HIGHLIGHTS OF PRESCRIBING INFORMATION

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

FLUARIX (Influenza Virus Vaccine)
Suspension for Intramuscular Injection
2012-2013 Formula
Initial U.S. Approval: 2005

----------RECENT MAJOR CHANGES----------

Warnings and Precautions, Syncope (5.3) 03/2012

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

FLUARIX is a vaccine indicated for active immunization for the prevention of disease caused by influenza virus subtypes A and type B contained in the vaccine. FLUARIX is approved for use in persons 3 years of age and older. (1)

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

Children: 0.5 mL dose by intramuscular injection (2.2)

- Children 3 years to <9 years of age previously unvaccinated or vaccinated for the first time last season with only one dose receive two 0.5-mL doses; each 0.5-mL dose is administered at least 4 weeks apart.
- Children 3 years to <9 years of age previously vaccinated with 2 doses of any influenza vaccine receive only one 0.5-mL dose.
- Children 9 years of age and older receive only one 0.5-mL dose.

Adults: a single 0.5-mL dose by intramuscular injection. (2.2)

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

Suspension for injection in 0.5-mL single-dose prefilled syringes. (3)

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

Known severe allergic reactions (e.g., anaphylaxis) to egg proteins (a vaccine component) or a life-threatening reaction to previous influenza vaccination. (4, 11)

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

- If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLUARIX should be based on potential benefits and risks. (5.1)
- The tip caps of the prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex-sensitive individuals. (5.2)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including FLUARIX. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.3)
- Immunosuppressed persons may have a reduced immune response to FLUARIX. (5.4)

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

- In adults, the most common (≥10%) local and general adverse events were pain and redness at the injection site, muscle aches, fatigue, and headache. (6.1)
- In children 5 years to <18 years of age, the most common (≥10%) local and general adverse events were similar to those in adults but also included swelling at the injection site. (6.1)
- In children 3 years to <5 years of age, the most common (≥10%) local and general adverse events were pain, redness, and swelling at the injection site, irritability, loss of appetite, and drowsiness. (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 with any other vaccine in the same syringe or vial. (7.1)

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

- Safety and effectiveness have not been established in pregnant women or nursing mothers. (8.1, 8.3)
- Register women who receive FLUARIX while pregnant in the pregnancy registry by calling 1-888-452-9622. (8.1)
- In a clinical study of children <3 years of age, antibody titers were lower after FLUARIX than after an active comparator. (8.4)
- Geriatric Use: Antibody responses were lower in geriatric subjects than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: xx/xxxx

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FLUARIX® is indicated for active immunization for the prevention of disease caused by influenza virus subtypes A and type B contained in the vaccine. FLUARIX is approved for use in persons 3 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Shake well before administration. 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.

Attach a sterile needle to the prefilled syringe and administer intramuscularly.

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

2.2 Recommended Dose and Schedule

FLUARIX should be administered as an intramuscular injection preferably in the region of the deltoid muscle of the upper arm. Do not inject in the gluteal area or areas where there may be a major nerve trunk.

Children: Children 3 years to <9 years of age previously unvaccinated or vaccinated for the first time last season with only one dose receive two 0.5-mL doses; each 0.5-mL dose is administered at least 4 weeks apart.

Children 3 years to <9 years of age who have been previously vaccinated with 2 doses of any influenza vaccine receive only one 0.5-mL dose.

Children 9 years of age and older receive only one 0.5-mL dose.

Adults: Administer as a single 0.5-mL dose.

3 DOSAGE FORMS AND STRENGTHS

FLUARIX is a suspension available in 0.5-mL single-dose prefilled TIP-LOK® syringes.

4 CONTRAINDICATIONS

Do not administer FLUARIX to anyone with known severe allergic reactions (e.g., anaphylaxis) to egg proteins (a vaccine component) or a life-threatening reaction to previous administration of any influenza vaccine *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

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

5.2 Latex

The tip caps of the prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex-sensitive individuals *[see Description (11)]*.

5.3 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including FLUARIX. 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.

5.4 Altered Immunocompetence

If FLUARIX is administered to immunosuppressed persons, including individuals receiving immunosuppressive therapy, the immune response may be lower than in immunocompetent persons.

5.5 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of FLUARIX.

5.6 Limitations of Vaccine Effectiveness

Vaccination with FLUARIX may not protect all susceptible individuals.

5.7 Persons at Risk of Bleeding

As with other intramuscular injections, FLUARIX should be given with caution in individuals with bleeding disorders such as hemophilia or on anticoagulant therapy, to avoid the risk of hematoma following the injection.

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. There is the possibility that broad use of FLUARIX could reveal adverse reactions not observed in clinical trials.

Adults: In adults, the most common (≥10%) local adverse reactions and general adverse events observed with FLUARIX were pain and redness at the injection site, muscle aches, fatigue, and headache.

FLUARIX has been administered to 10,317 adults 18 to 64 years of age and 606 subjects ≥65 years of age in 4 clinical trials.

One of the 4 clinical trials was a randomized, double-blind, placebo-controlled study that evaluated a total of 952 subjects: FLUARIX (N = 760) and placebo (N = 192). The population was 18 to 64 years of age (mean 39.1), 54% were female and 80% were white. Solicited events were collected for 4 days (day of vaccination and the next 3 days) (Table 1). 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.

Table 1. Percentage of Subjects With Solicited Local Adverse Reactions or General Adverse Events Within 4 Days[a] of Vaccination (Total Vaccinated Cohort)

	FLUARIX N = 760 %	Placebo N = 192 %
Local Adverse Reactions		
Pain	55	12
Redness	18	10
Swelling	9	6
General Adverse Events		
Muscle aches	23	12
Fatigue	20	18
Headache	19	21
Arthralgia	6	6
Shivering	3	3
Fever ≥100.4°F (38.0°C)	2	2

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

[a] 4 days included day of vaccination and the subsequent 3 days.

Unsolicited adverse events that occurred in ≥1% of recipients of FLUARIX and at a rate greater than placebo included upper respiratory tract infection (3.9% versus 2.6%), nasopharyngitis (2.5% versus 1.6%), nasal congestion (2.2% versus 2.1%), diarrhea (1.6% versus 0%), influenza-like illness (1.6% versus 0.5%), vomiting (1.4% versus 0%), and dysmenorrhea (1.3% versus 1.0%).

A randomized, single-blind, active-controlled US study evaluated subjects randomized to receive FLUARIX (N = 917) or FLUZONE (N = 910), a US-licensed trivalent, inactivated influenza virus vaccine (Sanofi Pasteur SA) stratified by age: 18 to 64 years and ≥65 years of age. In the overall population, 59% of subjects were female and 91% were white. Solicited events were collected using diary cards for 4 days (day of vaccination and the next 3 days) (Table 2). Unsolicited events that occurred within 21 days of vaccination (day 0-20) were recorded using diary cards.

Table 2. Percentage of Subjects With Solicited Local Adverse Reactions or General Adverse Events Within 4 Days[a] of Vaccination With FLUARIX or Comparator Influenza Vaccine by Age Group (Total Vaccinated Cohort)

	18 to 64 Years of Age		≥65 Years of Age	
	FLUARIX N = 315 %	Comparator Influenza Vaccine N = 314 %	FLUARIX N = 601-602 %	Comparator Influenza Vaccine N = 596 %
Local Adverse Reactions				
Pain	48	53	19	18
Redness	13	16	11	13
Swelling	9	11	6	9
General Adverse Events				
Fatigue	21	18	9	10
Headache	20	21	8	8
Muscle aches	16	13	7	7
Arthralgia	9	9	6	5
Shivering	3	5	2	2
Fever ≥99.5°F (37.5°C)	3	1	2	1

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

[a] 4 days included day of vaccination and the subsequent 3 days.

Unsolicited adverse events that occurred in ≥1% of all recipients of FLUARIX or the comparator influenza vaccine in the 21-day post-vaccination period included headache (2.8% versus 2.3%), back pain (1.5% versus 0.4%), pain in extremity (1.2% versus 0.7%), pharyngolaryngeal pain (1.2% versus 0.9%), cough (1.1% versus 0.9%), fatigue (1.1% versus 0.7%), nasopharyngitis (1.0% versus 1.3%), nausea (0.4% versus 1.0%), arthralgia (0.3% versus 1.0%), and injection site pruritus (0.2% versus 1.0%).

A double-blind, placebo-controlled study in subjects 18 to 64 years of age randomized (2:1) to receive FLUARIX (N = 5,103) or placebo (N = 2,549) was conducted to evaluate the efficacy of FLUARIX. In the total population, 60% were female and 99.9% were white. In a subset (FLUARIX [N = 305] and placebo [N = 155]), unsolicited events that occurred within 21 days of vaccination (day 0-20) were recorded on diary cards. The percentage of subjects reporting at least one unsolicited event was similar among the groups (24.3% for FLUARIX and 22.6% for placebo). Unsolicited adverse events that occurred in ≥1% of recipients of FLUARIX and at a rate greater than placebo included injection site pain (5.2% versus 1.3%), dysmenorrhea (1.3% versus 0.6%), and migraine (1.0% versus 0.0%).

Incidence of Adverse Events Reported in ≥1% of Subjects in Non-US Clinical Trials: The following additional adverse events have been observed in adults in non-US clinical trials with FLUARIX. No adverse events were observed at an incidence of >10%.

General Disorders and Administration Site Conditions: Injection site ecchymosis, injection site induration, malaise.

Infections and Infestations: Rhinitis.

Musculoskeletal and Connective Tissue Disorders: Musculoskeletal pain, neck pain.

Skin and Subcutaneous Tissue Disorders: Sweating.

Serious Adverse Events: In the 4 clinical trials in adults (N = 10,923), there was a single case of anaphylaxis reported with FLUARIX (<0.01%).

Children: In children 5 years to <18 years of age, the most common (≥10%) local and general adverse events were similar to those in adults but also included swelling at the injection site. In children 3 years to <5 years of age, the most common (≥10%) local and general adverse events included pain, redness, and swelling at the injection site, irritability, loss of appetite, and drowsiness.

A single-blind, active-controlled US study evaluated subjects 6 months to <18 years of age who received FLUARIX (N = 2,081) or FLUZONE (N = 1,173), a US-licensed trivalent, inactivated influenza virus vaccine (Sanofi Pasteur SA) (Study 005). Children 6 months to <9 years of age with no history of influenza vaccination received 2 doses approximately 28 days apart. Children 6 months to <9 years of age with a history of influenza vaccination and children 9 years of age and older received 1 dose. Children 6 months to <3 years of age received 0.25 mL of FLUARIX or comparator influenza vaccine, and children 3 years of age and older received 0.5 mL of FLUARIX or comparator influenza vaccine.

Study subjects were 6 months to <18 years of age and 49% were female; 68% were white, 18% were black, 3% were Asian, and 11% were of other racial/ethnic groups.

Solicited local and general adverse events were collected using diary cards for 4 days (day of vaccination and the next 3 days). Unsolicited adverse events that occurred within 28 days of vaccination (day 0-27) after the first vaccination in all subjects and 21 days (day 0-20) after the second vaccination in unprimed subjects were recorded using diary cards.

The frequencies of solicited adverse events for children 3 years to <5 years of age and for children 5 years to <18 years of age were similar for FLUARIX and the comparator vaccine (Table 3).

Table 3. Percentage of Subjects With Solicited Local Adverse Reactions or General Adverse Events Within 4 Days[a] of First Vaccination With FLUARIX or Comparator Influenza Vaccine by Age Group in Children 3 Years to <18 Years of Age

	Age Group: 3 Years to <5 Years		Age Group: 5 Years to <18 Years	
	FLUARIX N = 350 %	Comparator Influenza Vaccine N = 341 %	FLUARIX N = 1,348 %	Comparator Influenza Vaccine N = 451 %
Local Adverse Reactions				
Pain	35	38	56	56
Redness	23	20	18	16
Swelling	14	13	14	13
General Adverse Events				
Irritability	21	22	–	–
Loss of appetite	13	15	–	–
Drowsiness	13	20	–	–
Fever ≥99.5°F (37.5°C)	7	8	4	3
Muscle aches	–	–	29	29
Fatigue	–	–	20	19
Headache	–	–	15	16
Arthralgia	–	–	6	6
Shivering	–	–	3	4

[a] 4 days included day of vaccination and the subsequent 3 days.

In children who received a second dose of FLUARIX or the comparator vaccine, the incidences of adverse events following the second dose were similar to those observed after the first dose.

Unsolicited adverse events that occurred in ≥1% of recipients of FLUARIX 6 months to <18 years of age included upper respiratory tract infection (5.5%), pyrexia (4.8%), cough (4.7%), vomiting (3.2%), headache (2.8%), rhinorrhea (2.7%), diarrhea (2.5%), pharyngolaryngeal pain (2.4%), nasopharyngitis (2.3%), otitis media (2.0%), nasal congestion (1.8%), upper abdominal pain (1.4%), and upper respiratory tract congestion (1.0%). The incidences of these events were similar in recipients of the comparator vaccine.

6.2 Postmarketing Experience

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 FLUARIX. 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 the vaccine.

Blood and Lymphatic System Disorders: Lymphadenopathy.

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 Administration Site Conditions: Asthenia, chest pain, chills, feeling hot, injection site mass, injection site reaction, injection site warmth, body aches.

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, syncope.

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

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

Vascular Disorders: Henoch-Schönlein purpura, vasculitis.

6.3 Adverse Events Associated With Influenza Vaccines

Immediate and presumably allergic reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) rarely occur after influenza vaccination. 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 (4)]*.

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

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

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

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration

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

There are insufficient data to assess the concurrent administration of FLUARIX 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 FLUARIX.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

A reproductive and developmental toxicity study has been performed in female rats at a dose approximately 56 times the human dose (on a mg/kg basis) and revealed no evidence of impaired female fertility or harm to the fetus due to FLUARIX. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, FLUARIX should be given to a pregnant woman only if clearly needed.

In a reproductive and developmental toxicity study, the effect of FLUARIX on embryo-fetal and pre-weaning development was evaluated in pregnant rats. Animals were administered FLUARIX by intramuscular injection once prior to gestation, and during the period of organogenesis (gestation days 6, 8, 11, and 15), 0.1 mL/rat/occasion (approximately 56-fold excess relative to the projected human dose on a body weight basis). No adverse effects on mating, female fertility, pregnancy, parturition, lactation parameters, and embryo-fetal or pre-weaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis.

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

8.3 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.

8.4 Pediatric Use

The immune response to FLUARIX has been evaluated in children 6 months to <5 years of age. In a randomized, controlled study, serum hemagglutination-inhibition (HI) antibody titers were lower in children 6 months to <3 years of age compared to a US-licensed vaccine. Based on

these data, FLUARIX is not approved for use in children younger than 3 years of age. Immune responses in children 3 years to <5 years of age receiving FLUARIX or a US-licensed vaccine have been evaluated *[see Clinical Studies (14.2)]*. Safety has been evaluated in children 6 months to <18 years of age. The frequencies of solicited and unsolicited adverse events for children 3 years to <5 years of age and for children 5 years to <18 years of age were similar for FLUARIX and the comparator vaccine *[see Adverse Reactions (6.1)]*.

8.5 Geriatric Use

A randomized, single-blind, active-controlled study evaluated immunological non-inferiority in a cohort of subjects ≥65 years of age who received FLUARIX (N = 606) or another US-licensed trivalent, inactivated influenza virus vaccine (N = 604) (Sanofi Pasteur SA). In subjects receiving FLUARIX or the comparator vaccine, geometric mean antibody titers post-vaccination were lower in geriatric subjects than in younger subjects (18 to 64 years of age). FLUARIX was non-inferior to the comparator vaccine for each of the 3 influenza strains based on mean antibody titers and seroconversion rates. *[See Clinical Studies (14.2).]* Solicited local and general adverse events were similar for FLUARIX and the comparator vaccine among geriatric subjects (Table 2). For both vaccines, the frequency of solicited events in subjects ≥65 years of age was lower than in younger subjects (Table 2). *[See Adverse Reactions (6.1).]*

11 DESCRIPTION

FLUARIX, Influenza Virus Vaccine, for intramuscular injection, is a sterile colorless and slightly opalescent suspension. FLUARIX is a vaccine 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 2012-2013 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/Christchurch/16/2010 NIB-74XP (H1N1) (an A/California/7/2009-like virus), A/Victoria/361/2011 IVR-165 (H3N2), and B/Hubei-Wujiagang/158/2009 NYMC BX-39 (a B/Wisconsin/1/2010-like virus).

FLUARIX is formulated without preservatives. FLUARIX does not contain thimerosal. Each 0.5-mL dose also contains octoxynol-10 (TRITON® X-100) ≤0.085 mg, α-tocopheryl hydrogen succinate ≤0.1 mg, and polysorbate 80 (Tween 80) ≤0.415 mg. Each dose may also contain residual amounts of hydrocortisone ≤0.0016 mcg, gentamicin sulfate ≤0.15 mcg, ovalbumin ≤0.05 mcg, formaldehyde ≤5 mcg, and sodium deoxycholate ≤50 mcg from the

manufacturing process.

The tip caps of the prefilled syringes may contain natural rubber latex. The rubber plungers do not contain latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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. 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.

Annual revaccination with the current vaccine is recommended because immunity declines during the year after vaccination, and because circulating strains of influenza virus change from year to year.[3]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

14.1 Efficacy Against Culture-Confirmed Influenza

The efficacy of FLUARIX was evaluated in a randomized, double-blind, placebo-controlled study conducted in 2 European countries during the 2006-2007 influenza season. Efficacy of FLUARIX, containing A/New Caledonia/20/1999 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004 influenza strains, was defined as the prevention of culture-confirmed influenza A and/or B cases, for vaccine antigenically matched strains, compared with placebo. Healthy subjects 18 to 64 years of age (mean 39.9 years) were randomized (2:1) to receive FLUARIX (N = 5,103) or placebo (N = 2,549) and monitored for influenza-like illnesses (ILI) starting 2 weeks post-vaccination and lasting for approximately 7 months. In the overall population, 60% of subjects were female and 99.9% were white. Culture-confirmed influenza

was assessed by active and passive surveillance of ILI. Influenza-like illness was defined as at least one general symptom (fever ≥100°F and/or myalgia) and at least one respiratory symptom (cough and/or sore throat). After an episode of ILI, nose and throat swab samples were collected for analysis; attack rates and vaccine efficacy were calculated (Table 4).

Table 4. Attack Rates and Vaccine Efficacy Against Culture-Confirmed Influenza A and/or B in Adults 18 to 64 Years of Age (Total Vaccinated Cohort)

			Attack Rates (n/N)	Vaccine Efficacy		
	N	N	%	%	LL	UL
Antigenically Matched Strains[a]						
FLUARIX	5,103	49	1.0	66.9[b]	51.9	77.4
Placebo	2,549	74	2.9	–	–	–
All Culture-Confirmed Influenza (Matched, Unmatched, and Untyped)[c]						
FLUARIX	5,103	63	1.2	61.6[b]	46.0	72.8
Placebo	2,549	82	3.2	–	–	–

[a] There were no vaccine matched culture-confirmed cases of A/New Caledonia/20/1999 (H1N1) or B/Malaysia/2506/2004 influenza strains with FLUARIX or placebo.

[b] Vaccine efficacy for FLUARIX exceeded a pre-defined threshold of 35% for the lower limit of the 2-sided 95% CI.

[c] Of the 22 additional cases, 18 were unmatched and 4 were untyped; 15 of the 22 cases were A (H3N2) (11 cases with FLUARIX and 4 cases with placebo).

In a post-hoc, exploratory analysis by age, vaccine efficacy (against culture-confirmed influenza A and/or B cases, for vaccine antigenically matched strains) in subjects 18 to 49 years of age was 73.4% (95% CI: 59.3, 82.8) [number of influenza cases: FLUARIX (n = 35/3,602) and placebo (n = 66/1,810)]. In subjects 50 to 64 years of age, vaccine efficacy was 13.8% (95% CI: -137.0, 66.3) [number of influenza cases: FLUARIX (n = 14/1,501) and placebo (n = 8/739)]. As the study lacked statistical power to evaluate efficacy within age subgroups, the clinical significance of these results is unknown.

14.2 Immunological Evaluation

Adults: In a randomized, double-blind, placebo-controlled study conducted in healthy subjects 18 to 64 years of age (mean 39.1 years) in the United States, 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). In the overall population, 54% of subjects were female and 80% were white. For each of the influenza antigens, the percentage of subjects who achieved seroconversion, defined as at least a 4-fold increase in serum hemagglutination-inhibition (HI) titer over baseline to ≥1:40 following vaccination, and the percentage of subjects who achieved HI titers of ≥1:40 are presented in Table 5. 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.

Table 5. Rates With HI Titers ≥1:40 and Rates of Seroconversion to Each Antigen Following FLUARIX or Placebo (21 Days After Vaccination) in Adults 18 to 64 Years of Age (ATP Cohort)

	FLUARIX[a] 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[b]	**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 = according-to-protocol; CI = Confidence Interval.
ATP cohort for immunogenicity included subjects for whom assay results were available after vaccination for at least one study vaccine antigen.
[a] Results obtained following vaccination with FLUARIX manufactured for the 2004-2005 season.
[b] Seroconversion defined as at least a 4-fold increase in serum titers of HI antibodies to ≥1:40.

Non-Inferiority Study: In a randomized, single-blind, active-controlled US study, immunological non-inferiority of FLUARIX (N = 923) was compared with FLUZONE (N = 922), a US-licensed trivalent, inactivated influenza virus vaccine (Sanofi Pasteur SA). Subjects 18 to 64 years and ≥65 years of age were evaluated for immune responses to each of the vaccine antigens 21 days following vaccination *[see Use in Specific Populations (8.5)]*. In the overall population, 59% of subjects were female and 91% were white. The co-primary immunogenicity endpoints were geometric mean titers (GMTs) of serum HI antibodies and the percentage of subjects who achieved seroconversion, defined as at least a 4-fold increase in serum HI titer over baseline to ≥1:40, following vaccination. The primary immunogenicity analyses were performed on the According-to-Protocol (ATP) cohort which included all eligible

and evaluable subjects with results of at least one serological assay. For each of the influenza antigens, the GMTs and the percentage of subjects who achieved seroconversion are presented in Table 6. FLUARIX was non-inferior to the comparator influenza vaccine based on antibody GMTs (upper limit of the 2-sided 95% CI for the GMT ratio [comparator influenza vaccine/FLUARIX] ≤1.5) and seroconversion rates (upper limit of the 2-sided 95% CI on difference of the comparator influenza vaccine minus FLUARIX ≤10%).

Table 6. Immune Responses 21 Days After Vaccination With FLUARIX Compared With Comparator Influenza Vaccine in Adults ≥18 Years of Age (ATP Cohort)

	FLUARIX N = 858-866 (95% CI)		**Comparator Influenza Vaccine N = 846-854 (95% CI)**	
GMTs	**Pre-vaccination**	**Post-vaccination**	**Pre-vaccination**	**Post-vaccination**
Anti-H1	27.9 (25.6, 30.5)	138.0 (125.2, 152.1)	29.1 (26.6, 31.7)	92.0 (84.5, 100.3)
Anti-H3	16.3 (15.1, 17.6)	121.6 (110.5, 133.7)	16.5 (15.4, 17.6)	114.0 (104.4, 124.5)
Anti-B	47.7 (44.1, 51.6)	231.9 (215.4, 249.6)	54.1 (49.9, 58.6)	273.7 (253.4, 295.7)
Seroconversion[a]	**% (95% CI) Post-vaccination**		**% (95% CI) Post-vaccination**	
A/New Caledonia/20/99 (H1N1)	45.7 (42.3, 49.1)		33.8 (30.6, 37.1)	
A/New York/55/2004 (H3N2)	67.1 (63.9, 70.3)		65.5 (62.2, 68.7)	
B/Jiangsu/10/2003	52.7 (49.3, 56.1)		53.8 (50.4, 57.2)	

Comparator influenza vaccine manufactured by Sanofi Pasteur SA.
ATP = according-to-protocol; GMT = geometric mean antibody titer; CI = Confidence Interval; H1 = A/New Caledonia/20/99 (H1N1); H3 = A/New York/55/2004 (H3N2) for FLUARIX and A/California/7/2004 (H3N2) for comparator influenza vaccine; B = B/Jiangsu/10/2003.
ATP cohort included all eligible and evaluable subjects with results of at least one serological assay.
[a] Seroconversion defined as at least a 4-fold increase in serum titers of HI antibodies to ≥1:40.

Children: The immune response of FLUARIX was compared to FLUZONE, a US-licensed trivalent, inactivated influenza virus vaccine (Sanofi Pasteur SA), in a single-blind, randomized study in a subset of children 6 months to <5 years of age (Study 005). The immune

responses to each of the antigens contained in FLUARIX formulated for the 2006-2007 season were evaluated in sera obtained after 1 or 2 doses of FLUARIX (N = 426) and were compared to those following administration of the comparator influenza vaccine (N = 445). Further details on the clinical study design and demographic information have been previously described *[see Adverse Reactions (6.1)]*.

Non-inferiority of the immune response for FLUARIX to comparator influenza vaccine for subjects 6 months to <5 years of age was not demonstrated mainly due to lower antibody response to FLUARIX compared to the comparator influenza vaccine in subjects 6 months to <3 years of age. In subjects 3 years to <5 years of age, FLUARIX met at least one of the pre-specified criteria for demonstration of non-inferiority (GMT and seroconversion rate) for the influenza A strains but not for the influenza B strain. Seroconversion rates and the percentage of subjects with HI titers ≥1:40 were analyzed as secondary endpoints. In subjects 3 years to <5 years of age, the lower limit of the 95% Confidence Interval of the seroconversion rate for FLUARIX or the comparator influenza vaccine exceeded 40% for all 3 strains; also in this age group, the lower limit of the 95% Confidence Interval of the rate with HI titer ≥1:40 for FLUARIX or the comparator influenza vaccine exceeded 70% for both A strains (Table 7).

Table 7. Rates With HI Titers ≥1:40 and Rates of Seroconversion to Each Antigen Following FLUARIX or Comparator Influenza Vaccine in Children 3 Years to <5 Years of Age (ATP Cohort)

	FLUARIX[a] % (95% CI)		**Comparator Influenza Vaccine[b] % (95% CI)**	
% with HI titers ≥1:40	**Pre-vaccination N = 220**	**Post-vaccination N = 220**	**Pre-vaccination N = 220**	**Post-vaccination N = 221**
A/New Caledonia	17.3 (12.5, 22.9)	81.8 (76.1, 86.7)	20.5 (15.3, 26.4)	85.5 (80.2, 89.9)
A/Wisconsin	59.5 (52.7, 66.1)	88.2 (83.2, 92.1)	55.5 (48.6, 62.1)	93.7 (89.6, 96.5)
B/Malaysia	13.6 (9.4, 18.9)	55.0 (48.2, 61.7)	11.8 (7.9, 16.8)	58.4 (51.6, 64.9)
Seroconversion[c]	**Post-vaccination**		**Post-vaccination**	
A/New Caledonia	72.7 (66.3, 78.5)		72.3 (65.9, 78.1)	
A/Wisconsin	70.9 (64.4, 76.8)		70.5 (64.0, 76.4)	
B/Malaysia	53.2 (46.4, 59.9)		55.5 (48.6, 62.1)	

HI = hemagglutination inhibition; ATP = according-to-protocol; CI = Confidence Interval.

[a] Results obtained following vaccination with FLUARIX manufactured for the 2006–2007

season.

[b] US-licensed trivalent, inactivated influenza virus vaccine (Sanofi Pasteur SA) without preservative manufactured for the 2006-2007 season.

[c] Seroconversion defined as at least a 4-fold increase in serum titers of HI antibodies to ≥1:40.

15 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 with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2010;59(RR-8):1-62.

16 HOW SUPPLIED/STORAGE AND HANDLING

FLUARIX is supplied in 0.5-mL single-dose prefilled TIP-LOK syringes (packaged without needles).

NDC 58160-879-41 Syringe (tip cap may contain latex; plunger contains no latex) in Package of 10: NDC 58160-879-52

Store 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.

17 PATIENT COUNSELING INFORMATION

The vaccine recipient or guardian should be:

- informed of the potential benefits and risks of immunization with FLUARIX.
- educated regarding potential side effects, emphasizing that: (1) FLUARIX contains non-infectious killed viruses and cannot cause influenza and (2) FLUARIX is intended to provide protection against illness due to influenza viruses only, and cannot provide protection against all respiratory illness.
- instructed to report any adverse events to their healthcare provider.
- informed that safety and efficacy have not been established in pregnant women. Register women who receive FLUARIX while pregnant in the pregnancy registry by calling 1-888-452-9622.
- 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 Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).
- instructed that annual revaccination is recommended.

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