PRESCRIBING INFORMATION

TWINRIX®

[Hepatitis A & Hepatitis B (Recombinant) Vaccine]

DESCRIPTION

TWINRIX® [Hepatitis A & Hepatitis B (Recombinant) Vaccine] is a sterile bivalent vaccine containing the antigenic components used in producing HAVRIX® (Hepatitis A Vaccine) and ENGERIX-B® [Hepatitis B Vaccine (Recombinant)]. TWINRIX is a sterile suspension of inactivated hepatitis A virus (strain HM175) propagated in MRC-5 cells, and combined with purified surface antigen of the hepatitis B virus. The hepatitis A virus is inactivated with formalin. The purified hepatitis B surface antigen (HBsAg) is obtained by culturing genetically engineered *Saccharomyces cerevisiae* cells, which carry the surface antigen gene of the hepatitis B virus, in synthetic media containing inorganic salts, amino acids, dextrose, and vitamins. Bulk preparations of each antigen are adsorbed separately onto aluminum salts and then pooled during formulation.

A 1.0-mL dose of vaccine contains 720 ELISA Units of inactivated hepatitis A virus and 20 mcg of recombinant HBsAg protein. One dose of vaccine also contains 0.45 mg of aluminum in the form of aluminum phosphate and aluminum hydroxide as adjuvants, amino acids, sodium chloride, phosphate buffer, polysorbate 20, Water for Injection, traces of formalin (not more than 0.1 mg), and residual MRC-5 cellular proteins (not more than 2.5 mcg). Neomycin sulfate, an aminoglycoside antibiotic, is included in the cell growth media; only trace amounts (not more than 20 ng) remain following purification. The manufacturing procedures used to manufacture TWINRIX result in a product that contains no more than 5% yeast protein.

TWINRIX is formulated without preservatives.

TWINRIX is available in vials and 2 types of prefilled syringes. One type of prefilled syringe has a tip cap which may contain natural rubber latex. The other type has a tip cap and a rubber plunger which contain dry natural latex rubber. The vial stopper does not contain latex. (See HOW SUPPLIED.)

TWINRIX is supplied as a sterile suspension for intramuscular administration. The vaccine is ready for use without reconstitution; it must be well shaken before administration to obtain a homogeneous, turbid, white suspension.

CLINICAL PHARMACOLOGY

Several hepatitis viruses (A, B, C, D, and E) are known to cause a systemic infection resulting in major pathologic changes in the liver. Features of hepatitis A and hepatitis B are described below.

Hepatitis A: The hepatitis A virus (HAV) belongs to the picornavirus family.

Hepatitis A is a highly contagious disease with the predominant mode of transmission being person-to-person via the fecal-oral route. Infection has been shown to be spread (1) by contaminated water or food; (2) by infected food handlers[1]; (3) after breakdown in usual sanitary

conditions or after floods or natural disasters; (4) by ingestion of raw or undercooked shellfish (oysters, clams, mussels) from contaminated waters[2]; (5) during travel to areas of the world with poor hygienic conditions[3]; (6) among institutionalized children and adults[4]; (7) in day-care centers[5]; (8) by parenteral transmission, either blood transfusions or sharing needles with infected people[6]; and (9) sexually, especially among men who have sex with men.[7]

The incubation period for hepatitis A averages 28 days (range: 15 to 50 days).[7] The course of hepatitis A infection is extremely variable, ranging from asymptomatic infection to icteric hepatitis and death.[8]

Chronic shedding of HAV in feces has not been demonstrated, but relapses of hepatitis A can occur in as many as 20% of patients[9,10] and fecal shedding of HAV may recur at this time.[9] Approximately 70% of pediatric patients less than 6 years of age infected with hepatitis A are asymptomatic, and serve as a reservoir for infection among adults.[7]

The presence of antibodies to HAV (anti-HAV) confers protection against hepatitis A disease. However, the lowest titer needed to confer protection has not been determined. Natural infection provides lifelong immunity even when antibodies to hepatitis A are undetectable. At present, studies show the duration of protection afforded by TWINRIX against hepatitis A lasts at least 4 years.[11]

Hepatitis B: The hepatitis B virus (HBV) belongs to a family of genetically related DNA-containing animal viruses, which are hepatotropic. The incubation period of hepatitis B ranges between 30 and 180 days.[12]

HBV infection occurs throughout the world with highly variable prevalences. A human reservoir of persistently infected persons is present in nearly all communities of the world. In the United States, parenteral drug abuse, unprotected sexual activity, occupationally acquired infection, or travelers returning from high prevalence countries may be the principal mechanisms of HBV transmission.

Modes of transmission of hepatitis B virus include sexual contact with an infected person, percutaneous or mucosal exposure to infectious blood, and perinatal exposure to an infected mother. Antibody concentrations ≥10 mIU/mL against HBsAg are recognized as conferring protection against hepatitis B.[13]

Clinical infection with hepatitis B may occur in 2 major forms: Asymptomatic or symptomatic hepatitis. Asymptomatic HBV infection can be subclinical or inapparent. In subclinical infection, patients have abnormal liver enzymes without jaundice, while inapparent asymptomatic infection is identified only by serological testing. One in 4 adults who has symptomatic disease has jaundice (anicteric/icteric hepatitis).

HBV infection can have serious consequences including acute massive hepatic necrosis, chronic active hepatitis, and cirrhosis of the liver. As many as 90% of infants and approximately 5% of adults who are infected with HBV will become HBV carriers.[7] More than 350 million people are chronic carriers of HBV worldwide.[7] The Centers for Disease Control and Prevention (CDC) estimates that there are approximately 1 million to 1.25 million chronic carriers of HBV in the United States.[7] The annual number of unreported infections may be 10 times greater than

the number of reported cases.[7] Close contact (sexual contact or household contact) or exposure to blood from infected individuals is associated with increased risk of infection.[7] Those patients who become chronic carriers can infect others and are at increased risk of developing primary hepatocellular carcinoma. Among other factors, infection with HBV may be the single most important factor for development of this carcinoma.[7,14]

Reduced Risk of Hepatocellular Carcinoma: According to the Centers for Disease Control and Prevention (CDC), hepatitis B vaccine is recognized as an anti-cancer vaccine because it can prevent primary liver cancer.[15] In a Taiwanese study, the institution of universal childhood immunization against hepatitis B virus has been shown to decrease the incidence of hepatocellular carcinoma among children.[16] In a Korean study in adult males, vaccination against the hepatitis B virus has been shown to decrease the incidence and risk of developing hepatocellular carcinoma in adults.[17]

Clinical Trials: *Immunogenicity in Adults:* Sera from 1,551 healthy adult volunteers ages 17 to 70, including 555 male subjects and 996 female subjects, in 11 clinical trials were analyzed following administration of 3 doses of TWINRIX on a 0-, 1-, and 6-month schedule. Seroconversion for antibodies against HAV was elicited in 99.9% of vaccinees, and protective antibodies against HBV were detected in 98.5%, 1 month after completion of the 3-dose series.

Table 1. Immunogenicity in TWINRIX Worldwide Clinical Trials

TWINRIX Dose	N	% Seroconversion for Hepatitis A[a]	% Seroprotection for Hepatitis B[b]
1	1587	93.8	30.8
2	1571	98.8	78.2
3	1551	99.9	98.5

[a] Anti-HAV titer ≥assay cut-off: 20 mIU/mL (HAVAB Test) or 33 mIU/mL (ENZYMUN-TEST®).

[b] Anti-HBsAg titer ≥10 mIU/mL (AUSAB®).

One of the 11 trials was a comparative trial conducted in a US population given either TWINRIX (on a 0-, 1-, and 6-month schedule) or HAVRIX (0- and 6-month schedule) and ENGERIX-B (0-, 1-, and 6-month schedule). The monovalent vaccines were given concurrently in opposite arms. Of a total of 773 adults (ages 18 to 70 years) enrolled in this trial, an immunogenicity analysis was performed in 533 subjects who completed the study according to protocol. Of these, 264 subjects received TWINRIX and 269 subjects received HAVRIX and ENGERIX-B. Seroconversion against HAV and seroprotection against HBV are shown in Table 2.

Table 2. Percentage of Seroconversion or Seroprotection Rates in the TWINRIX US Clinical Trial

Vaccine	N	Timepoint	% Seroconversion for Hepatitis A[a] (95% CI)	% Seroprotection for Hepatitis B[b] (95% CI)
TWINRIX	264	Month 1	91.6	17.9
		Month 2	97.7	61.2
		Month 7	99.6 (97.9-100.0)	95.1 (91.7-97.4)
HAVRIX and ENGERIX-B	269	Month 1	98.1	7.5
		Month 2	98.9	50.4
		Month 7	99.3 (97.3-99.9)	92.2 (88.3-95.1)

[a] Anti-HAV titer ≥assay cut-off: 33 mIU/mL (ENZYMUN-TEST®).

[b] Anti-HBsAg titer ≥10 mIU/mL (AUSAB®).

Since the immune responses to hepatitis A and hepatitis B induced by TWINRIX were non-inferior to the monovalent vaccines, efficacy is expected to be similar to the efficacy for each of the monovalent vaccines (Table 3).

Table 3. Geometric Mean Titers in the TWINRIX US Clinical Trial

Vaccine	N	Timepoint	GMT to Hepatitis A (95% CI)	GMT to Hepatitis B (95% CI)
TWINRIX	263	Month 1	335	8
	259	Month 2	636	23
	264	Month 7	4756 (4152-5448)	2099 (1663-2649)
HAVRIX and	268	Month 1	444	6
ENGERIX-B	269	Month 2	257	18
	269	Month 7	2948 (2638-3294)	1871 (1428-2450)

It was noted that the antibody titers achieved 1 month after the final dose of TWINRIX were higher than titers achieved 1 month after the final dose of HAVRIX in these clinical trials. This may have been due to a difference in the recommended dosage regimens for these 2 vaccines, whereby TWINRIX vaccinees received 3 doses of 720 EL.U. of hepatitis A antigen at 0, 1, and 6 months, whereas HAVRIX vaccinees received 2 doses of 1440 EL.U. of the same antigen (at 0 and 6 months). However, these differences in peak titer have not been shown to be clinically significant.

Two clinical trials involving a total of 129 subjects demonstrated that antibodies to both HAV and HBV persisted for at least 4 years after the first vaccine dose in a 3-dose series of TWINRIX, given on a 0-, 1-, and 6-month schedule. For comparison, after the recommended immunization regimens for HAVRIX and ENGERIX-B, respectively, similar studies involving a total of 114 subjects have shown that seropositivity to HAV and HBV also persists for at least

4 years.

The effect of age on immune response to TWINRIX was studied in 2 trials comparing subjects over 40 years of age (n = 183, mean age = 48 in one trial and n = 72, mean age = 50 in the other) with those ≤40 (n = 191; mean age 32.5). The response to the hepatitis A component of TWINRIX declined slightly with age, but >99% of subjects achieved protective antibody levels in both age groups, and antibody titers were comparable to 2 doses of hepatitis A vaccine alone in age matched controls.

The response to hepatitis B immunization is known to decline in vaccinees over 40 years of age. TWINRIX elicited a seroprotective response to hepatitis B in 97% of younger subjects and 93% to 94% of the older subjects, as compared to 92% of older subjects given hepatitis B vaccine alone. Geometric mean titers elicited by TWINRIX were 2,285 in the younger subjects and 1,890 or 1,038 for the older subjects in the 2 trials. Hepatitis B vaccine alone gave titers of 2,896 in younger subjects and 1,157 in those over 40 years of age.

It has been shown in open randomized clinical trials that combining the hepatitis A antigen with the hepatitis B surface antigen in TWINRIX resulted in comparable anti-HAV or anti-HBsAg titers, relative to vaccination with the individual monovalent vaccines or the concomitant administration of each vaccine in opposite arms.

Accelerated Dosing Schedule: In 496 healthy adults, the safety and immunogenicity of TWINRIX given on a 0-, 7-, and 21- to 30-day schedule followed by a booster dose at 12 months (N = 250), was compared to separate vaccinations with monovalent hepatitis A vaccine (HAVRIX at 0 and 12 months) and hepatitis B vaccine (ENGERIX-B at 0, 1, 2, and 12 months) as a control group (N = 246).

Following a booster dose at month 12, the seroprotection rate for hepatitis B and seroconversion rate for hepatitis A at month 13 (the coprimary endpoints) following TWINRIX were non-inferior as compared to the control group. The immune responses for the According to Protocol (ATP) cohort for immunogenicity are shown in Table 4 and Figure 1.

At day 37, following 3 doses of TWINRIX, the seroprotection rate for hepatitis B was 63.2% and in the control group, who received 2 doses of ENGERIX-B, was 43.5%. This difference of 19.76% [95% CI for the difference is 10.16% to 28.99%] is statistically significant (P <0.001). No statistical significant difference in the hepatitis A seroconversion rates was observed between groups at day 37. At day 90, the hepatitis A seroconversion rate following TWINRIX was 100% compared to 95.6% in the control group (P = 0.004). At month 12 before the booster dose, the hepatitis A seroconversion rates between groups, 96.9% following TWINRIX and 86.9% in the control group, were statistically significantly different (P <0.001).

Table 4. Seroconversion and Seroprotection Rates Up to One Month After the Last Dose of Vaccines (According To Protocol Cohort)

	Timepoint	TWINRIX[a]	HAVRIX and ENGERIX-B[b]
		(N = 194-204)	**(N = 197-207)**
% Seroconversion for Hepatitis A[c] (95% CI)	Day 37	98.5 (95.8-99.7)	98.6 (95.8-99.7)
	Day 90	100 (98.2-100)	95.6 (91.9-98.0)
	Month 12	96.9 (93.4-98.9)	86.9 (81.4-91.2)
	Month 13	100 (98.1-100)	100 (98.1-100)
% Seroprotection for Hepatitis B[d] (95% CI)	Day 37	63.2 (56.2-69.9)	43.5 (36.6-50.5)
	Day 90	83.2 (77.3-88.1)	76.7 (70.3-82.3)
	Month 12	82.1 (75.9-87.2)	77.8 (71.3-83.4)
	Month 13	96.4 (92.7-98.5)	93.4 (89.0-96.4)

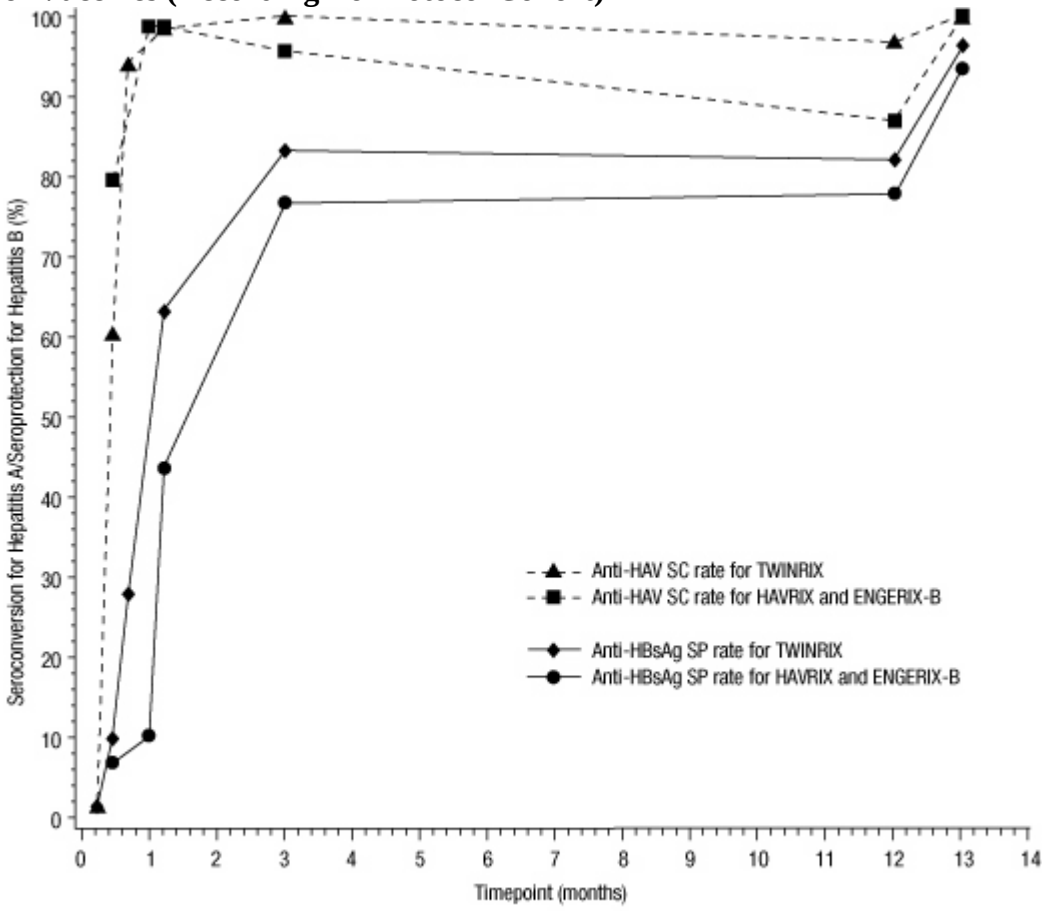
[a] TWINRIX given on a 0-, 7-, and 21- to 30-day schedule followed by a booster at month 12.

[b] HAVRIX 1440 EL.U./1 mL given on a 0- and 12-month schedule and ENGERIX-B 20 mcg/1 mL given on a 0-, 1-, 2-, and 12-month schedule.

[c] Anti-HAV titer ≥assay cut-off: 15 mIU/mL (anti-HAV Behring).

[d] Anti-HBsAg titer ≥10 mIU/mL (AUSAB®).

Figure 1. Seroconversion and Seroprotection Rates Up to One Month After the Last Dose of Vaccines (According To Protocol Cohort)



Anti-HAV titer assay cut-off: 15 mIU/mL (anti-HAV Behring).
Anti-HBsAg titer 10 mIU/mL (AUSAB®).

Immune Response to Simultaneously Administered Vaccines: Limited immunogenicity data are available on the concurrent administration of TWINRIX with other vaccines.

Preservative Free, Thimerosal Free Formulation: In one randomized comparative clinical trial with 446 adults, the preservative free, thimerosal free formulation performed as well as the formulation that contained 2-phenyoxyethanol and trace amounts of thimerosal.

INDICATIONS AND USAGE

TWINRIX is indicated for active immunization of persons 18 years of age or older against disease caused by hepatitis A virus and infection by all known subtypes of hepatitis B virus. As with any vaccine, vaccination with TWINRIX may not protect 100% of recipients. As hepatitis D (caused by the delta virus) does not occur in the absence of HBV infection, it can be expected that hepatitis D will also be prevented by vaccination with TWINRIX.

Immunization is recommended for all susceptible persons 18 years of age or older who are, or

will be, at risk of exposure to both hepatitis A and hepatitis B viruses, including but not limited to:

- *Travelers:* Persons traveling to areas of high/intermediate endemicity for *both* HAV and HBV *who are at increased risk of HBV infection due to behavioral or occupational factors.* (See CLINICAL PHARMACOLOGY.) Vaccine recipients should consult with CDC to determine regions of high or intermediate endemicity for hepatitis A and hepatitis B.
- *Patients With Chronic Liver Disease,* including:
  - alcoholic cirrhosis
  - chronic hepatitis C
  - autoimmune hepatitis
  - primary biliary cirrhosis
- *Persons at Risk Through Their Work:*
  - Laboratory workers who handle live hepatitis A and hepatitis B virus.
  - Police and other personnel who render first-aid or medical assistance.
  - Workers who come in contact with feces or sewage.
  - Healthcare personnel who render first-aid or emergency medical assistance.
  - Personnel employed in day-care centers and correctional facilities.
  - Staff of hemodialysis units.
  - Military recruits and other military personnel at increased risk for HBV.
- *Persons at Increased Risk of Disease due to Their Sexual Practices:*[18,19]
  - Men who have sex with men.
- *Others:*
  - Residents of drug and alcohol treatment centers.
  - People living in, or relocating to, areas of high/intermediate endemicity of HAV and who have risk factors for HBV.
  - Patients frequently receiving blood products including persons who have clotting factor disorders (hemophiliacs and other recipients of therapeutic blood products).
  - Users of injectable illicit drugs.
  - Individuals who are at increased risk for HBV infection and who are close household contacts of patients with acute or relapsing hepatitis A and individuals who are at increased risk for HAV infection and who are close household contacts of individuals with acute or chronic hepatitis B infection.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including yeast and neomycin, is a contraindication (see DESCRIPTION). This vaccine is contraindicated in patients with previous hypersensitivity to TWINRIX or monovalent hepatitis A or hepatitis B vaccines.

WARNINGS

There have been rare reports of anaphylaxis/anaphylactoid reactions following routine clinical use of TWINRIX. (See ADVERSE REACTIONS, Postmarketing Reports.)

TWINRIX is available in vials and 2 types of prefilled syringes. One type of prefilled syringe has a tip cap which may contain natural rubber latex. The other type has a tip cap and a rubber plunger which contain dry natural latex rubber. Use of these syringes may cause allergic reactions in latex sensitive individuals. The vial stopper does not contain latex. (See HOW SUPPLIED.)

Hepatitis A and hepatitis B have relatively long incubation periods. The vaccine may not prevent hepatitis A or hepatitis B infection in individuals who have an unrecognized hepatitis A or hepatitis B infection at the time of vaccination. Additionally, it may not prevent infection in individuals who do not achieve protective antibody titers.

PRECAUTIONS

General: Prior to immunization with TWINRIX, the patient's current health status and medical history should be reviewed. The physician should review the patient's immunization history for possible vaccine sensitivity, previous vaccination-related adverse reactions and occurrence of any adverse–event-related symptoms and/or signs, in order to determine the existence of any contraindication to immunization with TWINRIX and to allow an assessment of benefits and risks. Appropriate medical treatment and supervision should be readily available for immediate use in case of a rare anaphylactic reaction following the administration of the vaccine. Epinephrine injection (1:1,000) and other appropriate agents used for the control of immediate allergic reactions must be immediately available. As with other vaccines, although a moderate or severe acute illness is sufficient reason to postpone vaccination, minor illnesses such as mild upper respiratory infections with or without low-grade fever are not contraindications.[20]

TWINRIX should be given with caution in persons with bleeding disorders such as hemophilia or thrombocytopenia and in persons on anticoagulant therapy, with steps taken to avoid the risk of hematoma following the injection.[20]

A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent the transmission of other infectious agents from person to person. Needles should be disposed of properly and should not be recapped.

As with any vaccine, if administered to immunosuppressed persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.

Multiple Sclerosis: Results from 2 clinical studies indicate that there is no association between hepatitis B vaccination and the development of multiple sclerosis,[21] and that vaccination with hepatitis B vaccine does not appear to increase the short-term risk of relapse in multiple sclerosis.[22]

Information for Vaccine Recipients: Vaccine recipients should be informed by their healthcare provider of the potential benefits and risks of immunization with TWINRIX. When educating vaccine recipients regarding potential side effects, clinicians should emphasize that components of TWINRIX cannot cause hepatitis A or hepatitis B infection.

Vaccine recipients should be instructed to report any severe or unusual adverse reactions to their healthcare provider.

The vaccine recipients should be given the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the CDC website (www.cdc.gov/vaccines). The Vaccine Adverse Events Reporting System (VAERS) toll-free number is 1-800-822-7967. Reporting forms may also be obtained at the VAERS website at www.vaers.hhs.gov.

Carcinogenesis, Mutagenesis, Impairment of Fertility: TWINRIX has not been evaluated for its carcinogenic potential, mutagenic potential, or potential for impairment of fertility.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with TWINRIX. It is also not known whether TWINRIX can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TWINRIX should be given to a pregnant woman only if clearly indicated (see INDICATIONS AND USAGE).

Pregnancy Registry: GlaxoSmithKline maintains a surveillance registry to collect data on pregnancy outcomes and newborn health status outcomes following vaccination with TWINRIX during pregnancy. Women who receive TWINRIX during pregnancy should be encouraged to contact GlaxoSmithKline directly or their healthcare provider should contact GlaxoSmithKline by calling 1-888-452-9622.

Nursing Mothers: It is not known whether TWINRIX is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TWINRIX is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

Geriatric Use: Clinical studies of TWINRIX did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine, and may not reflect the rates observed in practice. As with any vaccine, there is the possibility that broad use of TWINRIX could reveal adverse events not observed in clinical trials.

The safety of TWINRIX has been evaluated in clinical trials involving the administration of approximately 7,500 doses to more than 2,500 individuals.

Of 773 volunteers who participated in the comparative trial conducted in the United States, 389 subjects received at least 1 dose of TWINRIX (0-, 1-, and 6-month schedule) and 384 received at least 1 dose each of ENGERIX-B and HAVRIX as separate but simultaneous injections. Solicited adverse events reported following the administration of TWINRIX are shown in Table 5, compared with adverse events reported after administration of ENGERIX-B and HAVRIX.

Table 5. Rate of Adverse Events Reported After Administration of TWINRIX or ENGERIX-B and HAVRIX

Adverse Event	TWINRIX			ENGERIX-B			HAVRIX	
	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2
Local	(N = 385) %	(N = 382) %	(N = 374) %	(N = 382) %	(N = 376) %	(N = 369) %	(N = 382) %	(N = 369) %
Soreness	37	35	41	41	25	30	53	47
Redness	8	9	11	6	7	9	7	9
Swelling	4	4	6	3	5	5	5	5

Adverse Event	TWINRIX			ENGERIX-B and HAVRIX		
	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3
General	(N = 385) %	(N = 382) %	(N = 374) %	(N = 382) %	(N = 376) %	(N = 369) %
Headache	22	15	13	19	12	14
Fatigue	14	13	11	14	9	10
Diarrhea	5	4	6	5	3	3
Nausea	4	3	2	7	3	5
Fever	4	3	2	4	2	4
Vomiting	1	1	0	1	1	1

Adverse reactions seen with TWINRIX were similar to those observed after vaccination with the monovalent components. The frequency of solicited adverse events did not increase with successive doses of TWINRIX. Most events reported were considered by the subjects as mild and self-limiting and did not last more than 48 hours.

In a clinical trial in which TWINRIX was given on a 0-, 7-, and 21- to 30-day schedule followed by a booster dose at 12 months, solicited local or general adverse events were comparable to those seen in other clinical trials of TWINRIX given on a 0-, 1-, and 6-month schedule.

Among 2,299 subjects in 14 clinical trials, the following adverse experiences were reported to occur within 30 days following vaccination with the frequency shown below. Adverse experiences within 30 days of vaccination in the US clinical trial of TWINRIX given on a 0-, 7-, and 21- to 30-day schedule followed by a booster dose at 12 months were similar to those reported in other clinical trials and postmarketing surveillance.

Incidence 1% to 10% of Injections, Seen in Clinical Trials With TWINRIX:

Infections and Infestations: Upper respiratory tract infections.

General Disorders and Administration Site Conditions: Injection site induration.

Incidence <1% of Injections, Seen in Clinical Trials With TWINRIX:

Infections and Infestations: Respiratory tract illnesses.

Metabolism and Nutrition Disorders: Anorexia.

Psychiatric Disorders: Agitation, insomnia.

Nervous System Disorders: Dizziness, migraine, paresthesia, somnolence, syncope.

Ear and Labyrinth Disorders: Vertigo.

Vascular Disorders: Flushing.

Gastrointestinal System: Abdominal pain, vomiting.

Skin and Subcutaneous Tissue Disorders: Erythema, petechiae, rash, sweating, urticaria.

Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain, myalgia.

General Disorders and Administration Site Conditions: Injection site ecchymosis, injection site pruritus, influenza-like symptoms, irritability, weakness.

Incidence <1% of Injections, Seen in Clinical Trials With HAVRIX[a] and/or ENGERIX-B[b]:

Blood and Lymphatic System Disorders: Lymphadenopathy.[a+b]

Nervous System: Dysgeusia,[a] hypertonic episode,[a] tingling.[b]

Eye Disorders: Photophobia.[a]

Vascular Disorders: Hypotension.[b]

Gastrointestinal Disorders: Constipation.[b]

Investigations: Elevation of creatine phosphokinase.[a]

Postmarketing Reports: Worldwide voluntary reports of adverse events received for TWINRIX, HAVRIX, and/or ENGERIX-B since market introduction of these vaccines are listed below. These lists include serious events or events which have suspected causal connections to components of these or other vaccines or drugs. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Postmarketing Reports With TWINRIX:

Infections and Infestations: Herpes zoster, meningitis.

Blood and Lymphatic System Disorders: Thrombocytopenia, thrombocytopenic purpura.

Immune System Disorders: Allergic reaction, anaphylactoid reaction, anaphylaxis, serum sickness–like syndrome days to weeks after vaccination including arthralgia/arthritis (usually transient), fever, urticaria, erythema multiforme, ecchymoses, and erythema nodosum.

Nervous System Disorders: Bell's palsy, convulsions, encephalitis, encephalopathy, Guillain-Barré syndrome, hypoesthesia, myelitis, multiple sclerosis, neuritis, neuropathy, optic neuritis, paralysis, paresis, transverse myelitis.

Eye Disorders: Conjunctivitis, visual disturbances.

Ear and Labyrinth Disorders: Earache, tinnitus.

Cardiac Disorders: Palpitations, tachycardia.

Vascular Disorders: Vasculitis.

Respiratory, Thoracic and Mediastinal Disorders: Bronchospasm including

asthma-like symptoms, dyspnea.

Gastrointestinal Disorders: Dyspepsia.

Hepatobiliary disorders: Hepatitis, jaundice.

Skin and Subcutaneous Tissue Disorders: Alopecia, angioedema, eczema, erythema multiforme, erythema nodosum, hyperhydrosis, lichen planus.

Musculoskeletal and Connective Tissue Disorders: Arthritis, muscular weakness.

General Disorders and Administration Site Conditions: Chills, injection site reaction, malaise.

Investigations: Abnormal liver function tests.

Postmarketing Reports With HAVRIX and/or ENGERIX-B: Worldwide voluntary reports of adverse events received for HAVRIX and/or ENGERIX-B but not already reported for TWINRIX are listed below.

Eye Disorders: Keratitis.[b]

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome.[b]

Congenital, Familial and Genetic Disorders: Congenital abnormality.[a]

[a]Following HAVRIX.

[b]Following ENGERIX-B.

[a+b]Following either HAVRIX or ENGERIX-B.

Reporting of Adverse Events: The US Department of Health and Human Services has established VAERS to accept reports of suspected adverse events after the administration of any vaccine, including, but not limited to, the reporting of events required by the National Childhood Vaccine Injury Act of 1986. The toll-free number for VAERS forms and information is 1-800-822-7967.[23] Reporting forms may also be obtained at the VAERS website at www.vaers.hhs.gov.

DOSAGE AND ADMINISTRATION

TWINRIX should be administered by intramuscular injection. *Do not inject intravenously or intradermally*. In adults, the injection should be given in the deltoid region. TWINRIX should not be administered in the gluteal region; such injections may result in a suboptimal response.

Primary immunization for adults consists of 3 doses, given on a 0-, 1-, and 6-month schedule. Alternatively, a 4-dose schedule, given on days 0, 7 and 21 to 30 followed by a booster dose at month 12 may be used. Each 1-mL dose contains 720 EL.U. of inactivated hepatitis A virus and 20 mcg of hepatitis B surface antigen.

When concomitant administration of other vaccines or immunoglobulin (IG) is required, they should be given with different syringes and at different injection sites.

Preparation for Administration: Shake vial or syringe well before withdrawal and use. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered. With thorough agitation, TWINRIX is a slightly turbid white suspension. Do not administer if it appears otherwise.

The vaccine should be used as supplied; no dilution or reconstitution is necessary. The full

recommended dose of the vaccine should be used. After removal of the appropriate volume from a single-dose vial, any vaccine remaining in the vial should be discarded.

STORAGE

Store TWINRIX refrigerated between 2° and 8° C (36° and 46° F). **Do not freeze.** Discard if the vaccine has been frozen. Do not use after expiration date shown on the label.

HOW SUPPLIED

TWINRIX is available in single-dose vials and prefilled disposable TIP-LOK® syringes (packaged without needles) (Preservative Free Formulation):
NDC 58160-815-01 Vial (contains no latex) in Package of 10: NDC 58160-815-11
NDC 58160-815-34 Syringe (tip cap may contain latex) in Package of 1: NDC 58160-815-34
NDC 58160-815-43 Syringe (tip cap may contain latex) in Package of 5: NDC 58160-815-48
NDC 58160-815-43 Syringe (tip cap may contain latex) in Package of 10: NDC 58160-815-52
NDC 58160-815-32 Syringe (tip cap and plunger contain latex) in Package of 1: NDC 58160-815-32
NDC 58160-815-41 Syringe (tip cap and plunger contain latex) in Package of 5: NDC 58160-815-46

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