HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TWINRIX safely and effectively. See full prescribing information for TWINRIX.

TWINRIX [Hepatitis A & Hepatitis B (Recombinant) Vaccine]
Suspension for Intramuscular Injection
Initial U.S. Approval: 2001

----------INDICATIONS AND USAGE----------

TWINRIX is a vaccine indicated for active immunization against disease caused by hepatitis A virus and infection by all known subtypes of hepatitis B virus. TWINRIX is approved for use in persons 18 years of age or older. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- TWINRIX is administered by intramuscular injection. (2.2)
- Standard Dosing: A series of 3 doses (1 mL each) given on a 0-, 1-, and 6-month schedule. (2.3)
- Accelerated Dosing: A series of 4 doses (1 mL each) given on days 0, 7, and 21 to 30 followed by a booster dose at month 12. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

Suspension for injection available in 1-mL single-dose vials and prefilled syringes. (3, 11, 16)

----------CONTRAINDICATIONS----------

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis A-containing or hepatitis B-containing vaccine, or to any component of TWINRIX, including yeast and neomycin. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions. (5.1)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including TWINRIX. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.2)

---------- ADVERSE REACTIONS ----------

Following any dose of TWINRIX, the most common (≥10%) solicited injection site reactions were injection site soreness (35% to 41%) and redness (8% to 11%); the most common solicited systemic adverse events were headache (13% to 22%) and fatigue (11% to 14%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

----------DRUG INTERACTIONS----------

Do not mix TWINRIX with any other vaccine or product in the same syringe or vial. (7.1)

---------- USE IN SPECIFIC POPULATIONS ----------

- Safety and effectiveness of TWINRIX have not been established in pregnant women, nursing mothers, and pediatric patients. (8.1, 8.3, 8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: X/201X

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TWINRIX® is indicated for active immunization against disease caused by hepatitis A virus and infection by all known subtypes of hepatitis B virus. TWINRIX is approved for use in persons 18 years of age or older.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Shake well before use. With thorough agitation, TWINRIX is a slightly turbid white suspension. Do not administer if it appears otherwise. 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.

For the prefilled syringes, attach a sterile needle and administer intramuscularly.

For the vials, use a sterile needle and sterile syringe to withdraw the 1-mL dose and administer intramuscularly. Changing needles between drawing vaccine from a vial and injecting it into a recipient is not necessary unless the needle has been damaged or contaminated. Use a separate sterile needle and syringe for each individual.

2.2 Administration

TWINRIX should be administered by intramuscular injection only as a 1-mL dose. Administer in the deltoid region. Do not administer in the gluteal region; such injections may result in a suboptimal response.

Do not administer this product intravenously, intradermally, or subcutaneously.

2.3 Recommended Dose and Schedule

Standard dosing schedule consists of 3 doses (1 mL each), given intramuscularly at 0, 1, and 6 months. Alternatively, an accelerated schedule of 4 doses (1 mL each), given intramuscularly on days 0, 7, and 21 to 30 followed by a booster dose at month 12 may be used.

3 DOSAGE FORMS AND STRENGTHS

Suspension for injection available in 1-mL single-dose vials and prefilled TIP-LOK® syringes *[see Description (11) and How Supplied/Storage and Handling (16)]*.

4 CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis A-containing or hepatitis B-containing vaccine, or to any component of TWINRIX, including yeast and neomycin, is a contraindication to administration of TWINRIX *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Latex

The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions.

5.2 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including TWINRIX. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

5.3 Preventing and Managing Allergic Vaccine Reactions

Prior to immunization, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an assessment of benefits and risks. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. *[See Contraindications (4).]*

5.4 Moderate or Severe Acute Illness

To avoid diagnostic confusion between manifestations of an acute illness and possible vaccine adverse effects, vaccination with TWINRIX should be postponed in persons with moderate or severe acute febrile illness unless they are at immediate risk of hepatitis A or hepatitis B infection.

5.5 Altered Immunocompetence

Immunocompromised persons, including individuals receiving immunosuppressive therapy, may have a diminished immune response to TWINRIX.

5.6 Multiple Sclerosis

Results from 2 clinical studies indicate that there is no association between hepatitis B vaccination and the development of multiple sclerosis,[1] and that vaccination with hepatitis B vaccine does not appear to increase the short-term risk of relapse in multiple sclerosis.[2]

5.7 Limitations of Vaccine Effectiveness

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, vaccination with TWINRIX may not protect all individuals.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction 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.

Following any dose of TWINRIX, the most common (≥10%) solicited injection site reactions were injection site soreness (35% to 41%) and redness (8% to 11%); the most common solicited systemic adverse events were headache (13% to 22%) and fatigue (11% to 14%).

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

In a US study, 773 subjects (18 to 70 years of age) were randomized 1:1 to receive TWINRIX (0-, 1-, and 6-month schedule) or concurrent administration of ENGERIX-B (0-, 1-, and 6-month schedule) and HAVRIX (0- and 6-month schedule). Solicited local adverse reactions and systemic adverse events were recorded by parents/guardians on diary cards for 4 days (days 0 to 3) after vaccination. Unsolicited adverse events were recorded for 31 days after vaccination. Solicited events reported following the administration of TWINRIX or ENGERIX-B and HAVRIX are presented in Table 1.

Table 1. Rates of Local Adverse Reactions and Systemic Adverse Events within 4 Days of Vaccination[a] with TWINRIX[b] or ENGERIX-B and HAVRIX[c]

	TWINRIX			ENGERIX-B			HAVRIX	
	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2
	(N = 385)	(N = 382)	(N = 374)	(N = 382)	(N = 376)	(N = 369)	(N = 382)	(N = 369)
Local	%	%	%	%	%	%	%	%
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

	TWINRIX			ENGERIX-B and HAVRIX		
	Dose 1	Dose 2	Dose 3	Dose 1[d]	Dose 2[e]	Dose 3[d]
	(N = 385)	(N = 382)	(N = 374)	(N = 382)	(N = 376)	(N = 369)
Systemic	%	%	%	%	%	%
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

[a] Within 4 days of vaccination defined as day of vaccination and the next 3 days.

[b] 389 subjects received at least 1 dose of TWINRIX.

[c] 384 subjects received at least 1 dose each of ENGERIX-B and HAVRIX.

[d] Doses 1 and 3 included ENGERIX-B and HAVRIX in the control group receiving separate vaccinations.

[e] Dose 2 included only ENGERIX-B in the control group receiving separate vaccinations.

Most solicited local adverse reactions and systemic adverse events seen with TWINRIX 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 adverse reactions or systemic 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 events were reported to occur within 30 days following vaccination:

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 Disorders: 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 and/or ENGERIX-B

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

Nervous System Disorders: Dysgeusia,[a] hypertonia,[a] tingling.[b]

Eye Disorders: Photophobia.[a]

Vascular Disorders: Hypotension.[b]

Gastrointestinal Disorders: Constipation.[b]

Investigations: Creatine phosphokinase increased.[a]

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

[a] Following HAVRIX.

[b] Following ENGERIX-B.

Adverse events 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 comparable to those reported in other clinical trials.

6.2 Postmarketing Experience

The following adverse events have been identified during postapproval use of TWINRIX, HAVRIX, or ENGERIX-B. 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 product exposure.

Postmarketing Experience with TWINRIX

The following list includes serious events or events which have suspected causal connection to components of 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, immediate injection site pain, stinging, and burning sensation, injection site reaction, malaise.

Investigations: Abnormal liver function tests.

<u>Postmarketing Experience with HAVRIX and/or ENGERIX-B</u>

The following list includes serious events or events which have suspected causal connection to components of HAVRIX and/or ENGERIX-B, not already reported above for TWINRIX.

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.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Vaccines and Immune Globulin

Do not mix TWINRIX with any other vaccine or product in the same syringe or vial.

When concomitant administration of immunoglobulin is required, it should be given with a different syringe and at a different injection site.

There are no data to assess the concomitant use of TWINRIX with other vaccines.

7.2 Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to TWINRIX.

8 USE IN SPECIFIC POPULATIONS

8.1 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 needed.

8.3 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.

8.4 Pediatric Use

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

8.5 Geriatric Use

Clinical studies of TWINRIX did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects *[see Clinical Studies (14.1, 14.3)]*.

11 DESCRIPTION

TWINRIX [Hepatitis A & Hepatitis B (Recombinant) Vaccine] is a 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 for intramuscular administration that contains inactivated hepatitis A virus (strain HM175) and noninfectious hepatitis B virus surface antigen (HBsAg). The hepatitis A virus is propagated in

MRC-5 human diploid cells and inactivated with formalin. The purified HBsAg is obtained by culturing genetically engineered *Saccharomyces cerevisiae* yeast cells, which carry the surface antigen gene of the hepatitis B virus. Bulk preparations of each antigen are adsorbed separately onto aluminum salts and then pooled during formulation.

A 1-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, and Water for Injection. From the manufacturing process each 1-mL dose of TWINRIX also contains residual formalin (not more than 0.1 mg), MRC-5 cellular proteins (not more than 2.5 mcg), neomycin sulfate (an aminoglycoside antibiotic included in the cell growth media; not more than 20 ng) and yeast protein (no more than 5%).

TWINRIX is available in vials and prefilled syringes. The tip caps of the prefilled syringes contain natural rubber latex; the plungers are not made with natural rubber latex. The vial stoppers are not made with natural rubber latex.

TWINRIX is formulated without preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hepatitis A

The course of infection with hepatitis A virus (HAV) is extremely variable, ranging from asymptomatic infection to fulminant hepatitis.[3]

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. Seroconversion is defined as antibody titers equal to or greater than the assay cut-off (cut-off values vary depending on the assay used) in those previously seronegative.

Hepatitis B

Infection with hepatitis B virus (HBV) can have serious consequences including acute massive hepatic necrosis and chronic active hepatitis. Chronically infected persons are at increased risk for cirrhosis and hepatocellular carcinoma.

Antibody concentrations ≥10 mIU/mL against HBsAg are recognized as conferring protection against hepatitis B virus infection.[4]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

TWINRIX has not been evaluated for its carcinogenic or mutagenic potential, or for impairment of fertility.

14 CLINICAL STUDIES

14.1 Immunogenicity: Standard 0-, 1-, and 6-Month Dosing Schedule

In 11 clinical trials, sera from 1,551 healthy adults 17 to 70 years of age, including 555 male subjects and 996 female subjects, were analyzed following administration of 3 doses of TWINRIX on a 0-, 1-, and 6-month schedule. Seroconversion (defined as equal to or greater than assay cut-off depending on assay used) for antibodies against HAV was elicited in 99.9% of vaccinees, and protective antibodies (defined as ≥10 mIU/mL) against HBV surface antigen were detected in 98.5% of vaccinees, 1 month after completion of the 3-dose series (Table 2).

Table 2. Seroconversion and Seroprotection Rates in Worldwide Clinical Trials

TWINRIX Dose	N	% Seroconversion for Hepatitis A[a]	% Seroprotection for Hepatitis B[b]
1	1,587	93.8	30.8
2	1,571	98.8	78.2
3	1,551	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® Test).

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 the 773 adults (18 to 70 years of age) 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 rates against HAV and seroprotection rates against HBV are presented in Table 3; GMTs are presented in Table 4. The absolute difference in anti-HAV seropositivity rates between groups was 0.36% (90% CI: -1.8, 3.1). Non-inferiority in terms of anti-HAV response was demonstrated (lower limit of the 90% CI was higher than the pre-specified non-inferiority criterion of -4.3%). The absolute difference in anti-HBsAg seroprotection rates between groups was 2.8% (90% CI: -1.3, 7.7). Non-inferiority in terms of anti-HBV response was demonstrated (lower limit of the 90% CI was higher than the pre-specified non-inferiority criterion of -9.4%).

Table 3. Seroconversion and Seroprotection Rates in a 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)

CI = Confidence Interval

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

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

Table 4. Geometric Mean Titers in a 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 ENGERIX-B	268	Month 1	444	6
	269	Month 2	257	18
	269	Month 7	2948 (2638, 3294)	1871 (1428, 2450)

GMT = Geometric mean titer; CI = Confidence Interval

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.

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 this clinical trial. 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.

14.2 Immunogenicity: Accelerated Dosing Schedule (Day 0-, 7-, and 21-30, Month 12)

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, seroprotection rates for hepatitis B and seroconversion rates for hepatitis A at month 13 following TWINRIX were non-inferior to the control group. The absolute difference in anti-HBs seroprotection rates between groups (HAVRIX + ENGERIX-B minus TWINRIX) was -2.99 (95% CI: -7.80, 1.49). Non-inferiority was demonstrated as the upper limit of the 95% CI was lower than the pre-defined limit of 7%. The absolute difference in anti-HAV seroprotection rates between groups (HAVRIX + ENGERIX-B minus TWINRIX) was 0 (95% CI: -1.91, 1.94). Non-inferiority was demonstrated as the upper limit of the 95% CI was lower than the pre-defined limit of 7%. The immune responses are presented in Table 5.

Table 5. 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)

CI = Confidence Interval

[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 Test).

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

14.3 Immunogenicity in Adults Older than 40 Years of Age

The effect of age on immune response to TWINRIX was studied in 2 trials. The first trial evaluated subjects 41 to 63 years of age (N = 72; mean age = 50). All subjects were seropositive for anti-HAV antibodies following the third dose of TWINRIX. For the hepatitis B response, 94% of subjects were seroprotected after the third dose of TWINRIX.

The second trial included subjects 19 years of age and older with a comparison between those older than 40 years of age (N = 183, 41 to 70 years of age; mean age = 48) with those 40 years of

age or younger (N = 191; 19 to 40 years of age; mean age 33). Over 99% of subjects in both age groups achieved a seropositive response for anti-HAV antibodies and GMTs were comparable between the age groups. In the older subjects who received TWINRIX, 92.9% (95% CI: 88.2, 96.2) achieved seroprotection against hepatitis B compared to 96.9% (95% CI: 93.3, 98.8) of the younger subjects. The GMT was 1,890 mIU/mL in the older subjects compared to 2,285 mIU/mL in the younger subjects.

14.4 Duration of Immunity

Two clinical trials involving a total of 129 subjects demonstrated that antibodies to both HAV and HBV surface antigen 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.

15 REFERENCES

1. Ascherio A, Zhang SM, Hernán MA, et al. Hepatitis B vaccination and the risk of multiple sclerosis. *N Engl J Med.* 2001;344(5):327-332.
2. Confavreux C, Suissa S, Saddier P, et al. Vaccination and the risk of relapse in multiple sclerosis. *N Engl J Med.* 2001;344(5):319-326.
3. Lemon SM. Type A viral hepatitis: new developments in an old disease. *N Engl J Med.* 1985;313(17):1059-1067.
4. Frisch-Niggemeyer W, Ambrosch F, Hofmann H. The assessment of immunity against hepatitis B after vaccination. *J Bio Stand.* 1986;14(3):255-258.

16 HOW SUPPLIED/STORAGE AND HANDLING

TWINRIX is available in 1-mL single-dose vials and 1-mL single-dose prefilled disposable TIP-LOK syringes (packaged without needles) (Preservative Free Formulation):

NDC 58160-815-01 Vial in Package of 10: NDC 58160-815-11

NDC 58160-815-05 Syringe in Package of 1: NDC 58160-815-34

NDC 58160-815-43 Syringe in Package of 10: NDC 58160-815-52

Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze; discard if product has been frozen.

17 PATIENT COUNSELING INFORMATION

- Inform vaccine recipients of the potential benefits and risks of immunization with TWINRIX.

- Emphasize, when educating vaccine recipients regarding potential side effects, that components of TWINRIX cannot cause hepatitis A or hepatitis B infection.
- Instruct vaccine recipients to report any adverse events to their healthcare provider.
- Inform that safety and efficacy have not been established in pregnant women.
- Give vaccine recipients 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 Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

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