TWINRIX (720/20) is indicated for active immunisation against hepatitis A and hepatitis B virus infection in adults and children from 1 year of age. TWINRIX Junior (360/10) is indicated for use in children aged 1 to 15 years.

Immunisation against hepatitis A is recommended in the following individuals:

Travellers: Persons travelling to areas of intermediate or high endemicity for hepatitis A. This includes all developing countries.

Armed Forces: Armed forces personnel who travel to higher endemicity areas or to areas where hygiene is poor, have an increased risk of HAV infection.

Persons for whom hepatitis A is an occupational hazard or for whom there is an increased risk of transmission. These include:

- employees in day-care centres particularly in situations where children have not been toilet trained
- teachers and other close contacts of the intellectually disabled
- staff and residents of residential facilities for the intellectually disabled
- healthcare workers and teachers in remote Aboriginal and Torres Strait Islander communities
- nursing staff and other healthcare workers in contact with patients in paediatric wards, infectious diseases wards, emergency rooms and intensive care units
- sewerage workers
- food handlers, since food hygiene procedures and food processing methods are not always adequate to protect from contamination from food handlers

Homosexual men: Increased incidence of hepatitis A infection among homosexual males suggests that the disease may be sexually transmitted in this group.

Contacts of infected persons: Since virus shedding from infected persons may occur for a prolonged period, active immunisation of close contacts is recommended. The use of vaccine in outbreak control has been shown to be more effective than the use of immunoglobulin.

Specific population groups known to have a higher incidence of hepatitis A: eg. Australian Aboriginals, those in settings with recognised community-wide HAV epidemics.

Individuals with chronic liver disease and recipients of liver transplants, as hepatitis A infections is likely to be more severe in these groups. Many injecting drug users will have pre-existing liver disease from hepatitis B or hepatitis C infection.

Recipients of blood products, such as Factor VIII concentrates.

Immunisation against hepatitis B is recommended in the following individuals:

Persons for whom hepatitis B is an occupational hazard or for whom there is an increased risk of transmission. These include:

- healthcare workers directly involved in patient care, or in the handling of human blood or tissue
- embalmers

- staff and residents of residential facilities for the intellectually disabled
- inmates of long term correctional facilities and staff of correctional facilities

Individuals with chronic liver disease and/or hepatitis C.

Haemodialysis patients and recipients of certain blood products such as Factor VIII concentrates.

Sexually active homosexual men and persons with multiple sexual partners : e.g. clients of STD (sexually transmitted disease) clinics. Sexual risk occurs in susceptible (anti-HBs negative) partners of HBV carriers and patients with acute hepatitis B.

Abusers of injectable drugs.

Close residential contacts of deinstitutionalised intellectually disabled individuals who are HBV carriers.

Household contacts of patients with acute hepatitis B and chronic hepatitis B carriers.

Others in whom vaccination against hepatitis B might be justified

Police and members of the armed forces

Travellers to areas of high endemicity for hepatitis B

Participants in contact sports

CONTRAINDICATIONS

TWINRIX should not be administered to subjects with known hypersensitivity to any component of the vaccine (eg neomycin sulphate), or to subjects having shown signs of hypersensitivity after previous administration of these combined vaccines or the monovalent hepatitis A or hepatitis B vaccines.

As for any vaccine, TWINRIX should not be administered to subjects suffering from acute severe febrile illness. However, the presence of minor infection does not contraindicate vaccination.

WARNINGS AND PRECAUTIONS

TWINRIX should never be administered intravenously.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of anaphylactic reactions following the administration of the vaccine.

TWINRIX should not be routinely administered in the gluteal region, intradermally, or subcutaneously since these routes of administration may not result in an optimum immune response.

TWINRIX should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.

In elderly subjects, haemodialysis patients and persons with an impaired immune system, adequate anti-HAV and anti-HBs antibody titres may not be obtained after a primary vaccination course. The monitoring of antibody titres and if appropriate the need for additional doses of the appropriate vaccine should be considered in such patients. The rapid schedule has not been studied and is not recommended in such patients.

Caution should be exercised in administering TWINRIX to patients in whom a systemic reaction due to the vaccine may pose a significant risk eg. in patients with severely compromised cardiopulmonary function.

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 will prevent hepatitis A and hepatitis B in such cases. These vaccines will not induce the production of anti-HBs antibodies in hepatitis B carriers.

The vaccines will not protect against infection caused by hepatitis C or hepatitis E viruses, or other pathogens known to infect the liver.

Use in Pregnancy (Category B2)

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 a study in rats. There were no direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development, at 1/5 the adult human dose (9 times greater than the clinical adult exposure based on mg/m²).

Use in Lactation

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

Use in impaired renal function

See WARNINGS AND PRECAUTIONS statement regarding use in haemodialysis patients.

Interactions

Clinical studies have demonstrated that TWINRIX can be administered concomitantly with diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b and measles-mumps-rubella vaccines. In these trials, the injectable vaccines were given at a different injection site to TWINRIX.

The concomitant administration of TWINRIX with other vaccines (e.g. pneumococcal, influenza) given at separate sites using separate syringes has not been specifically studied.

TWINRIX must not be mixed with other vaccines in the same syringe.

As with other vaccines, it may be expected that patients receiving immunosuppressive therapy or patients with an immunodeficiency, may not achieve an adequate immune response. (see WARNINGS AND PRECAUTIONS)

Concomitant administration of Normal Human Immunoglobulin with the first dose of hepatitis A vaccine does not influence the seroconversion rate, but may result in a relatively lower anti-HAV antibody titre than when the primary course of vaccine is given alone. TWINRIX and Normal Human Immunoglobulin should be administered at separate injection sites.

ADVERSE REACTIONS

Clinical Trial Data

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 of TWINRIX (720/20).

Events are listed within body systems and categorised by frequency according to the following definitions:

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

Gastrointestinal disorders: *Common:* gastrointestinal symptoms (such as diarrhoea, nausea, vomiting)

General disorders and administration site conditions: *Very common:* pain and redness at the injection site, fatigue; *Common:* injection site reaction, malaise, swelling at the injection site; *Uncommon:* fever ($\geq 37.5^{\circ}\text{C}$); *Rare:* influenza like illness, chills

Infections and infestations: *Common:* Viral infection; *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

Skin and subcutaneous tissue disorders: *Rare:* rash, pruritus; *Very rare:* urticaria

Musculoskeletal and connective tissue disorders: *Uncommon:* myalgia; *Rare:* arthralgia

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.

During clinical studies with TWINRIX Junior (360/10) (n=538 doses of vaccines administered) the frequency of local reactions in children, although still considered common, were almost half that reported with TWINRIX (720/20) in adults. Of the general reactions reported in these children, most were reported at a similar frequency to TWINRIX (720/20) in adults except upper respiratory tract infection, fever and vomiting which were commonly reported at frequencies of 9.3%, 3.7% and 1.9% respectively.

Other adverse events observed in clinical trials performed with TWINRIX Junior include:

Blood and lymphatic system disorders: *Rare:* lymphadenopathy

Metabolism and nutrition disorders: *Common:* appetite lost

General disorders and administration site conditions: *Very common:* pain and redness at the injection site; *Common:* irritability, swelling at the injection site, injection site reaction, fatigue, malaise, fever ($\geq 37.5^{\circ}\text{C}$)

Nervous system disorders: *Common:* drowsiness, headache; *Rare:* dizziness

Gastrointestinal disorders: *Common:* gastrointestinal symptoms (such as nausea, vomiting)

Skin and subcutaneous tissue disorders: *Uncommon:* rash; *Rare:* urticaria

In a comparative trial in children and adolescents, (n = 745 doses) the percentage of subjects reporting solicited adverse events after a primary course of TWINRIX (720/20) used in a two dose schedule was similar to that seen with TWINRIX Junior (360/10) given in a 3 dose schedule. Pain was reported in 50.7% of the Twinrix (720/20) group and in 39.1% of the TWINRIX Junior (360/10)

group. Incidence of redness was 16.1% and 11.9% and swelling was reported in 4.4% and 4.9% in the TWINRIX and TWINRIX Junior groups respectively.

General reactions solicited in controlled clinical trials that may occur in temporal association with TWINRIX used in a two dose schedule in children and adolescents include:

General disorders and administration site conditions: *Very rare:* influenza like illness, chills

Nervous system disorders: *Very rare:* hypoaesthesia, paraesthesia

Gastrointestinal disorders: *Common:* gastrointestinal symptoms (such as diarrhoea)

Musculoskeletal and connective tissue disorders: *Very rare:* myalgia, arthralgia

Skin and subcutaneous tissue disorders: *Very rare:* pruritus

Vascular disorders: *Very rare:* hypotension

Post Marketing Experience

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

DOSAGE AND 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. Discard if the contents of the vial appear otherwise. All parenteral drug and vaccine products should be inspected visually prior to administration for discolouration or particulate matter. Each dose of TWINRIX is for single use only. Any residual vaccine must be discarded.

TWINRIX 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.

Exceptionally, the vaccine may be administered subcutaneously in patients with thrombocytopenia or bleeding disorders (eg. haemophiliacs). (see WARNINGS AND PRECAUTIONS)

TWINRIX MUST NOT BE GIVEN INTRAVENOUSLY.

IMMUNISATION SCHEDULE

TWINRIX (720/20)

In children and adults not previously exposed to hepatitis A or hepatitis B viruses or vaccines the primary course of TWINRIX is as follows:

TWINRIX (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

The rapid schedule is used in exceptional circumstances in adults when more rapid protection is required, eg. in travellers commencing vaccination within one month or more of departure. When this rapid schedule is used, a fourth dose is recommended 12 months after the first dose to ensure adequate protection, as lower seroprotection rates against hepatitis B were observed after the third dose as compared to the standard 0, 1, 6 month schedule (See CLINICAL PHARMACOLOGY).

TWINRIX Junior (360/10)

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

TWINRIX Junior (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 clinical studies have demonstrated persistence of anti-HAV and anti-HBs antibodies 5 years after immunisation with TWINRIX (720/20) and 4 years after immunisation with TWINRIX Junior (360/10). As persistence of antibodies and kinetics of antibody decline were similar to those following the monovalent vaccines, general guidelines for booster vaccination can therefore be drawn from those for the monovalent vaccines.

Hepatitis B. The National Health and Medical Research Council recommends that booster doses against hepatitis B are not required in immunocompetent individuals, since there is good evidence that a completed primary course of hepatitis B vaccination provides long lasting protection in these individuals. This applies to adults, children and all subgroups (such as health care workers). However, booster doses are recommended for immunosuppressed individuals, for people living with HIV infection or with renal failure. The timing for boosting in these individuals should be decided by regular monitoring of hepatitis B antibody levels at six to twelve monthly intervals. (Source: *The Australian Immunisation Handbook, 7th edition, NHMRC*).

Hepatitis A. Data available from clinical studies using hepatitis A vaccine (Havrix) show persistence of antibodies after 8 years which is consistent with a projected 20 years persistence (based on mathematical calculations). Further long term follow-up of immunised cohorts will be required to determine the duration of protection following hepatitis A immunisation and whether and when booster doses may be required.

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

OVERDOSAGE

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

STORAGE

TWINRIX 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.

The shelf-life of TWINRIX is three years from the date of manufacture at temperatures between +2°C to +8°C. The expiry date of the vaccine is marked on the label and packaging.

PRESENTATIONS

TWINRIX and TWINRIX Junior are available as a monodose vial in packs of one or ten and as a pre-filled syringe in packs of one or ten.

The vials and pre-filled syringes are made of neutral glass type 1, which conforms to European Pharmacopoeia requirements.

MANUFACTURER

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Date of TGA Approval: 11 May 2009

Issue No. 9