PRODUCT MONOGRAPH

TWINRIX®

Combined hepatitis A (inactivated) and hepatitis B (recombinant) vaccine

Suspension for injection

Active immunizing agent against infection by hepatitis A and hepatitis B virus

ATC Code: J07BC20

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TWINRIX®

Combined hepatitis A (inactivated) and hepatitis B (recombinant) vaccine

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular injection	Suspension for injection/ TWINRIX®: 720 ELISA units HAV/20 µg HBV per 1 mL dose. TWINRIX® Junior: 360 ELISA units HAV/10 µg HBV per 0.5 mL dose.	Excipients: aluminum hydroxide, aluminum phosphate, sodium chloride and water for injection. Residues: amino acids for injection, formaldehyde, neomycin sulphate and polysorbate 20. *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

DESCRIPTION

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

INDICATIONS AND CLINICAL USE

TWINRIX® [combined hepatitis A (inactivated) and hepatitis B (recombinant) 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.

CONTRAINDICATIONS

TWINRIX® [combined hepatitis A (inactivated) and hepatitis B (recombinant) 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 monovalent hepatitis A or hepatitis B vaccines.
- TWINRIX® contains traces of neomycin. The vaccine should not be used in subjects with known hypersensitivity to neomycin
- For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

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 contraindication for vaccination.

WARNINGS AND 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 DOSAGE FORMS, COMPOSITION AND PACKAGING).

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® [combined hepatitis A (inactivated) and hepatitis B (recombinant) vaccine] will prevent hepatitis A and hepatitis B in such cases.

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.

TWINRIX® should under no circumstances be administered intravascularly.

Hematologic

TWINRIX® can 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.

Immune
As with other vaccines, in persons with an impaired immune system, adequate anti-HAV and anti-HBs antibody titres 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.

Renal
As with other vaccines, hemodialysis patients may not obtain adequate anti-HAV and anti-HBs antibody titres 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.

Special Populations

Pregnant Women: TWINRIX® should be used during pregnancy only when clearly needed, and when the possible advantages outweigh the possible risks for the fetus.

The effect of TWINRIX® on embryo-fetal, peri-natal and post-natal survival and development has not been prospectively evaluated in clinical trials.

The effect of TWINRIX® on embryo-fetal, 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/fetal development, parturition or post-natal development.

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

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adults

The safety profile presented below is based on data from more than 6000 subjects who received TWINRIX® at either the standard 3-dose 0, 1, 6 month schedule or the rapid 4-dose 0, 7, 21 days primary schedule.

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 below. After a fourth dose (booster) given at month 12, the incidence of systemic adverse reactions was comparable to that seen after vaccination at 0, 7, 21 days.

Adverse reactions considered by the investigator as being at least possibly related to TWINRIX® vaccination in adults

Frequency	**Adverse Event**	**System/Organ Class**
Very Common: ≥ 10%	headache	Nervous system disorders
	pain and redness at the injection site, fatigue	General disorders and administration site conditions
Common: ≥ 1% and < 10%	gastrointestinal symptoms (such as diarrhea, nausea, vomiting)	Gastrointestinal disorders
	swelling at the injection site, injection site reaction, malaise	General disorders and administration site conditions
Uncommon: ≥ 0.1% and < 1%	upper respiratory tract infection	Infection and infestations
	dizziness	Nervous system disorders
	myalgia	Musculoskeletal and connective tissue disorders
	fever (≥ 37.5°C)	General disorders and administration site conditions
Rare: ≥ 0.01% and < 0.1%	lymphadenopathy	Blood and lymphatic system disorders
	decreased appetite	Metabolism and nutrition disorders
	hypoaesthesia, paraesthesia	Nervous system disorders
	hypotension	Vascular disorders
	rash, pruritus	Skin and subcutaneous tissue disorders
	arthralgia	Musculoskeletal and connective tissue disorders
	influenza like illness, chills	General disorders and administration site conditions
Very Rare: < 0.01%	urticaria	Skin and subcutaneous tissue disorders

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.

Pediatric

The safety profile presented below is based on data from approximately 800 subjects who received TWINRIX® Junior at the standard 3-dose 0, 1, 6 month schedule.

Adverse reactions considered by the investigator as being at least possibly related to TWINRIX® Junior vaccination in children

Frequency	Adverse Event	System/Organ Class
Very Common: ≥ 10%	pain and redness at the injection site	General disorders and administration site conditions
Common: ≥ 1% and < 10%	appetite lost	Metabolism and nutrition disorders
	irritability	Psychiatric disorders
	drowsiness, headache	Nervous system disorders
	gastrointestinal symptoms (such as nausea, diarrhea*, vomiting)	Gastrointestinal disorders
	swelling at the injection site, injection site reaction, fatigue, malaise, fever (≥ 37.5°C)	General disorders and administration site conditions
Uncommon: ≥ 0.1% and < 1%	rash	Skin and subcutaneous tissue disorders
Rare: ≥ 0.01% and < 0.1%	lymphadenopathy	Blood and lymphatic system disorders
	dizziness	Nervous system disorders
	urticaria	Skin and subcutaneous tissue disorders
Very Rare: < 0.01%	paraesthesia*, hypoaesthesia*	Nervous system disorders
	hypotension*	Vascular disorders
	pruritus*	Skin and subcutaneous tissue disorders
	myalgia*, arthralgia*	Musculoskeletal and connective tissue disorders
	influenza like illness*, chills*	General disorders and administration site conditions

* Refers to adverse reactions observed in clinical trials with TWINRIX®

The safety profile presented below is based on data from approximately 778 subjects who received TWINRIX® at the alternate 2-dose 0, 6 to 12 month schedule.

Adverse reactions considered by the investigator as being at least possibly related to TWINRIX® vaccination in children

Frequency	Adverse Event	System/Organ Class
Very Common: ≥ 10%	appetite lost	Metabolism and nutrition disorders
	irritability	Psychiatric disorders
	headache	Nervous system disorders
	fatigue, pain and redness at the injection site	General disorders and administration site conditions
Common: ≥ 1% and < 10%	drowsiness	Nervous system disorders
	gastrointestinal symptoms	Gastrointestinal disorders
	fever, swelling at the injection site	General disorders and administration site conditions

Post-Market Adverse Drug Reactions

The following adverse reactions have been reported with either TWINRIX® or with GlaxoSmithKline monovalent hepatitis A or B vaccines.

Adverse Event	System/Organ Class
Meningitis	Infections and infestations
Thrombocytopenia, thrombocytopenic purpura	Blood and lymphatic system disorder
Anaphylaxis, allergic reactions including anaphylactoid reactions and mimicking serum sickness	Immune system disorders
Encephalopathy, encephalitis, neuritis, neuropathy, paralysis, convulsions, multiple sclerosis*, Guillain-Barre syndrome*, optic neuritis*, myelitis*, facial palsy*, hypoaesthesia, syncope or vasovagal responses to injection	Nervous system disorders
Vasculitis	Vascular disorders
Angioneurotic oedema, lichen planus, erythema multiforme	Skin and subcutaneous tissue disorders
Arthritis, muscular weakness	Musculoskeletal and connective tissue disorders
Abdominal pain*	Gastrointestinal disorders
Abnormal liver function tests*	Hepatic system disorders
Immediate injection site pain, stinging and burning sensation	General disorders and administration site conditions

* "A number of studies have demonstrated no link between hepatitis B vaccine and multiple sclerosis, Guillain-Barre syndrome (GBS), …." (Canadian Immunization Guide 7th Edition 2006).

DRUG INTERACTIONS

Overview

TWINRIX®

Clinical studies have demonstrated that TWINRIX® [combined hepatitis A (inactivated) and hepatitis B (recombinant) vaccine] 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.

TWINRIX® Junior

TWINRIX® Junior may be administered concomitantly with the Human Papillomavirus vaccine (CERVARIX®). Administration of TWINRIX® Junior at the same time as CERVARIX® has shown no clinically relevant interference in the antibody response to the HPV16/18 antigens in CERVARIX® and the hepatitis A antigen in TWINRIX® Junior. Anti-hepatitis B geometric mean antibody titres were lower on co-administration of the vaccines but the percentage of subjects reaching anti-HBs ≥ 10mIU/ml (seroprotection) was 98.3% for concomitant vaccination and 100% for TWINRIX® Junior given alone. The clinical relevance of the reduced antibody titre and the risk of a substantially reduced immune response to hepatitis B if doses of hepatitis B vaccine are missed are not known.

Only the concomitant administration of TWINRIX® Junior with CERVARIX® has been specifically studied. It is advised that vaccines other than CERVARIX® should not be administered at the same time as TWINRIX® Junior.

Drug-Drug Interactions

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.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
Effects on the ability to drive and use machines
TWINRIX® has no or negligible influence on the ability to drive and use machines.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Vaccination Schedule*	Age	Vaccine	Dose/volume HAV ELU/ HBV µg	Dosing Schedule (months)			
				0	1	6	12
Standard (3 dose)	Adults over 19 years of age	TWINRIX®	(720/20)/1 mL	**X**	**X**	**X**	
Standard (3 dose)	1 – 18 years	TWINRIX® Junior	(360/10)/0.5 mL	**X**	**X**	**X**	
Rapid (4 dose)	Adults over 19 years of age	TWINRIX®	(720/20)/1 mL	0,7d,21d **XXX** d=days			**X**
Alternate (2 dose)	1 - 15 years	TWINRIX®	(720/20)/1 mL	**X**		**6 to 12 months**	

*The recommended schedule should be adhered to. Once initiated, the primary course of vaccination should be completed with the same vaccine.

Primary Course

Standard Schedule
The standard primary course of vaccination with TWINRIX® [combined hepatitis A (inactivated) and hepatitis B (recombinant) 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.

There are no data to support a rapid vaccination schedule for children and adolescents (1 to 15 years old).

Alternate Schedule
The alternate schedule, **for children and adolescents only**, consists of two doses of TWINRIX® (720 ELU HAV/20 µg 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 programs.

Booster Dose

Long-term antibody persistence data following vaccination with TWINRIX® are available up to 15 years after vaccination in adults and up to 10 years 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 the 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.

Immunocompromized 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 immunocompromized individuals who are at continued risk of HBV exposure is not known and should be based on the severity of the compromized 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 may be ensured by immunological memory. 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 is desired, TWINRIX® can be given. Alternatively, subjects primed with TWINRIX® may be administered a booster dose of either of the monovalent vaccines.

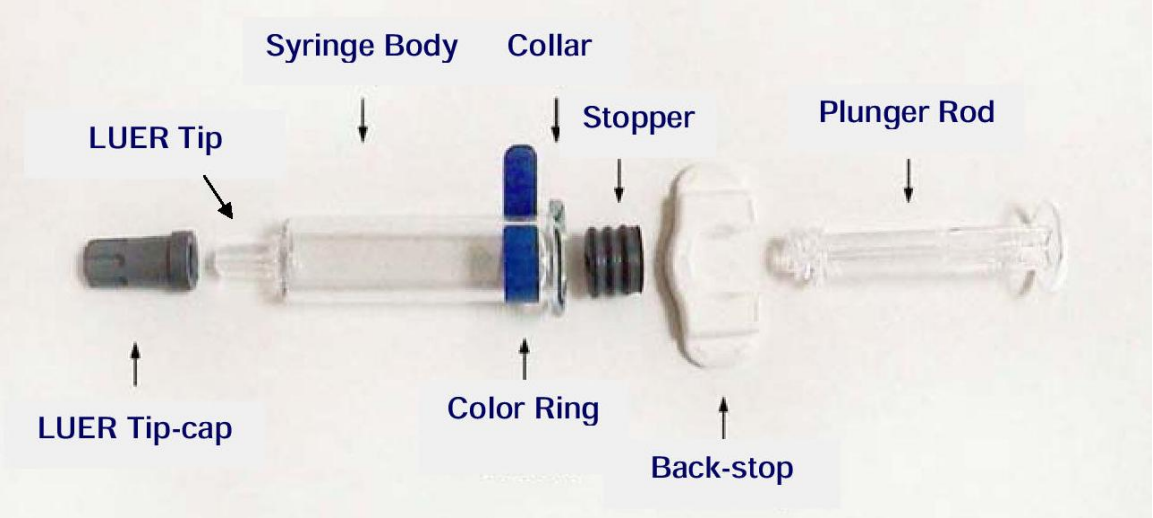
Administration
TWINRIX® is for **intramuscular** injection, preferably in the deltoid region, or in the anterolateral thigh in infants. The vaccine **should not** be administered intramuscularly in the gluteal region or subcutaneously/intradermally since administration by these routes may result in a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

Upon storage, a fine white deposit with a clear colourless supernatant may be observed. The vaccine should be well shaken before use to obtain a slightly opaque, white suspension.

As with all parenterals, 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.

Syringe Instructions
Do not remove the white back-stop from the syringe. Prior to administration, ensure that the plunger rod is firmly attached to the rubber stopper by turning the plunger clockwise until slight resistance is felt. **Do not** over tighten. Remove syringe LUER Tip-cap and needle cap. Attach needle by pressing and twisting in a clockwise rotation until secured to the syringe.



TWINRIX® should never be administered intravenously.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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

ACTION AND CLINICAL PHARMACOLOGY

Data has been obtained from clinical studies involving over 980 adults, adolescents, children and infants using the standard 3 dose vaccination schedule with TWINRIX® [combined hepatitis A (inactivated) and hepatitis B (recombinant) vaccine] 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/ 20 µg HBV per 1 mL dose.

Anti-HAV response
In a clinical study involving subjects 18-75 years of age, anti-HAV seropositivity rates were 91.1% one month after the first dose of vaccine, 97.6% one month after the second dose of vaccine and 99.5% one month after the third dose of vaccine.

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%.

Anti-HAV response and Anti-HBV response
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® 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® were 92% and 57% at 7 and 48 months following the first dose respectively, versus 80% and 40% after the GlaxoSmithKline Biologicals monovalent 20 µg hepatitis B vaccine, and 71% and 27% after another licensed monovalent 10 µg 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® 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® 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.

Rapid Dosing Schedule (4 doses at 0, 7, and 21 days and booster at 12 months)
720 ELISA units HAV/ 20 µg 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 standard vaccination 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 µg HBV per 0.5 mL 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 titre 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 µg HBV per 1 mL 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 10 years following the initiation of a 0, 6 month schedule of TWINRIX® (2 dose schedule). After 10 years, anti-HAV seropositivity rates were 100% in both subjects aged 1-11 years and in subjects aged 12-15 years at primary vaccination.

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 10 years following the initiation of a 0, 6 month schedule. The anti-HBs seroprotection rates at this time point were 77.3% and 85.9% respectively, in children aged 1-11 and 12-15 years old.

In this 2 dose study conducted in subjects aged 12-15 years at primary vaccination, 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 µg of the hepatitis B surface antigen in a 0.5 mL dose.

In a 6 year long term follow-up study involving subjects aged 12-15 years at primary vaccination, anti-HAV seropositivity rates were 100% following a 0, 6 month or a 0, 12 month schedule. The anti-HBs seroprotection rates were 84.8% and 92.9%, respectively.

Duration of Effect

Adults
Protection against hepatitis A and hepatitis B develops within 2 to 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.

In two long term clinical studies conducted in adults, 15 years after the primary vaccination with TWINRIX®, the anti-HAV seropositivity rates were 100% in both studies and the anti-HBs seroprotection rates were 89.3% and 92.9% respectively in study HAB-142 (LT-ATP, n=28) and in study HAB-147 (LT-ATP, n=28).

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 10 years following the course of vaccination 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 decline of anti-HAV and anti-HBs antibodies were shown to be similar to those of monovalent vaccines.

STORAGE AND STABILITY

The expiry date of the vaccine is indicated on the label and packaging. TWINRIX® [combined hepatitis A (inactivated) and hepatitis B (recombinant) vaccine] should be stored at +2 to +8°C.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

TWINRIX® [combined hepatitis A (inactivated) and hepatitis B (recombinant) vaccine] is available as:

- TWINRIX® (720 ELISA units HAV/ 20 µg HBV per 1 mL dose) in single dose vials and syringes in packages of 1, 10 and 25 (adult presentation).
- TWINRIX® Junior (360 ELISA units HAV/ 10 µg HBV per 0.5 mL dose) in single dose vials in packages of 1, 3 and 10 and syringes in packages of 1 and 10 (pediatric/adolescent presentation).

TWINRIX® vaccine contains as active ingredients per dose:

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

The liquid suspension is made isotonic with sodium chloride in water for injection.

Excipients: aluminum hydroxide, aluminum phosphate, sodium chloride and water for injection.

Residues: amino acids for injection, formaldehyde, neomycin sulphate and polysorbate 20.

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Product Characteristics

TWINRIX® [combined hepatitis A (inactivated) and hepatitis B (recombinant) vaccine] is a combined vaccine formulated of the purified, inactivated hepatitis A (HA) virus and purified hepatitis B surface antigen (HBsAg) (genetically engineered yeast (*Saccharomyces cerevisiae*) cells), separately adsorbed onto aluminum salts.

CLINICAL TRIALS

Study Demographics and Study Designs

Study HAB-129 performed in healthy adults, compared TWINRIX® with thiomersal-free, preservative-free TWINRIX® (both vaccines with 20 μg HBsAg and ≥ 720 EL.U HAV/1.0 mL dose). An overview of some of the principal features of the study is provided in Table 1. (See also PART I, ACTION AND CLINICAL PHARMACOLOGY).

Table 1 Features of clinical studies investigating the immunogenicity and safety of thiomersal-free and preservative-free combined hepatitis A/hepatitis B vaccine

Study No.	Countries	Vaccine(s) (Dose)	Population Age	Enrolled	Design	Objectives
HAB - 129	The Netherlands Germany UK Sweden	• TWINRIX® • PFTF-TWINRIX® (20 μg HBsAg and 720 EL.U. HAV antigen/dose)	Adults 18 yrs or older	466	Comparative, double-blind, randomized (1:1), controlled, multi-centre (5 centres), parallel study with 2 groups 0, 1 and 6 months schedule	**Primary:** To demonstrate non-inferiority of the anti-HAV and anti-HBs response induced by PFTF-TWINRIX® compared to TWINRIX® **Secondary:** Evaluation of immunogenicity, safety and reactogenicity

TWINRIX® = vaccine with residual thiomersal from HBsAg bulk and 2-phenoxyethanol as preservative
PFTF-TWINRIX® = preservative-free, thiomersal-free TWINRIX®

Study Results

The protocol of the non-inferiority study HAB-129 specified the use for the inferential analyses of a 95% CI on the difference in seroprotection rates for anti-HBs antibodies and of a 95% CI on the difference in seropositivity rate for anti-HAV antibodies.

Table 2 and Table 3 document the results of the inferential analyses for the co-primary objectives of the bivalent vaccine study HAB-129.

The protocol defined criteria for the demonstration of clinical non-inferiority of the responses to the HBsAg and HAV components of the preservative-free and thiomersal-free bivalent vaccine were met.

Table 2 Anti-HBs seroprotection rates at Month 7, ATP cohort, study HAB-129

Antigen(s), schedule and dose	Vaccine	Descriptive statistics					Inferential statistics				Pre-defined criteria for clinical non-inferiority
			Seroprotection rate (≥ 10 mIU/mL) Month 7				Difference between group in anti-HBs seroprotection rates (≥ 10 mIU/mL) at Month 7				
		N	n	%	95% CI†		Between groups	Value %	95% CI*		
					LL	UL			LL	UL	
Combination HBsAg 20 µg and HAV 720 EL.U. 0, 1 and 6 months	TWINRIX®	213	208	97.7	94.6	99.2	PFTF-TWINRIX® - TWINRIX®	-2.1	-6.11	1.55	Lower limit of the CI for the differences in seroprotection rates greater than -7%; non-inferiority demonstrated
	PFTF-TWINRIX®	204	195	95.6	91.8	98.0					

N = number of subjects tested
n/% = number/percentage of subjects seroprotected
† = exact 95% confidence intervals. LL = lower limit. UL = upper limit
* = Standardized two-sided asymptotic 95% CI

Table 3 Anti-HAV seropositivity rates at Month 7, ATP cohort, study HAB-129

Group	Descriptive statistics					Inferential statistics				Pre-defined criteria for clinical non-inferiority
		Seroprotection rate (≥ 15 mIU/mL) Month 7				Difference between group in anti-HAV seropositivity rates (≥ 15 mIU/mL) at Month 7				
	N	n	%	95% CI†		Between groups	Value %	95% CI*		
				LL	UL			LL	UL	
TWINRIX®	213	212	99.5	97.4	100	PFTF-TWINRIX® - TWINRIX®	-0.02	-2.29	2.16	Lower limit of the CI for the differences in seropositivity rates greater than -7%; non-inferiority demonstrated
PFTF-TWINRIX®	204	203	99.5	97.3	100					

N = number of subjects tested
n/% = number/percentage of subjects seropositive
† = exact 95% confidence intervals. LL = lower limit. UL = upper limit
* = Standardized two-sided asymptotic 95% CI

DETAILED PHARMACOLOGY

Not applicable.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

The effect of TWINRIX® vaccine on embryo-foetal, peri-natal and post-natal development was assessed in sexually mature female rats.

Two groups of 56 animals received 30 days prior to pairing, by intramuscular administration, either 200 µl of saline or 200 µl of TWINRIX® vaccine. The 44 animals selected to continue treatment during gestation received on day 6, 8, 11 and 15 after mating either 200 µl of saline or 200 µl of TWINRIX® vaccine.

From each group, a total of 22 females had their uterine contents examined on Day 20 after mating, and the remaining 22 females in each group were allowed to give birth and rear their offspring to weaning at Day 25 of age.

Treatment of parental females did not adversely affect their clinical condition or bodyweight and food consumption throughout the study. All treated females allocated to the embryo-foetal or littering phases were pregnant. Embryo-foetal development was unaffected by treatment. All littering phase females gave birth to a live litter, and the growth and development of the offspring appeared to be unimpaired in all groups to Day 25 of age.

It was concluded from this study that intramuscular administration of 200 µl TWINRIX® vaccine to female rats during gestation animals was well tolerated. Treatment was not associated with any systemic toxicity to the parental females and there were no effects on pre- or post-natal development of the offspring to Day 25 of age.

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PART III: CONSUMER INFORMATION

TWINRIX®
combined hepatitis A (inactivated) and hepatitis B (recombinant) vaccine

This leaflet is part III of a three-part "Product Monograph" published when TWINRIX® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TWINRIX®. Contact your doctor or pharmacist if you have any questions about the vaccine.

ABOUT THIS VACCINE

What the vaccine is used for:
TWINRIX® ([combined hepatitis A (inactivated) and hepatitis B (recombinant) vaccine]) is a vaccine used in adults, adolescents, children and infants to prevent hepatitis A and hepatitis B diseases.

What it does:
The vaccine works by causing the body to produce its own protection (antibodies) against these diseases.

• **Hepatitis A**: Hepatitis A is an infectious disease, which can affect the liver. This disease is caused by the hepatitis A virus. The hepatitis A virus is generally spread from person to person by putting something in the mouth that has been contaminated with hepatitis A . Hepatitis A virus can survive up to 10 months in water and on dried surfaces for 7 days. Persons with hepatitis A virus infection may not have any signs or symptoms of the disease. Older persons are more likely to have symptoms than children. If symptoms are present, they usually occur abruptly and may include fever, tiredness, loss of appetite, nausea, abdominal discomfort, dark urine, and jaundice (yellowing of the skin and eyes). Symptoms usually last less than 2 months; a few persons are ill for as long as 6 months. It takes an average of 28 days (range: 15-50 days) for symptoms to appear. During this incubation period, a person may pass hepatitis A on to others, despite having no symptoms.

• **Hepatitis B**: Hepatitis B is an infectious disease, which affects the liver. The disease is caused by the hepatitis B virus. The virus is found in body fluids such as blood, semen, vaginal secretions, or saliva (spit) of infected people. The hepatitis B virus is generally spread from person to person via the transfer of virus through any perforation in the skin. Hepatitis B can survive on surfaces for at least 7 days and still be capable of causing infection. If symptoms occur, they occur on the average of 12 weeks (range 9-21 weeks) after exposure to hepatitis B virus. Symptoms occur in about 70% of patients. Symptoms are more likely to occur in adults than in children. Sometimes a person with hepatitis B viral infection has no symptoms at all. The older you are the more likely you are to have symptoms. You might be infected with hepatitis B virus (and be spreading the virus) and not know it. If you have symptoms, they might include: yellow skin or yellowing of the white of your eyes (jaundice), tiredness, loss of appetite, nausea, abdominal discomfort, dark urine, clay-colored bowel movements, joint pain.

Vaccination is the best way to protect against these diseases.

It is impossible to get Hepatitis A or B diseases from the TWINRIX® vaccine.

When it should not be used:
Do not use TWINRIX® if:

- you have experienced any health problems after previous administration of a vaccine.
- you have previously had any allergic reaction to TWINRIX®, or any ingredient contained in this vaccine (see What the medicinal ingredient is and What the important nonmedicinal ingredients are sections). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.
- you have previously had an allergic reaction to any vaccine against hepatitis A and hepatitis B diseases.
- you have a severe infection with a high temperature (over 38°C). A minor infection such as a cold should not be a problem, but talk to your doctor first.

What the medicinal ingredient is:
TWINRIX® contains the following active ingredients:

- inactivated hepatitis A virus [adsorbed on aluminum-oxide hydrated].
- hepatitis B virus surface antigen recombinant (S protein) [adsorbed on aluminum phosphate produced on genetically-engineered yeast cells (*Saccharomyces cerevisiae*)].

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What the important nonmedicinal ingredients are:
TWINRIX® contains the following nonmedicinal ingredients: aluminum hydroxide, aluminum phosphate, sodium chloride and water for injection. The vaccine also contains traces of: amino acids for injection, formaldehyde, neomycin sulphate and polysorbate 20.

What dosage forms it comes in:
TWINRIX® is available in single dose vials and syringes in packages of 1, 10 and 25.
TWINRIX® Junior is available in single dose vials in packages of 1, 3 and 10 and syringes in packages of 1 and 10.

WARNINGS AND PRECAUTIONS

BEFORE you use TWINRIX® talk to your doctor or pharmacist if:

- you are or think you may be pregnant or if you intend to become pregnant. Your doctor will discuss with you the possible risks and benefits of having TWINRIX® during pregnancy.
- you are breastfeeding. It is not known if TWINRIX® passes into breast milk, however the vaccine is not expected to cause problems in breast-fed babies.
- you have a poor immune system due to illness or drug treatment.
- you have a bleeding problem or bruise easily.
- you are taking any other medicine or have recently received any other vaccine.
- you have any known allergies.

As with other vaccines, a lower immune response is more common in older people, men rather than women, smokers, obese people, and people with long standing illnesses, or people on some type of drug treatments. Your doctor may advise you to have a blood test after you have completed the course of vaccinations to check if you have a satisfactory hepatitis B (antigen) response. If not, your doctor will advise you on the possible need to have extra doses.

In these cases, your doctor can determine the right time and schedule of vaccination for you.

Fainting (Syncope) can occur following, or even before, any needle injection; therefore, tell the doctor or nurse if you or your child fainted with a previous injection so that procedures can be put in place to avoid injury from faints.

INTERACTIONS WITH THIS VACCINE

TWINRIX® can be given at the same time as either a combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, and *Haemophilus influenzae* type b vaccine or a combined measles, mumps and rubella vaccine, in the second year of life. TWINRIX® Junior can be given at the same time as CERVARIX®, a Human Papillomavirus vaccine.

Ask your health professional for advice about which vaccines may be given at the same time as TWINRIX® or TWINRIX® Junior.

TWINRIX® may not have an optimal effect if used with medicines that suppress the immune system.

PROPER USE OF THIS VACCINE

Usual dose:

TWINRIX® will be administered by your health professional as an injection into the muscle. TWINRIX® can be administered at the following dosing schedules; your doctor will advise you of the appropriate dosing for you:

Pediatric Dosing Schedule:

Vaccination Schedule	Age	Vaccine	Dosing Schedule (months)			
			0	1	6	12
Standard (3 dose)	1-18 years	TWINRIX® Junior (0.5 mL)	X	X	X	
Alternate (2 dose)	1-15 years	TWINRIX® (1 mL)	X		6 to 12 months	

Adult Dosing Schedule:

Vaccination Schedule	Age	Vaccine	Dosing Schedule (months)			
			0	1	6	12
Standard (3 dose)	Adults over 19 years of age	TWINRIX® (1 mL)	X	X	X	
Vaccination Schedule	**Age**	**Vaccine**	**Dosing Schedule**			
			(days)			**(months)**
			0	7	21	12
Rapid (4 dose)	Adults over 19 years of age	TWINRIX® (1 mL)	X	X	X	X

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a scheduled injection, talk to your doctor and arrange another visit.

Make sure you finish the complete vaccination course. If not, you may not be fully protected against the diseases.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Any vaccine can have some side effects.

Side effects that occurred in adults during clinical trials with the standard (3 dose) and rapid (4 dose) TWINRIX® vaccination schedule were as follows:

Very common (more than 10% of doses): Pain or discomfort, redness at the injection site, headache and tiredness.

Common (between 1% and 10% of doses): Swelling at the injection site, diarrhea, nausea and vomiting and generally feeling unwell.

Uncommon (between 0.1% and 1% of doses): Fever (more than 37.5°C) , dizziness, upper respiratory tract infection, and aching muscles.

Rare (between 0.01% and 0.1% of doses): Swollen glands in the neck, armpit or groin, loss of appetite, pins and needles, low blood pressure, rash and itching, muscle and joint pain and flu-like symptoms, such as high temperature, sore throat, runny nose, cough and chills.

Very Rare (less than 0.01% of doses): Hives.

Side effects that occurred in children during clinical trials who received the standard (3 dose) TWINRIX® Junior vaccination schedule were as follows:

Very common (more than 10% of doses): Pain and redness at the injection site.

Common (between 1% and 10% of doses): Swelling at the injection site, fever (more than 37.5°C), irritability, drowsiness, headache, loss of appetite, diarrhea, nausea and vomiting and generally feeling unwell.

Uncommon (between 0.1% and 1% of doses): Rash.

Rare (between 0.01% and 0.1% of doses): Swollen glands in the neck, armpit or groin, dizziness and hives.

Very Rare (less than 0.01% of doses): Pins and needles, loss of skin sensitivity to pain or touch, numbness of the arms and legs, low blood pressure, rash and itching, aching muscles and joint pain and flu-like symptoms, such as high temperature, sore throat, runny nose, cough and chills.

Side effects that occurred in children during clinical trials who received the alternate (2 dose) TWINRIX® vaccination schedule were as follows:

Very common (more than 10% of doses): Pain and redness at the injection site, tiredness, headache, irritability, and loss of appetite.

Common (between 1% and 10% of doses): Swelling at the injection site, fever, drowsiness, stomach and digestive complaints.

Do not be alarmed by this list of possible side effects. It is likely that you will have no side effects from vaccination.

This is not a complete list of side effects. For any unexpected effects while taking TWINRIX®, *contact your doctor or pharmacist.*

HOW TO STORE IT

Store in a refrigerator (2 - 8°C).

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.

For health care professionals:
If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local Health Unit in your province/territory.

For the General Public:
Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada:

By toll-free telephone: 1-866-844-0018
By toll-free fax: 1-866-844-5931
By email: caefi@phac-aspc.gc.ca
At the following website:
http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php

By regular mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road
Ottawa, Ontario
K1A 0K9 Address Locator 6502A

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

Store in the original package in order to protect from light.

Do not freeze. Freezing destroys the vaccine.

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the pack. The date for last use corresponds to the last day of the month mentioned.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.gsk.ca or by contacting the sponsor,
GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4
1-800-387-7374

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PERSONAL VACCINATION RECORD OF TWINRIX® [Combined hepatitis A (inactivated) and hepatitis B (recombinant) vaccine]

The table on the right is provided for you to record the TWINRIX® vaccine doses you have received and to remember future doses. Keep it in a safe place with other important health records

VACCINE	DOSE[1,2]	Scheduled Vaccination Date DD-MMM-YY	Date Administered DD-MMM-YY
TWINRIX® (combined hepatitis A & hepatitis B vaccine)	Dose 1		
	Dose 2		
	Dose 3		
	Booster[3]		

[1] For long-term protection, all scheduled doses must be received.
[2] Indicate Junior or Adult.
[3] Required only for rapid dosing.