

Product Monograph

TWINRIX[®]

Combined hepatitis A and hepatitis B vaccine

Suspension for Injection

Active Immunizing Agent

Against Infection by Hepatitis A and Hepatitis B virus

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TWINRIX®

Combined hepatitis A and hepatitis B vaccine Suspension for Injection

Clinical Pharmacology

TWINRIX® (combined hepatitis A and hepatitis B vaccine) confers immunity against HAV and HBV infection by inducing specific anti-HAV and anti-HBs antibodies.

Data has been obtained from clinical studies involving over 980 adults, adolescents, children and infants using the standard 3 dose vaccination schedule with Twinrix® and Twinrix® Junior respectively, and a total of 819 children and adolescents aged 1-15 years of age using the alternate 2 dose vaccination schedule with Twinrix.

Twinrix in Adults

Standard Vaccination Schedule (3 doses at 0, 1, 6 months)

(720 ELISA units HAV/ 20µg HBV per 1mL dose)

Anti-HAV response

In clinical studies involving subjects 18 -50 years of age, specific humoral antibodies against HAV were detected in more than 88% of vaccinees at day 15 and 99% of vaccinees one month after the second dose. One month after the third dose, 100% of subjects were anti-HAV sero-positive.

Anti-HBV response

The seroconversion rate one month after the second dose of vaccine was more than 96.5% in adult subjects. At month 7, one month after dose 3, seroprotection

was close to 100%.

Rapid Dosing Schedule (4 doses at 0,7, and 21 days and booster at 12 months)

(720 ELISA units HAV/ 20µg HBV per 1 mL dose)

Anti-HAV response

In a clinical trial comparing Twinrix® at the 0, 7, 21 day primary schedule to the monovalent vaccines administered concomitantly (currently marketed Engerix-B® and Havrix® 1440), seropositivity rates for anti-HAV antibodies were 100% and 99.5% at 1 and 5 weeks respectively after the third dose, and reached 100% one month after the fourth dose.

Anti-HBV response

Twinrix given according to the 0, 7, 21 day primary schedule, resulted in 82% and 85% of vaccinees having seroprotective levels of anti-HBV antibodies at 1 and 5 weeks respectively following the third dose in adults. One month after the fourth dose, all vaccinees demonstrated seroprotective levels of anti-HBs antibodies.

Anti-HAV response and Anti-HBV response

After the fourth dose of the rapid schedule, the immune response to both antigen components was comparable to that seen after completion of the currently marketed schedule of Twinrix (0, 1, 6 months).

No statistically significant differences in anti-HAV seropositivity or anti-HBs seroprotection rates were observed at any time point between the two cohorts receiving either Twinrix or the monovalent vaccines.

Twinrix Junior in Pediatrics

Standard Vaccination Schedule (3 doses at 0, 1, 6 months)

(360 ELISA units HAV/ 10 μ g HBV per 0.5mL dose)

Anti-HAV response

In clinical studies involving subjects 1-18 years of age, specific humoral antibodies against HAV were detected in more than 93% of the vaccinees at day 15, and 100% of vaccinees one month following vaccination with the 3 dose schedule.

Anti-HBV response

The seroconversion rate one month after the second dose was > 98.0% in subjects aged 1-18 years of age. Immunogenicity of the vaccine was analyzed one month after the third vaccine dose. The seroprotection rate (>10 IU/L) for hepatitis B was 100%. An anti-HBs antibody titer above 10 IU/L correlates with protection to HBV infection.

Twinrix in Subjects aged 1-15 years

Alternate Vaccination Schedule (2 doses at 0 and 6 to 12 months)

(720 ELISA units HAV/ 20 μ g HBV per 1mL dose)

Anti-HAV response

In clinical trials using the alternate vaccination schedule subjects aged 1 to 15 years, demonstrated seropositivity rates for anti-HAV antibodies to be 99.1% one month after the first dose and 100% one month after the second dose (i.e. month 7) when given at month 6. When the second dose was administered at month 12, seropositivity rates for anti-HAV were 99.0% one month later (i.e. month 13).

Anti-HAV antibodies have been shown to persist for at least 24 months following the initiation of a 0, 6 month schedule of Twinrix (2 dose schedule).

Seropositivity rates were 100% for anti-HAV antibodies at month 24.

Anti-HBV response

For children and adolescents (1 to 15 years of age), using the alternate schedule, seropositivity rates for anti-HBs antibodies were shown to be 74.2% one month after the first dose and 100% one month after the second dose (i.e. month 7) when given at month 6. 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 with serology testing one month later (i.e. month 13), seropositivity rate for anti-HBs were 99.0%, with seroprotection rates of 97.0%.

Anti-HBs antibodies have been shown to persist for at least 24 months following the initiation of 0, 6 month schedule. Seropositivity rates were 94.2% for anti-HBs antibodies at month 24. The seroprotection rate for anti-HBs at this time point was 93.3%.

In this 2 dose study, the immune response to both antigen components was comparable to that seen after a 3-dose regimen of the combined vaccine containing 360 ELISA units of hepatitis A virus and 10 μ g of the hepatitis B surface antigen in a 0.5mL dose.

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.

Long term persistence:

Adults:

Protection against hepatitis A and hepatitis B develops within 2-4 weeks. In 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.

Two clinical studies conducted in adults demonstrated the persistence of anti-HAV and anti-HBs antibodies up to 60 months following the initiation of a primary vaccination course of Twinrix in the majority of vaccinees.

The seropositivity rates for anti-HAV and anti-HBs observed were 100% and 97.7% respectively at month 60, with a seroprotection rate of 93.2% for anti-HBs in one study.

All subjects were seropositive in the other study for both anti-HAV and anti-HBs antibodies at month 60, while 95.7% of vaccinees were seroprotected against hepatitis B.

Pediatrics:

In clinical studies of the pediatric population, specific humoral antibodies against hepatitis A were observed in approximately 89% of the subjects one month after the first dose, and in 100% after the third dose (i.e. month 7). Specific humoral antibodies against hepatitis B were observed in approximately 67% of the subjects after the first dose and 100% after the third dose.

In a long term clinical trial conducted in the pediatric population, persistence of anti-HAV and anti-HBs antibodies has been demonstrated up to 48 months following the course of vaccination in the majority of vaccinees.

From month 36 to month 48, the percentage of decrease in anti-HAV titers was generally similar in all studies when compared to the adult population titers. At month 48, the anti-HAV GMTs obtained in the pediatric study were in the range of those seen in the adult vaccinated population.

The anti-HBs GMTs obtained at either month 36 or 48 in the pediatric group, revealed similar or even higher titers than those reported in the adult vaccinated population.

Indications and Clinical Use

TWINRIX® (combined hepatitis A and hepatitis B vaccine) is indicated for active immunization against hepatitis A and hepatitis B virus infection in adults, adolescents, children and infants.

The vaccine will not protect against infection caused by other agents such as hepatitis C, hepatitis E and other pathogens known to infect the liver. It can be expected that hepatitis D will also be prevented by immunization with Twinrix as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

Twinrix is recommended in susceptible subjects at risk of hepatitis A and hepatitis B infection, including and not limited to:

Travellers: Persons travelling to areas with a high endemicity of HBV and

HAV.¹⁻⁵

Persons originating from areas with a high endemicity of HBV and HAV.⁶⁻⁸

Armed Forces: Armed Forces personnel who travel to higher endemicity areas or to areas where hygiene is poor.⁹⁻¹²

Persons for whom Hepatitis A and B are an Occupational Hazard: These include employees in day-care centers, nursing, medical and paramedical personnel in hospitals and institutions, especially gastroenterology and pediatric units, and sewage workers, among others.¹³⁻²⁰

Personnel and residents of institutions.²¹⁻²⁴

Patients frequently receiving blood products: haemophiliac patients.²⁵⁻³⁰

Patients who are candidates for organ transplantation.³¹⁻³³

Anyone who through their work or personal lifestyle may be exposed to HBV and HAV: e.g. homosexuals, persons with multiple sexual partners, abusers of injectable drugs.³⁴⁻⁴⁷

Household contacts of any of the above groups and of patients with acute or chronic HBV infection.⁴⁸⁻⁵¹

Specific population groups known to have higher incidence of Hepatitis A and B.

Contraindications

TWINRIX® (combined hepatitis A and hepatitis B vaccine) 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 or the monovalent hepatitis A or hepatitis B vaccine.

As with other vaccines, the administration of Twinrix should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, is not a contra-indication for vaccination.

Precautions

General

As with all injectable vaccines, appropriate medication (e.g. adrenaline) should always be readily available in case of anaphylaxis or anaphylactoid reactions following administration of the vaccine. For this reason, the vaccinee should remain under medical supervision for 30 minutes after immunization.

Since there is a possibility that the vaccine may contain trace amounts of neomycin, the possibility of an allergic reaction in individuals sensitive to this substance should be kept in mind when considering the use of this vaccine (see PHARMACEUTICAL INFORMATION).

Twinrix® (combined hepatitis A and hepatitis B vaccine) should be administered subcutaneously to subjects with thrombocytopenia or bleeding disorders since bleeding may occur following an intramuscular administration to these subjects. Subcutaneous injection may result in a less than optimal antibody response.

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.

Twinrix is not recommended for postexposure prophylaxis (e.g. needle stick injury).

Use in Pregnancy

Adequate human data on use during pregnancy and adequate animal reproduction studies are not available. However, as with all inactivated viral vaccines, the risks to the fetus are considered to be negligible. Twinrix should be used during pregnancy only when clearly needed.

Nursing Mothers

Adequate human data on use during lactation and adequate animal reproduction studies are not available. Twinrix should therefore be used with caution in breast-feeding mothers.

Patients with Special Diseases and Conditions

As with other vaccines, haemodialysis patients and persons with an impaired immune system, adequate anti-HAV and anti-HBs antibody titers may not be obtained after the primary immunization course and such patients may therefore require administration of additional doses of vaccine. However, no specific dosing recommendations can be made at this time.

Drug Interactions

Clinical studies have demonstrated that Twinrix used in an alternate 2 dose schedule can be administered concomitantly with either diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, Haemophilus influenzae type b

(DTPa-IPV/Hib) or Measles-Mumps-Rubella (MMR) vaccines in the second year of life. In these trials, the injectable vaccines were given at different injection sites.

Although the concomitant administration of Twinrix 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.

As with other vaccines, it may be expected that in patients receiving immunosuppressive treatment or patients with immunodeficiency, an adequate response may not be achieved.

No data on concomitant administration of Twinrix 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.

Effects on the Ability to Drive and Use Machines

Twinrix has no or negligible influence on the ability to drive and use machines.

Adverse Reactions

In controlled clinical studies, signs and symptoms were actively monitored in approximately 1800 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.

Standard Vaccination Schedule (3 dose)

Injection site reactions, such as redness and swelling of >3 cm for longer than 24 hours and severe pain were reported in only 1 child of all administered doses, in both age groups of healthy children. In adults, injection site reactions were reported in 1.5% of all administered doses with the standard 3 dose schedule. No serious adverse events considered related to the vaccination were reported during clinical trials.

General reactions that may occur in temporal association with Twinrix vaccination include:

Frequencies were reported as: defined by CIOMS

Very common: $\geq 10\%$; Common: ≥ 1 and $<10\%$; Uncommon: ≥ 0.1 and $<1\%$;

Rare: ≥ 0.01 and $<0.1\%$; Very rare: $<0.01\%$

Very common: (10 %)

BODY AS A WHOLE: fatigue

Common: (1 and <10 %)

BODY AS A WHOLE: headache, malaise

GASTRO-INTESTINAL SYSTEM: nausea

Uncommon: (0.1 and <1 %)

BODY AS A WHOLE: fever

GASTRO-INTESTINAL SYSTEM: vomiting

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

Rapid Vaccination Schedule (4 dose)

During clinical studies, the most commonly reported adverse events were reactions at the injection site, including pain, redness and swelling.

General reactions that may occur in temporal association with Twinrix vaccination:

Very common: (≥ 10 %)

BODY AS A WHOLE: fatigue

Common: (≥ 1 and <10 %)

BODY AS A WHOLE: headache, malaise

GASTRO-INTESTINAL SYSTEM: nausea

Uncommon: (≥ 0.1 and <1 %)

BODY AS A WHOLE: fever

GASTRO-INTESTINAL SYSTEM: vomiting

Alternate Vaccination Schedule (2 dose)

In clinical trials, the most commonly reported adverse events were injection site reactions, which included pain, redness and swelling. No serious adverse events considered related to the vaccination were reported during clinical trials.

General reactions that may occur in temporal association with Twinrix vaccination include:

Very common: (≥ 10 %)

<i>BODY AS A WHOLE:</i>	fatigue, headache, irritability/fussiness
<i>GASTRO-INTESTINAL SYSTEM:</i>	loss of appetite

Common: (≥ 1 and < 10 %)

<i>BODY AS A WHOLE:</i>	fever
<i>CENTRAL AND PERIPHERAL NERVOUS SYSTEM:</i>	drowsiness
<i>GASTRO-INTESTINAL SYSTEM:</i>	gastro-intestinal symptoms

In a comparative trial, it was noted that the percentage of subjects reporting solicited adverse events after a 2 dose course of Twinrix was similar to that seen with Twinrix Junior (combined vaccine containing 360 EIU/10µg in a dose volume of 0.5mL).

Post-Marketing Surveillance

Monovalent vaccines: Hepatitis A: Havrix® and Hepatitis B: Engerix-B®.

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.

Rare: (≥ 0.01 and < 0.1 %)

<i>BODY AS A WHOLE:</i>	flu-like symptoms (fever, chills, headache, myalgia, arthralgia), fatigue
<i>CENTRAL AND PERIPHERAL NERVOUS SYSTEM:</i>	dizziness, paresthesia
<i>GASTRO-INTESTINAL SYSTEM:</i>	abdominal pain, decreased appetite, diarrhoea, nausea, vomiting
<i>LIVER AND BILIARY SYSTEM:</i>	abnormal liver function tests
<i>SKIN AND APPENDAGES:</i>	pruritis, rash, urticaria

Very Rare: (< 0.01 %)

<i>BODY AS A WHOLE:</i>	allergic reactions including anaphylactic and anaphylactoid reactions and serum sickness like disease
<i>CARDIOVASCULAR GENERAL:</i>	hypotension, syncope
<i>CENTRAL AND PERIPHERAL NERVOUS SYSTEM:</i>	cases of peripheral and /or central neurological disorders, and may include multiple sclerosis, optic neuritis, myelitis, Bell's palsy, polyneuritis such as Guillain-Barré syndrome (with ascending paralysis), meningitis, encephillitis, encephalopathy
<i>NEUROLOGICAL DISORDERS:</i>	convulsions
<i>PLATELET, BLEEDING AND CLOTTING:</i>	thrombocytopenia, thrombocytopenia purpura
<i>SKIN AND APPENDAGES:</i>	erythema exsudativum multiforme, pruritis, urticaria
<i>VASCULAR EXTRACARDIAC:</i>	vasculitis

WHITE CELL AND RETICULOENDOTHELIAL lymphadenopathy
SYSTEM:

Dosage and Administration

<u>Vaccination Schedule</u>	<u>Age</u>	<u>Vaccine</u>	<u>dose/volume</u> <u>HAV ELU /</u> <u>HBVmcg</u>	<u>Dosing Schedule</u> (months)			
				0	1	6	12
Standard (3 dose)	Adults over 19 years of age	Twinrix	(720 /20)/1ml	X	X	X	
Standard (3 dose)	1-18 years	Twinrix Junior	(360/10)/0.5ml	X	X	X	
Rapid (4 dose)	Adults over 19 years of age	Twinrix	(720 /20)/1ml	0,7d,21d XXX d=days			X
Alternate (2 dose)	1-15 years	Twinrix	(720/20)/1ml	X		X or	X

Primary Course

Standard Schedule

The standard primary course of vaccination with TWINRIX® (combined hepatitis A and hepatitis B vaccine) 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.

Rapid Schedule

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.

Alternate Schedule

The alternate schedule, **for children and adolescents only**, consists of two doses of Twinrix (720ELU HAV/20µg HBV), the first administered at the elected date and the second between six and twelve months after the first dose. The alternate schedule should be used where completion of the 2 dose vaccination course can be assured, such as school-based vaccination programmes.

Once initiated, the 2 dose course of vaccination should be completed with the same vaccine.

In situations where rapid protection is required in children and adolescents (1 to 15 years old), the standard 3 dose schedule is recommended. The alternate 2 dose schedule demonstrated similar antibody titres after completion of the vaccination course.

Booster Dose

Long term antibody persistence data following vaccination with Twinrix are available up to 60 months after vaccination in adults and up to 48 months in infants, children and adolescents. 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 shown to be similar.

General guidelines for booster vaccination can therefore be drawn from experience with the monovalent vaccines.

The anti-HBs and anti-HAV antibody titres observed following a 2 dose vaccination course with Twinrix are in the same range of what is seen following vaccination with the standard 3 dose schedule.

For the hepatitis B component:

Routine booster vaccinations in immunocompetent persons are not recommended since protection has been shown to last for at least 15 years. Studies of long term protective efficacy, however, will determine whether booster doses of vaccine are needed. It is important to recognise that the absence of detectable anti-HBs in a person who has been previously demonstrated to have anti-HBs, does not mean lack of protection, because immune memory persists. Booster doses in this situation are not indicated.

Immunocompromised persons often respond sub-optimally to the vaccine. Subsequent HBV exposures in these individuals can result in disease or the carrier state. Therefore, boosters may be necessary in this population. The optimal timing of booster doses for immunocompromised individuals who are at continued risk of HBV exposure is not known and should be based on the severity of the compromised state and annual monitoring for the presence of anti-HBs.

For the hepatitis A component:

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. Guidelines for boosting are based on the extrapolation from the data available required for protection; anti-HAV antibodies have been predicted to persist for at least 20 years (based on mathematical

calculations).

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

Method of Administration

Twinrix is for **INTRAMUSCULAR** injection, preferably in the deltoid region, or in the anterolateral thigh in infants. The vaccine **should not** be administered intramuscularly in the gluteal region or subcutaneously/intradermally since administration by these routes may result in a less than optimal anti-HAV antibody response.

As with all parenterals, vaccine products should be inspected visually for any foreign particulate matter or discoloration prior to administration. Before use of Twinrix, the vaccine should be well shaken to obtain a slightly opaque, white suspension. Discard if the contents of the vial or syringe appear otherwise.

Twinrix should never be administered intravenously.

Pharmaceutical Information

Composition

TWINRIX® (combined hepatitis A and hepatitis B vaccine) is a combined vaccine formulated of the purified, inactivated hepatitis A (HA) virus and purified hepatitis B surface antigen (HBsAg) (genetically engineered), separately adsorbed onto aluminium salts.

Twinrix® (combined hepatitis A and hepatitis B) vaccine contains as active ingredients per dose:

	ELISA units Hepatitis A	mcg (µg) Hepatitis B	Dose Volume
Twinrix® Adult	720	20	1.0mL
Twinrix® Junior	360	10	0.5mL

The liquid suspension is made isotonic with sodium chloride in water for injection. The vaccine contains 2-phenoxyethanol as a preservative agent. The Twinrix® formulation contains trace amounts of thimerosal from the manufacturing process.

Excipients: formaldehyde, polysorbate 20, amino acids for injection and traces of neomycin sulphate.

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

Stability and Storage Recommendations

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

Twinrix should be stored at +2°C to +8°C.

Do not freeze; discard if the vaccine has been frozen.

Studies of Twinrix show that the potency of the unopened vaccine is not significantly affected after exposure at 37°C for one month and 45°C for 7 days.

However, this is NOT a storage recommendation.

Availability of Dosage Forms

TWINRIX® is available as:

Twinrix® (720 ELISA units HAV/ 20µg HBV per 1mL dose) syringes in packages of 1, 10 and 25 (adult presentation).

Twinrix® Junior (360 ELISA units HAV/ 10µg HBV per 0.5mL dose) syringes in packages of 1 and 10 (pediatric/adolescent presentation).

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