PRESCRIBING INFORMATION

Influenza Virus Vaccine
FLUARIX®
2008-2009 Formula

DESCRIPTION

FLUARIX®, Influenza Virus Vaccine for intramuscular use, is a sterile suspension prepared from influenza viruses propagated in embryonated chicken eggs. Each of the influenza viruses is produced and purified separately. After harvesting the virus-containing fluids, each influenza virus is concentrated and purified by zonal centrifugation using a linear sucrose density gradient solution containing detergent to disrupt the viruses. Following dilution, the vaccine is further purified by diafiltration. Each influenza virus solution is inactivated by the consecutive effects of sodium deoxycholate and formaldehyde leading to the production of a "split virus." Each split inactivated virus is then suspended in sodium phosphate-buffered isotonic sodium chloride solution. The vaccine is formulated from the 3 split inactivated virus solutions.

FLUARIX has been standardized according to USPHS requirements for the 2008-2009 influenza season and is formulated to contain 45 micrograms (mcg) hemagglutinin (HA) per 0.5 mL dose, in the recommended ratio of 15 mcg HA of each of the following 3 strains: A/Brisbane/59/2007 (H1N1)-like virus (A/Brisbane/59/2007 IVR-148), A/Brisbane/10/2007 (H3N2)-like virus (A/Uruguay/716/2007 NYMC X-175C) and B/Florida/4/2006-like virus (B/Brisbane/3/2007).

FLUARIX is formulated without preservatives. FLUARIX does not contain thimerosal. Each 0.5 mL dose also contains octoxynol-10 (TRITON® X-100) ≤0.120 mg, α-tocopheryl hydrogen succinate ≤0.1 mg, and polysorbate 80 (Tween 80) ≤0.380 mg. Each dose may also contain residual amounts of hydrocortisone ≤0.0016 mcg, gentamicin sulfate ≤0.15 mcg, ovalbumin ≤1 mcg, formaldehyde ≤50 mcg, and sodium deoxycholate ≤50 mcg from the manufacturing process.

FLUARIX is supplied as a 0.5 mL dose in a prefilled syringe. FLUARIX, after shaking well, is colorless to slightly opalescent.

CLINICAL PHARMACOLOGY

Influenza illness and its complications follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. For example, since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. Specific levels of hemagglutination-inhibition (HI) antibody titer post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza illness but the HI antibody titers have been used as a measure of vaccine activity. In some human challenge studies, HI antibody titers of ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects.[1,2] Antibody against one influenza virus type or subtype

confers little or no protection against another virus. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virological basis for seasonal epidemics and the reason for the usual incorporation of one or more new strains in each year's influenza vaccine.[3] Therefore, inactivated influenza vaccines are standardized to contain the hemagglutinins of strains (i.e., typically 2 type A and 1 type B), representing the influenza viruses likely to circulate in the United States in the upcoming winter.

Immune Response to FLUARIX: In a randomized, double-blind, placebo-controlled study conducted in healthy subjects 18 to 64 years of age in the United States (Study FLUARIX-US-001), the immune responses to each of the antigens contained in FLUARIX were evaluated in sera obtained 21 days after administration of FLUARIX (n = 745) and were compared to those following administration of a placebo vaccine (n = 190). For each of the influenza antigens, the percentage of subjects who achieved seroconversion, defined as a 4-fold increase in HI titer over baseline following vaccination, and the percentage of subjects who achieved HI titers of ≥1:40 are shown in Table 1. The lower limit of the 2-sided 95% CI for the percentage of subjects who achieved seroconversion or an HI titer of ≥1:40 exceeded the pre-defined lower limits of 40% and 70%, respectively.

No controlled trials demonstrating a decrease in influenza disease after vaccination with FLUARIX have been performed.

Table 1. Rates With HI Titers ≥1:40 and Rates of Seroconversion to Each Antigen Following FLUARIX or Placebo (21 Days After Administration of a Dose) in Study FLUARIX-US-001 (ATP cohort)

	FLUARIX* N = 745 % (95% CI)		Placebo N = 190 % (95% CI)	
% With HI Titers ≥1:40	**Pre-vaccination**	**Post-vaccination**	**Pre-vaccination**	**Post-vaccination**
A/New Caledonia/20/99 (H1N1)	54.8 (51.1-58.4)	96.6 (95.1-97.8)	52.1 (44.8-59.4)	51.1 (43.7-58.4)
A/Wyoming/3/2003 (H3N2)	68.7 (65.3-72)	99.1 (98.1-99.6)	65.3 (58-72)	65.3 (58-72)
B/Jiangsu/10/2003	49.5 (45.9-53.2)	98.8 (97.7-99.4)	48.9 (41.6-56.3)	51.1 (43.7-58.4)
Seroconversion†	**Post-vaccination**		**Post-vaccination**	
A/New Caledonia/20/99 (H1N1)	59.6 (56-63.1)		0 (0-1.9)	
A/Wyoming/3/2003 (H3N2)	61.9 (58.3-65.4)		1.1 (0.1-3.8)	
B/Jiangsu/10/2003	77.6 (74.4-80.5)		1.1 (0.1-3.8)	

HI = hemagglutination-inhibition.

ATP cohort for immunogenicity included subjects for whom assay results were available after vaccination for at least one study vaccine antigen.

* Results obtained following vaccination with FLUARIX vaccine manufactured for the 2004–2005 season.

† Seroconversion = at least a 4-fold rise in serum titers of HI antibodies to ≥1:40.

Immune Response in Geriatric Patients: An open-label, randomized, multicenter study conducted in Europe compared the immunogenicity of FLUARIX with 2 European-licensed influenza vaccines in subjects >60 years of age (mean age 68). Additionally, 2 open-label studies evaluated immune responses to FLUARIX among adults ≥18 years of age. Post-hoc analyses combined results from these 3 studies in the subgroup of subjects ≥65 years of age (n = 246) who received FLUARIX. In these analyses, the lower limits of the 2-sided 95% confidence intervals of the percentages of subjects achieving an HI titer ≥1:40 were greater than 70% and for subjects achieving seroconversion were greater than 40%, for each antigen.

INDICATIONS AND USAGE

FLUARIX is indicated for active immunization of adults (18 years of age and older) against influenza disease caused by influenza virus types A and B contained in the vaccine.

This indication is based on immune response elicited by FLUARIX, and there have been no controlled trials demonstrating a decrease in influenza disease after vaccination with FLUARIX (see CLINICAL PHARMACOLOGY).

The Advisory Committee on Immunization Practices (ACIP) has issued recommendations regarding the use of the inactivated influenza virus vaccine.[3]

Annual vaccination with the current vaccine is necessary because immunity declines during the year after vaccination. Vaccine prepared for a previous influenza season should not be administered to provide protection for the current season.[3]

FLUARIX IS NOT INDICATED FOR USE IN CHILDREN.

Concomitant Administration With Other Vaccines: There are insufficient data to assess the concurrent administration of FLUARIX with other vaccines.

CONTRAINDICATIONS

FLUARIX should not be administered to anyone with known systemic hypersensitivity reactions to egg proteins (eggs or egg products), to chicken proteins, or to any component of FLUARIX or who has had a life-threatening reaction to previous administration of any influenza vaccine. (See DESCRIPTION and WARNINGS.)

WARNINGS

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give FLUARIX or any influenza vaccine should be based on careful consideration of the potential benefits and possible risks.[3]

As with other intramuscular injections, FLUARIX should not be given to individuals with bleeding disorders such as hemophilia or thrombocytopenia, or to persons on anticoagulant therapy unless the potential benefit clearly outweighs the risk of administration. If the decision is made to administer FLUARIX to such persons, it should be given with caution with steps taken to avoid the risk of hematoma following the injection.

Vaccination with FLUARIX may not protect 100% of susceptible individuals.

The tip cap and the rubber plunger of the needleless prefilled syringes contain dry natural latex rubber that may cause allergic reactions in latex sensitive individuals.

The ACIP has published guidelines for vaccination of persons with recent or acute illness (www.cdc.gov/nip).[3]

PRECAUTIONS

General: Do not administer by intravascular injection.

Prior to immunization of FLUARIX, 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 FLUARIX 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.

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

Influenza virus is remarkable in that minor antigenic changes occur frequently (antigenic drift), whereas a significant antigenic change leading to a pandemic strain (antigenic shift) is unpredictable. *FLUARIX is not effective against all possible strains of influenza virus. Protection is limited to those strains of virus from which the vaccine is prepared and to closely related strains.*

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

Information for Vaccine Recipients and Guardians: Vaccine recipients and guardians should be informed by their healthcare provider of the potential benefits and risks of immunization with FLUARIX. When educating vaccine recipients and guardians regarding potential side effects, clinicians should emphasize that: (1) FLUARIX contains non-infectious killed viruses and cannot cause influenza and (2) coincidental respiratory disease unrelated to influenza vaccine can occur after vaccination.[3]

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

The vaccine recipients or guardian 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/nip).

Drug Interactions: Although it has been reported that influenza vaccination may inhibit the clearance of warfarin, theophylline, and phenytoin, controlled studies have yielded inconsistent results regarding pharmacokinetic interactions between influenza vaccine and these medications.[4-9] Nevertheless, clinicians should consider the potential for an interaction when influenza vaccine is administered to persons receiving these drugs.

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

FLUARIX should not be mixed with any other vaccine in the same syringe or vial.

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

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with FLUARIX. It is not known whether FLUARIX can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. FLUARIX should be given to a pregnant woman only if clearly needed. The ACIP has issued recommendations regarding the use of the influenza virus vaccine in pregnant women.[3]

Nursing Mothers: It is not known whether FLUARIX is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FLUARIX is

administered to a nursing woman. The ACIP has issued recommendations regarding the use of the influenza virus vaccine in nursing mothers.[3]

Pediatric Use: FLUARIX IS NOT INDICATED FOR USE IN CHILDREN.

Geriatric Use: FLUARIX was administered to 246 subjects ≥65 years of age in 3 European studies (see CLINICAL PHARMACOLOGY). Solicited adverse events were similar in type and frequency to those reported in younger subjects (see ADVERSE REACTIONS).

ADVERSE REACTIONS

FLUARIX has been administered to 1,271 adults in clinical trials. Study FLUARIX-US-001 was a randomized, double-blinded, placebo-controlled study that evaluated a total of 952 subjects: FLUARIX n = 760, placebo n = 192. The population was 18 to 64 years of age (mean 39.1), 54% were female and 80% were Caucasian. Solicited adverse events were collected for 4 days (day of vaccination and the next 3 days). Unsolicited events that occurred within 21 days of vaccination (day 0-20) were recorded using diary cards supplemented by spontaneous reports and a medical history as reported by subjects.

Most events reported were considered by the subjects as mild and self-limiting. Table 2 provides the incidence of solicited adverse events for the FLUARIX and placebo groups from Study FLUARIX-US-001.

The adverse event information from clinical trials provides a basis for identifying adverse events that appear to be related to vaccine use and for approximating rates. However, 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.

Table 2. Percentage of Subjects With Solicited Local or Systemic Adverse Events Within 4 Days* of Vaccination From Study FLUARIX-US-001 (Total Vaccinated Cohort)

Adverse Event	FLUARIX (n = 760) % (95% CI)	Placebo (n = 192) % (95% CI)
Local		
Pain	54.7 (51.1-58.3)	12.0 (7.7-17.4)
Redness	17.5 (14.9-20.4)	10.4 (6.5-15.6)
Swelling	9.3 (7.4-11.6)	5.7 (2.9-10.0)
Systemic		
Muscle aches	23.0 (20.1-26.2)	12.0 (7.7-17.4)
Fatigue	19.7 (17.0-22.7)	17.7 (12.6-23.9)
Headache	19.3 (16.6-22.3)	21.4 (15.8-27.8)
Arthralgia	6.4 (4.8-8.4)	6.3 (3.3-10.7)
Shivering	3.3 (2.1-4.8)	2.6 (0.9-6.0)
Fever (≥100.4˚F)	1.7 (0.9-2.9)	1.6 (0.3-4.5)

Total Vaccinated Cohort for safety included all vaccinated subjects for whom safety data were available.

* 4 days included day of vaccination and the subsequent 3 days.

Solicited and unsolicited adverse events following administration of FLUARIX were collected in 3 additional studies. One randomized study enrolled adults >60 years of age. Two studies enrolled adults ≥18 years of age. From these 3 studies, a post-hoc analysis of solicited adverse events observed in the subsets of subjects ≥65 years of age (n = 245), pain was observed in 12.2%, redness in 15.9%, swelling in 16.7%, muscle aches in 10.2%, fatigue in 12.2%, headache in 14.3%, arthralgias in 11.0%, shivering in 6.9%, and fever in 0.4% of subjects.

Unsolicited adverse events from Study FLUARIX-US-001 that occurred in ≥1% of recipients of FLUARIX and at a rate greater than placebo included upper respiratory tract infection (3.9% vs. 2.6%), nasopharyngitis (2.5% vs. 1.6%), nasal congestion (2.2% vs. 2.1%), diarrhea (1.6% vs. 0%), influenza-like illness (1.6% vs. 0.5%), vomiting (1.4% vs. 0%), and dysmenorrhea (1.3% vs. 1.0%). One death due to atherosclerotic cardiovascular disease occurred 17 days after administration of FLUARIX.

Incidence of Adverse Events of 1% to 10% in Non-US Clinical Trials With FLUARIX: The following additional adverse events have been observed in non-US clinical trials with FLUARIX.

General Disorders and Administrative Site Conditions: Malaise.

Local Reactions at Injection Site: Ecchymosis, induration.

Skin and Subcutaneous Tissue Disorders: Sweating.

Two deaths were reported in non-US trials with FLUARIX: One death due to acute pancreatitis occurred 10 months after administration of FLUARIX and one death due to abdominal neoplasm occurred 9 months after administration of FLUARIX.

As with any vaccine, there is the possibility that broad use of FLUARIX could reveal adverse events not observed in clinical trials.

Postmarketing Reports: Worldwide voluntary reports of adverse events received for FLUARIX since market introduction of this vaccine are listed below. This list includes serious events or events which have causal connection to components of this or other vaccines or drugs. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Blood and Lymphatic System Disorders: Autoimmune hemolytic anemia, lymphadenopathy, thrombocytopenia.

Cardiac Disorders: Tachycardia.

Ear and Labyrinth Disorders: Vertigo.

Eye Disorders: Conjunctivitis, eye irritation, eye pain, eye redness, eye swelling, eyelid swelling.

Gastrointestinal Disorders: Abdominal pain or discomfort, nausea, swelling of the mouth, throat, and/or tongue.

General Disorders and Administrative Site Conditions: Asthenia, chest pain, chills, feeling hot, injection site mass, injection site reaction, injection site warmth, pain.

Immune System Disorders: Anaphylactic reaction including shock, anaphylactoid reaction, hypersensitivity, serum sickness.

Infections and Infestations: Injection site abscess, injection site cellulitis, pharyngitis, rhinitis, tonsillitis.

Musculoskeletal and Connective Tissue Disorders: Pain in extremity.

Nervous System Disorders: Convulsion, dizziness, encephalomyelitis, facial palsy, facial paresis, Guillain-Barré syndrome, hypoesthesia, myelitis, neuritis, neuropathy, paresthesia.

Respiratory, Thoracic and Mediastinal Disorders: Asthma, bronchospasm, cough, dyspnea, pneumonia, respiratory distress, stridor.

Skin and Subcutaneous Tissue Disorders: Angioneurotic edema, erythema, erythema multiforme, facial swelling, pruritus, rash, Stevens-Johnson syndrome, urticaria.

Vascular disorders: Henoch-Schönlein purpura, vasculitis.

Other Adverse Events: Immediate, presumably allergic, reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) rarely occur after influenza vaccination. Two subjects experienced urticaria in clinical trials of FLUARIX. These reactions probably result from hypersensitivity to certain vaccine components, such as residual egg protein. Although FLUARIX contains only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy (see CONTRAINDICATIONS).[3]

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS).[3,10] Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear.[3] If influenza vaccine does pose a risk, it is probably slightly more than 1 additional case/1 million persons vaccinated.[3]

Neurological disorders temporally associated with influenza vaccination such as encephalopathy, optic neuritis/neuropathy, partial facial paralysis, and brachial plexus neuropathy have been reported.[11,12]

Microscopic polyangitis (vasculitis) has been reported temporally associated with influenza vaccination.[13]

Reporting of Adverse Events: The US Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all 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.[14] The VAERS toll-free number is 1-800-822-7967. Reporting forms may also be obtained at the VAERS website at www.vaers.hhs.gov.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration whenever solution and container permit. If either of these conditions exist, the vaccine should not be administered.

The prefilled syringe should be shaken well before administration.

Do NOT inject intravenously.

The dose of FLUARIX is a single 0.5 mL injection in adults. Injections of FLUARIX should be administered intramuscularly, preferably in the region of the deltoid muscle. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk. A needle length of ≥1 inch is preferred because needles <1 inch might be of insufficient length to penetrate muscle tissue in certain adults. Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

STORAGE

Store FLUARIX refrigerated between 2º and 8ºC (36º and 46ºF). Do not freeze. Discard if the vaccine has been frozen. Store in the original package to protect from light.

HOW SUPPLIED

FLUARIX is supplied as a colorless to slightly opalescent suspension in prefilled syringes containing a 0.5-mL single dose.

Single-Dose Prefilled Disposable TIP-LOK® Syringes (packaged without needles)
NDC 58160-876-46 (package of 5)

REFERENCES

1. Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza vaccination. *Virus Res* 2004;103:133-138. **2.** Hobson D, Curry RL, Beare AS, et al. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. *J Hyg Camb* 1972;70:767-777. **3.** Centers for Disease Control and Prevention. Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2004;53(RR-6):1-44. **4.** Renton KW, Gray JD, Hall RI. Decreased elimination of theophylline after influenza vaccination. *Can Med Assoc J* 1980;123:288-290. **5.** Fischer RG, Booth BH, Mitchell DQ, et al. Influence of trivalent influenza vaccine on serum theophylline levels. *Can Med Assoc J* 1982;126:1312-1313. **6.** Lipsky BA, Pecoraro RE, Roben NJ, et al. Influenza vaccination and warfarin anticoagulation. *Ann Intern Med* 1984;100(6):835-837. **7.** Kramer P, Tsuru M, Cook CE, et al. Effect of influenza vaccine on warfarin anticoagulation. *Clin Pharmacol Ther* 1984;35(3):416-418. **8.** Patriarca PA, Kendal AP, Stricof RL, et al. Influenza vaccination and warfarin or theophylline toxicity in nursing-home residents. *New Engl J Med* 1983;308(26):1601-1602. **9.** Levine M, Jones MW, and Gribble M. Increased serum phenytoin concentration following influenza vaccination. *Clin Pharm* 1984;3:505-509. **10.** Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, et al. Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976-1977. *Am J Epidemiol* 1979;110(2):105-123. **11.** Hull TP and Bates JH. Optic neuritis after influenza vaccination. *Am J Ophthalmol* 1997;124(5):703-704. **12.** Kawasaki A, Purvin VA, Tang R. Bilateral anterior ischemic optic neuropathy following influenza vaccination. *J Neuro-Ophthalmol* 1998;18(1):56-59. **13.** Kelsall JT, Chalmers A, Sherlock CH, et al. Microscopic polyangitis after influenza vaccination. *J Rheumatol* 1997;1198-1202. **14.** Centers for Disease Control and Prevention. General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). *MMWR* 2002;51(RR-2):1-35.

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