Twinrix®

Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine

DESCRIPTION

Twinrix [Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine] is a sterile bivalent vaccine containing the antigenic components used in producing Havrix® (Hepatitis A Vaccine, Inactivated) 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 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 not less than 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, 5.0 mg 2-phenoxyethanol as a preservative, sodium chloride, phosphate buffer, polysorbate 20, Water for Injection, traces of formalin (not more than 0.1 mg), a trace amount of thimerosal (<1 mcg mercury) from the manufacturing process, 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/dose) remain following purification. The manufacturing procedures used to manufacture *Twinrix* result in a product that contains no more than 5% yeast protein.

Twinrix [Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine] is supplied as a sterile suspension for intramuscular administration. The vaccine is ready for use without reconstitution; it must be shaken before administration since a fine white deposit with a clear colorless supernatant may form on storage. After shaking, the vaccine is a slightly turbid white suspension.

CLINICAL PHARMACOLOGY

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

Hepatitis A: The hepatitis A virus (HAV) belongs to the picornavirus family. Only one serotype of HAV has been described.[1]

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[2]; (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[3]; (5) during travel to areas of the world with poor hygienic conditions[4]; (6) among institutionalized children and adults[5]; (7) in day-care centers[6]; (8) by parenteral transmission, either blood transfusions or sharing needles with infected people.[7]

In the United States, attack rates for hepatitis A disease are cyclical and vary by population. The rates have increased gradually from 10.4 per 100,000 in 1987 to 11.7 per 100,000 in 1996.[8]

The incubation period for hepatitis A averages 28 days (range: 15 to 50 days).[9] The course of hepatitis A infection is extremely variable, ranging from asymptomatic infection to icteric hepatitis. However, most adults (76% to 97%)[10] become symptomatic. Symptoms range from mild and transient to severe and prolonged and may include fever, nausea, vomiting and diarrhea in the prodromal phase, followed by jaundice in up to 88% of adults, as well as hepatomegaly and biochemical evidence of hepatocellular damage.[10] Recovery is generally complete and followed by protection against HAV infection. However, illness may be prolonged, and relapse of clinical illness and viral shedding have been described.[11] Up to 22% of adults who contract hepatitis A are hospitalized and approximately 100 patients die annually in the United States from complications of hepatitis A.[12]

Chronic shedding of HAV in feces has not been demonstrated, but relapses of hepatitis A can occur in as many as 20% of patients[11,13] and fecal shedding of HAV may recur at this time.[11] 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.[12]

The presence of antibodies to HAV, as detected in a standardized assay (HAVAB), is an indication of the presence of protective antibodies against hepatitis A disease. Natural infection provides lifelong immunity even when antibodies to hepatitis A are undetectable. At present, studies show the duration of protection afforded by Twinrix [Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine] against hepatitis A lasts at least 4 years.[14]

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. The mode of transmission of hepatitis B may be: by contact (contaminated body secretions including semen, vaginal secretions, blood, saliva); percutaneously (usually through accidental needlesticks or by sharing needles with infected people); or by maternal-neonatal transmission.[15]

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.

Clinical infection with hepatitis B may occur in two 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 four 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 6% to 10% of adults who are infected in the United States will become HBV carriers.[12] An estimated 200 to 300 million people are chronic carriers of HBV worldwide.[12] 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.[12] About 50,000 cases of hepatitis are reported per year,

about half of which are hepatitis B. Unreported cases may be 10 times greater. Close contact (sexual contact or household contact) or exposure to blood from infected individuals is associated with increased risk of infection. 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.[12,16]

Reduced Risk of Hepatocellular Carcinoma: A clear link has been demonstrated between chronic HBV infection and the occurrence of hepatocellular carcinoma. In a Taiwanese study, the institution of universal childhood immunization against HBV has been shown to decrease the incidence of hepatocellular carcinoma among children.[17] In a Korean study in adult males, vaccination against HBV has been shown to decrease the incidence of, and risk of, developing hepatocellular carcinoma in adults.[18]

There is no definitive treatment for acute HBV infection. However, those who develop antibodies to HBsAg after active infection are protected against subsequent infection. Antibody titers ≥10 mIU/mL against HBsAg are recognized as conferring protection against HBV.[19] Seroconversion is defined as an antibody titer ≥1 mIU/mL.

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 eleven clinical trials were analyzed following administration of three doses of Twinrix [Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine] 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%, one month after completion of the three-dose series.

Table 1. Immunogenicity in *Twinrix* Worldwide Clinical Trials

***Twinrix* Dose**	**N**	**% Seroconversion for Hepatitis A***	**% Seroprotection for Hepatitis B†**
1	1,587	93.8	30.8
2	1,571	98.8	78.2
3	1,551	99.9	98.5

*anti-HAV titer ≥assay cut-off: 20 mIU/mL (HAVAB Test) or 33 mIU/mL (Enzymun-Test®).
†anti-HBsAg titer ≥10 mIU/mL (AUSAB®).

One of the eleven trials was a comparative trial conducted in a U.S. population given either *Twinrix* (on a 0-, 1-, 6-month schedule) or *Havrix* (0-, 6-month schedule) and *Engerix-B* (0-, 1-, 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 [Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine] 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* U.S. Clinical Trial

Vaccine	N	Time-point	% Seroconversion for Hepatitis A* (95% CI)	% Seroprotection for Hepatitis 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)

*anti-HAV titer ≥assay cut-off: 33 mIU/mL (Enzymun-Test®).
†anti-HBsAg titer ≥10 mIU/mL (AUSAB®).

Since the *Twinrix*-induced immune responses to hepatitis A and hepatitis B 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* U.S. Clinical Trial

Vaccine	N	Time-point	GMT to Hep A (95% CI)	GMT to Hep B (95% CI)
Twinrix	263	Month 1	335	8
	259	Month 2	636	23
	264	Month 7	4,756 (4,152-5,448)	2,099 (1,663-2,649)
Havrix and *Engerix-B*	268	Month 1	444	6
	269	Month 2	257	18
	269	Month 7	2,948 (2,638-3,294)	1,871 (1,428-2,450)

It was noted that the antibody titers achieved one month after the final dose of *Twinrix* were higher than titers achieved one 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 two vaccines, whereby *Twinrix* vaccinees received three doses of 720 EL.U. of hepatitis A antigen at 0, 1 and 6 months, whereas *Havrix* vaccinees received two 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 three-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 two 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 two 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 [Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine] 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 two trials. Hepatitis B vaccine alone gave titers of 2,896 in younger subjects and 1,157 in those over forty.

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.

Immune response to simultaneously administered vaccines: There have been no studies of concomitant administration of *Twinrix* with other vaccines.

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*.

Twinrix [Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine] will not prevent hepatitis caused by other agents such as hepatitis C virus, hepatitis E virus or other pathogens known to infect the liver.

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 B viruses, including but not limited to:

Travelers to areas of high/intermediate endemicity for *both* HAV and HBV (see Table 4) *who are at increased risk of HBV infection due to behavioral or occupational factors.* (See CLINICAL PHARMACOLOGY.)

Table 4. Hepatitis A and B Endemicity by Region

Geographic Region	**HAV**	**HBV**
Africa	High	High (most)
Caribbean	High	Intermediate
Central America	High	Intermediate
South America (temperate)	High	Intermediate
South America (tropical)	High	High
South and Southeast Asia*	High	High
Middle East†	High	High
Eastern Europe	Intermediate	Intermediate
Southern Europe	Intermediate	Intermediate
Former Soviet Union	Intermediate	Intermediate

*Japan: Low HAV and intermediate HBV endemicity.
† Israel: Intermediate HBV endemicity.

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. Residents of drug and alcohol treatment centers. Staff of hemodialysis units.

People living in, or relocating to, areas of high/intermediate endemicity of HAV and who have risk factors for HBV.

Men who have sex with men.

Persons at increased risk of disease due to their sexual practices.[20, 21]

Patients frequently receiving blood products including persons who have clotting-factor disorders (hemophiliacs and other recipients of therapeutic blood products).

Military recruits and other military personnel at increased risk for HBV.

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

Twinrix [Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine] is contraindicated in people with known hypersensitivity to yeast or any other component of the vaccine or in subjects having shown signs of hypersensitivity after previous administration of *Twinrix* or monovalent hepatitis A or hepatitis B vaccines.

WARNINGS

There have been rare reports of anaphylaxis/anaphylactoid reactions following routine clinical use of *Havrix*. (See CONTRAINDICATIONS.)

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

PRECAUTIONS

General

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.[22]

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.

Multiple Sclerosis: Results from two clinical studies indicate that there is no association between hepatitis B vaccination and the development of multiple sclerosis[23] and that vaccination with hepatitis B vaccine does not appear to increase the short-term risk of relapse in multiple sclerosis.[24]

Twinrix should be administered with caution to people on anticoagulants, those with thrombocytopenia or a bleeding disorder since bleeding may occur following intramuscular administration to these subjects.

As with any vaccine, if administered to immunosuppressed persons or persons receiving immunosuppressive therapy, the expected immune response may not be obtained.[25]

Before the injection of any vaccine, the physician should take all reasonable precautions to prevent allergic or other adverse reactions, including understanding the use of the vaccine concerned, and the nature of the side effects and adverse reactions that may follow its use.

Prior to immunization with any vaccine, the patient's 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 [Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine] and to allow an assessment of benefits and risks. As with any parenteral vaccine, epinephrine injection (1:1000) and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

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

Information for Patients

Patients should be informed of the benefits and risks of immunization with *Twinrix*, and of the importance of completing the immunization series. As with any vaccine, it is important when a subject returns for the next dose in a series that he/she be questioned concerning the occurrence of any symptoms and/or signs after a previous dose of the same vaccine and that adverse events be reported. The U.S. Department of Health and Human Services has established the Vaccine Adverse Events Reporting System (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.[26]

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 Exposure Registry: Health care providers are encouraged to register pregnant women who receive *Twinrix* in the SmithKline Beecham Pharmaceuticals vaccination pregnancy registry by calling 1-888-825-5249.

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 [Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine] is administered to a nursing woman.

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

ADVERSE REACTIONS
In clinical trials involving the administration of 6,543 doses to 2,299 individuals and during routine clinical use of the vaccine outside the United States, *Twinrix* has been generally well tolerated.

Of 773 volunteers who participated in the comparative trial conducted in the United States, 389 subjects received at least one dose of *Twinrix* and 384 received at least one 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 [Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine].

Most events reported were considered by the subjects as mild and self-limiting and did not last more than 48 hours.

Among 2,299 subjects in fourteen clinical trials, the following adverse experiences were reported to occur within 30 days following vaccination with the frequency shown below.

Incidence 1% to 10% of injections

Local reactions at injection site: Induration.

Respiratory system: Upper respiratory tract infections.

Incidence <1% of injections

Local reactions at injection site: Pruritus, ecchymoses.

Body as a whole: Sweating, weakness, flushing, influenza-like symptoms.

Cardiovascular system: Syncope.

Gastrointestinal system: Abdominal pain, anorexia, vomiting.

Musculoskeletal system: Arthralgia, myalgia, back pain.

Nervous system: Migraine, paresthesia, vertigo, somnolence, insomnia, irritability, agitation, dizziness.

Respiratory system: Respiratory tract illnesses.

Skin and appendages: Rash, urticaria, petechiae, erythema.

As with any vaccine, it is possible that expanded routine clinical use of the vaccine could reveal rare adverse events.

Potential adverse effects

The following additional adverse effects have been reported with either *Engerix-B* or *Havrix* in clinical trials and/or during marketed use.

Incidence <1% of injections, seen in clinical trials with monovalent hepatitis A and/or hepatitis B vaccines

Body as a whole: Tingling.[b]

Cardiovascular system: Hypotension.[b]

Gastrointestinal: Constipation,[b] dysgeusia.[a]

Hematologic/lymphatic: Lymphadenopathy.[a+b]

Musculoskeletal system: Elevation of creatine phosphokinase.[a]

Nervous system: Hypertonic episode,[a] photophobia.[a]

Post-marketing Reports

Since market introduction, more than 61 million doses of *Havrix* and more than 600 million doses of *Engerix-B* have been distributed worldwide (circa 2000).[27] Voluntary reports of adverse events in people receiving either *Engerix-B* or *Havrix* that have been reported since market introduction of the vaccines include the following:

Body as a whole: Anaphylaxis/anaphylactoid reactions and allergic reactions.[a]

Hypersensitivity: Erythema multiforme including Stevens-Johnson syndrome,[b] angioedema,[b] arthritis,[b] serum-sickness-like syndrome days to weeks after vaccination including arthralgia/arthritis (usually transient), fever, urticaria, erythema multiforme, ecchymoses and erythema nodosum.[b]

Cardiovascular system: Tachycardia/palpitations.[b]

Skin and appendages: Erythema multiforme,[a] hyperhydrosis,[a] angioedema,[a] eczema,[b] herpes zoster,[b] erythema nodosum,[b] alopecia.[b]

Gastrointestinal system: Jaundice,[a] hepatitis,[a] abnormal liver function tests,[b] dyspepsia.[b]

Hematologic/lymphatic: Thrombocytopenia.[b]

Nervous system: Convulsions,[a] paresis,[b] encephalopathy,[a] neuropathy,[a+b] myelitis,[a] Guillain-Barré syndrome,[a+b] multiple sclerosis,[a+b] Bell's palsy,[b] transverse myelitis,[b] optic neuritis.[b]

Respiratory system: Dyspnea,[a] bronchospasm including asthma-like symptoms.[b]

Special senses: Conjunctivitis,[b] keratitis,[b] visual disturbances,[b] tinnitus,[b] earache.[b]

Other: Congenital abnormality.[a]

a: Following *Havrix.*
b: Following *Engerix-B.*
a+b: Following either *Havrix* or *Engerix-B.*

DOSAGE AND ADMINISTRATION

Twinrix [Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine] 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.

For individuals with clotting-factor disorders who are at risk of hemorrhage following intramuscular injection, the ACIP recommends that when any intramuscular vaccine is indicated for such patients, "...it should be administered intramuscularly if, in the opinion of a physician familiar with the patient's bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection."[28]

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 or discoloration prior to administration. With thorough agitation, *Twinrix* is a slightly turbid white suspension. Discard 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.

Primary immunization for adults consists of three doses, given on a 0-, 1- and 6-month schedule. Each 1 mL dose contains 720 EL.U. of inactivated hepatitis A virus and 20 mcg of hepatitis B surface antigen.

STORAGE

Store refrigerated between 2° and 8° C (36° and 46° F). **DO NOT FREEZE**; discard if product has been frozen. Do not dilute to administer.

HOW SUPPLIED

Twinrix [Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine] is supplied as a slightly turbid white suspension in vials and prefilled Tip-Lok® syringes containing a 1.0 mL single dose.

Single-Dose Vials
NDC 58160-850-01 (package of 1)
NDC 58160-850-11 (package of 10)

Single-Dose Prefilled Disposable Tip-Lok® Syringes (packaged without needles)
NDC 58160-850-46 (package of 5)

REFERENCES

1. Day SP, Lemon SM. Hepatitis A virus. In: Gorbach SL, Bartlett JG, Blacklow NR, eds. *Infectious Diseases*. Philadelphia, PA: WB Saunders Company; 1992:1787-1791. **2.** Dienstag JL, Routenberg JA, Purcell RH, et al. Foodhandler-associated outbreak of hepatitis type A. An immune electron microscopic study. *Ann Intern Med.* 1975;83:647-650. **3.** Mackowiak PA, Caraway CT, Portnoy BL. Oyster-associated hepatitis: Lessons from the Louisiana experience. *Am J Epidemiol.* 1976;103:181-191. **4.** Woodson RD, Clinton JJ. Hepatitis prophylaxis abroad. Effectiveness of immune serum globulin in protecting Peace Corps volunteers. *JAMA.* 1969;209(7):1053-1058. **5.** Krugman S, Giles JP. Viral hepatitis. New light on an old disease. *JAMA.* 1970;212:1019-1029. **6.** Hadler SC, Erben JJ, Francis DP, et al. Risk factors for hepatitis A in day-care centers. *J Infect Dis.* 1982;145:255-261. **7.** Hadler SC. Global impact of hepatitis A virus infection changing patterns. In: Hollinger FB, Lemon SM, Margolis H, eds. *Viral Hepatitis and Liver Disease*. Baltimore, MD: Williams & Wilkins; 1991:14-20. **8.** Centers for Disease Control: Summary of Notifiable Diseases, United States-1996. *MMWR.* 1997;45(No. 53):73. **9.** Centers for Disease Control: Prevention of hepatitis A through active or passive immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR.* 1999;48(No. RR-12):1-3. **10.** Lemon SM. Type A viral hepatitis: New developments in an old disease. *N Engl J Med.* Oct. 24, 1985;313(17):1059-1067. **11.** Sjogren MH, Tanno H, Fay O, et al. Hepatitis A virus in stool during clinical relapse. *Ann Intern Med.* 1987;106:221-226. **12.** Centers for Disease Control and Prevention: Epidemiology and Prevention of Vaccine-Preventable Diseases. Atkinson W, Furphy L, Gantt J, Mayfield M (eds). 6th ed. 2000:191-229. **13.** Chiriaco P, Gaudalupi C, Armigliato M, et al. Polyphasic course of hepatitis type A in children. *J Infect Dis.* 1986; 153:378-379. **14.** Data on file (TWR101), SmithKline Beecham Pharmaceuticals. **15.** Koff RS. Hepatitis B and Hepatitis D. In: Gorbach SL, Bartlett JG, Blacklow NR, eds. *Infectious Diseases*. Philadelphia, PA: WB Saunders Company; 1992:709-716. **16.** Beasley RP, et al. Efficacy of hepatitis B immune globulin for

prevention of perinatal transmission of hepatitis B virus carrier state: final report of a randomized double-blind, placebo-controlled trial. *Hepatology*. 1983;3:135-141. **17.** Chang MH, Chen CJ, Lai MS. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *N Engl J Med.* 1997;336(26):1855-1859. **18.** Lee MS, Kim DH, et al. Hepatitis B vaccination and reduced risk of primary liver cancer among male adults: A cohort study in Korea. *Int J Epidemiol.* 1998;27:316-319. **19.** Frisch-Niggemeyer W, Ambrosch F, Hofmann H. The assessment of immunity against hepatitis B after vaccination. *J Bio Stand.* 1986;14:255-258. **20.** Centers for Disease Control and Prevention: 1998 Guidelines for Treatment of Sexually Transmitted Diseases. *MMWR*. 1999;47 (RR-1):99-104. **21.** Centers for Disease Control and Prevention: Hepatitis Surveillance Report No. 57. Atlanta, GA:DHHS; Sept. 2000:12. **22.** Centers for Disease Control and Prevention: Health Information for International Travel, 1999-2000. Atlanta, GA: DHHS. **23.** 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. **24.** 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. **25.** Centers for Disease Control and Prevention: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Use of vaccines and immune globulins for persons with altered immunocompetence. *MMWR*. 1993;42 (No. RR-4):1-18. **26.** Centers for Disease Control and Prevention: Vaccine adverse event reporting system–United States. *MMWR*. 1990;39:730-733. **27.** Data on file (TWR201), SmithKline Beecham Pharmaceuticals. **28.** Centers for Disease Control and Prevention:General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR.* 1994;43(No. RR-1):23.

U.S. License No. 1090

Manufactured by
SmithKline Beecham Biologicals
Rixensart, Belgium

Distributed by
SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101

DATE OF ISSUANCE MAY 2002

TW:L4