HIGHLIGHTS OF PRESCRIBING INFORMATION

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

FLUARIX QUADRIVALENT (Influenza Vaccine)
Suspension for Intramuscular Injection
2016-2017 Formula
Initial U.S. Approval: 2012

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

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

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

For intramuscular injection only. (2)

Age	Vaccination Status	Dose and Schedule
Aged 3 through 8 years	Not previously vaccinated with influenza vaccine	Two doses (0.5-mL each) at least 4 weeks apart (2.1)
	Vaccinated with influenza vaccine in a previous season	One or two doses[a] (0.5-mL each) (2.1)
Aged 9 years and older	Not applicable	One 0.5-mL dose (2.1)

[a] One dose or two doses (0.5-mL each) depending on vaccination history as per the annual Advisory Committee on Immunization Practices (ACIP) recommendation on prevention and control of influenza with vaccines. If two doses, administer each 0.5-mL dose at least 4 weeks apart. (2.1)

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

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

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

History of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or following a previous dose of any influenza vaccine. (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 QUADRIVALENT should be based on careful consideration of potential benefits and risks. (5.1)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including FLUARIX QUADRIVALENT. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.2)

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

- In adults, the most common (≥10%) injection site adverse reaction was pain (36%); the most common systemic adverse events were muscle aches (16%), headache (16%), and fatigue (16%). (6.1)
- In children aged 3 through 17 years, the injection site adverse reactions were pain (44%), redness (23%), and swelling (19%). (6.1)
- In children aged 3 through 5 years, the most common (≥10%) systemic adverse events were drowsiness (17%), irritability (17%), and loss of appetite (16%); in children aged 6 through 17 years, the most common systemic adverse events were fatigue (20%), muscle aches (18%), headache (16%), arthralgia (10%), and gastrointestinal symptoms (10%). (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.

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

- Safety and effectiveness of FLUARIX QUADRIVALENT have not been established in pregnant women or nursing mothers. (8.1, 8.3)
- Register women who receive FLUARIX QUADRIVALENT while pregnant in the pregnancy registry by calling 1-888-452-9622. (8.1)
- Geriatric Use: Antibody responses were lower in geriatric subjects who received FLUARIX QUADRIVALENT than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: x/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FLUARIX® QUADRIVALENT is indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine *[see Description (11)]*. FLUARIX QUADRIVALENT is approved for use in persons 3 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Dosage and Schedule

The dose and schedule for FLUARIX QUADRIVALENT are presented in Table 1.

Table 1. FLUARIX QUADRIVALENT: Dosing

Age	Vaccination Status	Dose and Schedule
Aged 3 through 8 years	Not previously vaccinated with influenza vaccine	Two doses (0.5-mL each) at least 4 weeks apart
	Vaccinated with influenza vaccine in a previous season	One or two doses[a] (0.5-mL each)
Aged 9 years and older	Not applicable	One 0.5-mL dose

[a] One dose or two doses (0.5-mL each) depending on vaccination history as per the annual Advisory Committee on Immunization Practices (ACIP) recommendation on prevention and control of influenza with vaccines. If two doses, administer each 0.5-mL dose at least 4 weeks apart.

2.2 Administration Instructions

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.

The preferred site for intramuscular injection is the deltoid muscle of the upper arm. Do not inject in the gluteal area or areas where there may be a major nerve trunk.

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

3 DOSAGE FORMS AND STRENGTHS

FLUARIX QUADRIVALENT is a suspension for injection. Each 0.5-mL dose is supplied in single-dose prefilled TIP-LOK® syringes.

4 CONTRAINDICATIONS

Do not administer FLUARIX QUADRIVALENT to anyone with a history of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or following a previous administration of any influenza vaccine *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

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

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

5.2 Syncope

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

5.3 Preventing and Managing Allergic Vaccine Reactions

Prior to 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 QUADRIVALENT.

5.4 Altered Immunocompetence

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

5.5 Limitations of Vaccine Effectiveness

Vaccination with FLUARIX QUADRIVALENT may not protect all susceptible individuals.

5.6 Persons at Risk of Bleeding

As with other intramuscular injections, FLUARIX QUADRIVALENT 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

The safety experience with FLUARIX (trivalent influenza vaccine) is relevant to FLUARIX QUADRIVALENT because both vaccines are manufactured using the same process and have overlapping compositions *[see Description (11)]*.

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 with 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 QUADRIVALENT could reveal adverse reactions not observed in clinical trials.

In adults who received FLUARIX QUADRIVALENT, the most common (≥10%) injection site adverse reaction was pain (36%). The most common (≥10%) systemic adverse events were muscle aches (16%), headache (16%), and fatigue (16%).

In children aged 3 through 17 years who received FLUARIX QUADRIVALENT, injection site adverse reactions were pain (44%), redness (23%), and swelling (19%). In children aged 3 through 5 years, the most common (≥10%) systemic adverse events were drowsiness (17%), irritability (17%), and loss of appetite (16%); in children aged 6 through 17 years, the most common systemic adverse events were fatigue (20%), muscle aches (18%), headache (16%), arthralgia (10%), and gastrointestinal symptoms (10%).

FLUARIX QUADRIVALENT in Adults

Trial 1 was a randomized, double-blind (2 arms) and open-label (one arm), active-controlled, safety, and immunogenicity trial. In this trial, subjects received FLUARIX QUADRIVALENT (N = 3,036) or one of two formulations of comparator trivalent influenza vaccine (FLUARIX, TIV-1, N = 1,010 or TIV-2, N = 610), each containing an influenza type B virus that corresponded to one of the two type B viruses in FLUARIX QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The population was aged 18 years and older (mean age: 58 years) and 57% were female; 69% were white, 27% were Asian, and 4% were of other racial/ethnic groups. Solicited events were collected for 7 days (day of vaccination and the next 6 days). The frequencies of solicited adverse events are shown in Table 2.

Table 2. FLUARIX QUADRIVALENT: Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events within 7 Days[a] of Vaccination in Adults[b] (Total Vaccinated Cohort)

	FLUARIX QUADRIVALENT[c] N = 3,011-3,015 %	Trivalent Influenza Vaccine (TIV)	
		TIV-1 (B Victoria)[d] N = 1,003 %	TIV-2 (B Yamagata)[e] N = 607 %
Local			
Pain	36	37	31
Redness	2	2	2
Swelling	2	2	1
Systemic			
Muscle aches	16	19	16
Headache	16	16	13
Fatigue	16	18	15
Arthralgia	8	10	9
Gastrointestinal symptoms[f]	7	7	6
Shivering	4	5	4
Fever ≥99.5°F (37.5°C)	2	1	2

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

[a] 7 days included day of vaccination and the subsequent 6 days.

[b] Trial 1: NCT01204671.

[c] Contained the same composition as FLUARIX (trivalent formulation) manufactured for the 2010-2011 season and an additional influenza type B virus of Yamagata lineage.

[d] Contained the same composition as FLUARIX manufactured for the 2010-2011 season (2 influenza A subtype viruses and an influenza type B virus of Victoria lineage).

[e] Contained the same 2 influenza A subtype viruses as FLUARIX manufactured for the 2010-2011 season and an influenza type B virus of Yamagata lineage.

[f] Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

Unsolicited events occurring within 21 days of vaccination (Day 0 to 20) were reported in 13%, 14%, and 15% of subjects who received FLUARIX QUADRIVALENT, TIV-1, or TIV-2, respectively. The unsolicited adverse reactions that occurred most frequently (≥0.1% for FLUARIX QUADRIVALENT) included dizziness, injection site hematoma, injection site pruritus, and rash. Serious adverse events occurring within 21 days of vaccination were reported in 0.5%, 0.6%, and 0.2% of subjects who received FLUARIX QUADRIVALENT, TIV-1, or

TIV-2, respectively.

FLUARIX QUADRIVALENT in Children

Trial 2 was a randomized, double-blind, active-controlled, safety, and immunogenicity trial. In this trial, subjects received FLUARIX QUADRIVALENT (N = 915) or one of two formulations of comparator trivalent influenza vaccine (FLUARIX, TIV-1, N = 912 or TIV-2, N = 911), each containing an influenza type B virus that corresponded to one of the two type B viruses in FLUARIX QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). Subjects were aged 3 through 17 years and 52% were male; 56% were white, 29% were Asian, 12% were black, and 3% were of other racial/ethnic groups. Children aged 3 through 8 years with no history of influenza vaccination received 2 doses approximately 28 days apart. Children aged 3 through 8 years with a history of influenza vaccination and children aged 9 years and older received one dose. Solicited local adverse reactions and systemic adverse events were collected using diary cards for 7 days (day of vaccination and the next 6 days). The frequencies of solicited adverse events are shown in Table 3.

Table 3. FLUARIX QUADRIVALENT: Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events within 7 Days[a] after First Vaccination in Children Aged 3 through 17 Years[b] (Total Vaccinated Cohort)

	FLUARIX QUADRIVALENT[c] %	Trivalent Influenza Vaccine (TIV)	
		TIV-1 (B Victoria)[d] %	TIV-2 (B Yamagata)[e] %
	Aged 3 through 17 Years		
Local	**N = 903**	**N = 901**	**N = 905**
Pain[f]	44	42	40
Redness	23	21	21
Swelling	19	17	15
	Aged 3 through 5 Years		
Systemic	**N = 291**	**N = 314**	**N = 279**
Drowsiness	17	12	14
Irritability	17	13	14
Loss of appetite	16	8	10
Fever ≥99.5°F (37.5°C)	9	9	8
	Aged 6 through 17 Years		
Systemic	**N = 613**	**N = 588**	**N = 626**
Fatigue	20	19	16
Muscle aches	18	16	16
Headache	16	19	15
Arthralgia	10	9	7
Gastrointestinal symptoms[g]	10	10	7
Shivering	6	4	5
Fever ≥99.5°F (37.5°C)	6	9	6

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

[a] 7 days included day of vaccination and the subsequent 6 days.

[b] Trial 2: NCT01196988.

[c] Contained the same composition as FLUARIX (trivalent formulation) manufactured for the 2010-2011 season and an additional influenza type B virus of Yamagata lineage.

[d] Contained the same composition as FLUARIX manufactured for the 2010-2011 season (2 influenza A subtype viruses and an influenza type B virus of Victoria lineage).

[e] Contained the same 2 influenza A subtype viruses as FLUARIX manufactured for the 2010-2011 season and an influenza type B virus of Yamagata lineage.

[f] Percentage of subjects with pain by age subgroup: 39%, 38%, and 37% for FLUARIX

QUADRIVALENT, TIV-1, and TIV-2, respectively, in children aged 3 through 8 years and 52%, 50%, and 46% for FLUARIX QUADRIVALENT, TIV-1, and TIV-2, respectively, in children aged 9 through 17 years.

[g] Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

In children who received a second dose of FLUARIX QUADRIVALENT, TIV-1, or TIV-2, the incidences of adverse events following the second dose were generally lower than those observed after the first dose.

Unsolicited adverse events occurring within 28 days of any vaccination were reported in 31%, 33%, and 34% of subjects who received FLUARIX QUADRIVALENT, TIV-1, or TIV-2, respectively. The unsolicited adverse reactions that occurred most frequently (≥0.1% for FLUARIX QUADRIVALENT) included injection site pruritus and rash. Serious adverse events occurring within 28 days of any vaccination were reported in 0.1%, 0.1%, and 0.1% of subjects who received FLUARIX QUADRIVALENT, TIV-1, or TIV-2, respectively.

FLUARIX (Trivalent Formulation)

FLUARIX has been administered to 10,317 adults aged 18 through 64 years, 606 subjects aged 65 years and older, and 2,115 children aged 6 months through 17 years in clinical trials. The incidence of solicited adverse events in each age group is shown in Tables 4 and 5.

Table 4. FLUARIX (Trivalent Formulation): Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events within 4 Days[a] of Vaccination in Adults (Total Vaccinated Cohort)

	Trial 3[b]		Trial 4[c]	
	Aged 18 through 64 Years		Aged 65 Years and Older	
	FLUARIX N = 760 %	Placebo N = 192 %	FLUARIX N = 601-602 %	Comparator N = 596 %
Local				
Pain	55	12	19	18
Redness	18	10	11	13
Swelling	9	6	6	9
Systemic				
Muscle aches	23	12	7	7
Fatigue	20	18	9	10
Headache	19	21	8	8
Arthralgia	6	6	6	5
Shivering	3	3	2	2
Fever ≥100.4°F (38.0°C)	2	2	–	–
Fever ≥99.5°F (37.5°C)	–	–	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.

[b] Trial 3 was a randomized, double-blind, placebo-controlled, safety, and immunogenicity trial (NCT00100399).

[c] Trial 4 was a randomized, single-blind, active-controlled, safety, and immunogenicity trial (NCT00197288). The active control was FLUZONE®, a US-licensed trivalent, inactivated influenza vaccine (Sanofi Pasteur SA).

Table 5. FLUARIX (Trivalent Formulation): Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events within 4 Days[a] of First Vaccination in Children Aged 3 through 17 Years[b] (Total Vaccinated Cohort)

	Aged 3 through 4 Years		Aged 5 through 17 Years	
	FLUARIX N = 350 %	Comparator N = 341 %	FLUARIX N = 1,348 %	Comparator N = 451 %
Local				
Pain	35	38	56	56
Redness	23	20	18	16
Swelling	14	13	14	13
Systemic				
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

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.

[b] Trial 6 was a single-blind, active-controlled, safety, and immunogenicity US trial (NCT00383123). The active control was FLUZONE, a US-licensed trivalent, inactivated influenza vaccine (Sanofi Pasteur SA).

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.

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

6.2 Postmarketing Experience

Beyond those events reported above in the clinical trials for FLUARIX QUADRIVALENT or FLUARIX, the following adverse events have been spontaneously reported during postapproval use of FLUARIX (trivalent influenza vaccine). 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, swelling of the mouth, throat, and/or tongue.

General Disorders and Administration Site Conditions

Asthenia, chest pain, 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.

Nervous System Disorders

Convulsion, encephalomyelitis, facial palsy, facial paresis, Guillain-Barré syndrome, hypoesthesia, myelitis, neuritis, neuropathy, paresthesia, syncope.

Respiratory, Thoracic, and Mediastinal Disorders

Asthma, bronchospasm, dyspnea, respiratory distress, stridor.

Skin and Subcutaneous Tissue Disorders

Angioedema, erythema, erythema multiforme, facial swelling, pruritus, Stevens-Johnson syndrome, sweating, urticaria.

Vascular Disorders

Henoch-Schönlein purpura, vasculitis.

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration

FLUARIX QUADRIVALENT 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 QUADRIVALENT with other vaccines. When concomitant administration of other vaccines is required, the vaccines should be administered at different injection sites.

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 QUADRIVALENT.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. A reproductive and developmental toxicity study has been performed in female rats at doses approximately 80 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 QUADRIVALENT. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, FLUARIX QUADRIVALENT should be given to a pregnant woman only if clearly needed.

In a reproductive and developmental toxicity study, the effect of FLUARIX QUADRIVALENT on embryo-fetal and pre-weaning development was evaluated in rats. Animals were administered FLUARIX QUADRIVALENT by intramuscular injection twice prior to gestation, during the period of organogenesis (gestation Days 3, 8, 11, and 15), and during lactation (Day 7), 0.2 mL/rat/occasion (approximately 80-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 QUADRIVALENT during pregnancy. Women who receive FLUARIX QUADRIVALENT 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 QUADRIVALENT is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FLUARIX QUADRIVALENT is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of FLUARIX QUADRIVALENT in children younger than 3 years have not been established.

Safety and immunogenicity of FLUARIX QUADRIVALENT in children aged 3 through 17 years have been evaluated *[see Adverse Reactions (6.1), Clinical Studies (14.3)]*.

8.5 Geriatric Use

In a randomized, double-blind (2 arms) and open-label (one arm), active-controlled trial, immunogenicity and safety were evaluated in a cohort of subjects aged 65 years and older who received FLUARIX QUADRIVALENT (N = 1,517); 469 of these subjects were aged 75 years and older. In subjects aged 65 years and older, the geometric mean antibody titers (GMTs) post-vaccination and seroconversion rates were lower than in younger subjects (aged 18 through 64 years) and the frequencies of solicited and unsolicited adverse events were generally lower than in younger subjects.

11 DESCRIPTION

FLUARIX QUADRIVALENT, Influenza Vaccine, for intramuscular injection, is a sterile colorless and slightly opalescent suspension. FLUARIX QUADRIVALENT is 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. Each vaccine is formulated from the split inactivated virus solutions.

FLUARIX QUADRIVALENT has been standardized according to USPHS requirements for the 2016-2017 influenza season and is formulated to contain 60 micrograms (mcg) hemagglutinin (HA) per 0.5-mL dose, in the recommended ratio of 15 mcg HA of each of the following 4 influenza virus strains: A/Christchurch/16/2010 (H1N1) NIB-74XP (an A/California/7/2009 (H1N1) pdm09-like virus), A/Hong Kong/4801/2014 (H3N2) NYMC X-263B, B/Phuket/3073/2013, and B/Brisbane/60/2008.

FLUARIX QUADRIVALENT is formulated without preservatives. FLUARIX QUADRIVALENT does not contain thimerosal. Each 0.5-mL dose also contains octoxynol-10 (TRITON® X-100) ≤0.115 mg, α-tocopheryl hydrogen succinate ≤0.135 mg, and polysorbate 80 (Tween 80) ≤0.550 mg. Each dose may also contain residual amounts of hydrocortisone ≤0.0016 mcg, gentamicin sulfate ≤0.15 mcg, ovalbumin ≤0.050 mcg, formaldehyde ≤5 mcg, and sodium deoxycholate ≤65 mcg from the manufacturing process.

The tip caps and plungers of the prefilled syringes of FLUARIX QUADRIVALENT are not made with natural rubber 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. Since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation.

Public health authorities give annual influenza vaccine composition recommendations. Inactivated influenza vaccines are standardized to contain the hemagglutinins of influenza viruses representing the virus types or subtypes likely to circulate in the United States during the influenza season. Two influenza type B virus lineages (Victoria and Yamagata) are of public health importance because they have co-circulated since 2001. FLUARIX (trivalent influenza vaccine) contains 2 influenza A subtype viruses and one influenza type B virus.

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 replacement of one or more influenza viruses in each year's influenza vaccine.

Annual revaccination 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 QUADRIVALENT has not been evaluated for carcinogenic or mutagenic potential. Vaccination of female rats with FLUARIX QUADRIVALENT, at doses shown to be immunogenic in the rat, had no effect on fertility.

14 CLINICAL STUDIES

14.1 Efficacy against Culture-confirmed Influenza

The efficacy experience with FLUARIX is relevant to FLUARIX QUADRIVALENT because both vaccines are manufactured using the same process and have overlapping compositions *[see*

Description (11)].

The efficacy of FLUARIX was evaluated in a randomized, double-blind, placebo-controlled trial 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 virus 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 aged 18 through 64 years (mean age: 40 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 6).

Table 6. FLUARIX (Trivalent Formulation): Attack Rates and Vaccine Efficacy against Culture-confirmed Influenza A and/or B in Adults (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 virus 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 aged 18 through 49 years 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 aged 50 through 64 years, 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 trial lacked statistical power to evaluate efficacy within age subgroups, the clinical significance of these results is unknown.

14.2 Immunological Evaluation of FLUARIX QUADRIVALENT in Adults

Trial 1 was a randomized, double-blind (2 arms) and open-label (one arm), active-controlled, safety, immunogenicity, and non-inferiority trial. In this trial, subjects received FLUARIX QUADRIVALENT (N = 1,809) or one of two formulations of comparator trivalent influenza vaccine (FLUARIX, TIV-1, N = 608 or TIV-2, N = 534), each containing an influenza type B virus that corresponded to one of the two type B viruses in FLUARIX QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). Subjects aged 18 years and older (mean age: 58 years) were evaluated for immune responses to each of the vaccine antigens 21 days following vaccination. In the overall population, 57% of subjects were female; 69% were white, 27% were Asian, and 4% were of other racial/ethnic groups.

The immunogenicity endpoints were GMTs of serum hemagglutination-inhibition (HI) antibodies adjusted for baseline, and the percentage of subjects who achieved seroconversion, defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥1:40 or at least a 4-fold increase in serum HI antibody titer over baseline to ≥1:40 following vaccination, performed on the According-to-Protocol (ATP) cohort for whom immunogenicity assay results were available after vaccination. FLUARIX QUADRIVALENT was non-inferior to both TIVs based on adjusted GMTs (upper limit of the 2-sided 95% CI for the GMT ratio [TIV/FLUARIX QUADRIVALENT] ≤1.5) and seroconversion rates (upper limit of the 2-sided 95% CI on difference of the TIV minus FLUARIX QUADRIVALENT ≤10%). The antibody response to influenza B strains contained in FLUARIX QUADRIVALENT was higher than the antibody response after vaccination with a TIV containing an influenza B strain from a different lineage. There was no evidence that the addition of the second B strain resulted in immune interference to other strains included in the vaccine (Table 7).

Table 7. FLUARIX QUADRIVALENT: Immune Responses to Each Antigen 21 Days after Vaccination in Adults (ATP Cohort for Immunogenicity)

		Trivalent Influenza Vaccine (TIV)	
	FLUARIX QUADRIVALENT[a]	**TIV-1 (B Victoria)[b]**	**TIV-2 (B Yamagata)[c]**
GMTs	**N = 1,809 (95% CI)**	**N = 608 (95% CI)**	**N = 534 (95% CI)**
A/California/7/2009 (H1N1)	201.1 (188.1, 215.1)	218.4 (194.2, 245.6)	213.0 (187.6, 241.9)
A/Victoria/210/2009 (H3N2)	314.7 (296.8, 333.6)	298.2 (268.4, 331.3)	340.4 (304.3, 380.9)
B/Brisbane/60/2008 (Victoria lineage)	404.6 (386.6, 423.4)	393.8 (362.7, 427.6)	258.5 (234.6, 284.8)
B/Brisbane/3/2007 (Yamagata lineage)	601.8 (573.3, 631.6)	386.6 (351.5, 425.3)	582.5 (534.6, 634.7)
Seroconversion[d]	**N = 1,801 % (95% CI)**	**N = 605 % (95% CI)**	**N = 530 % (95% CI)**
A/California/7/2009 (H1N1)	77.5 (75.5, 79.4)	77.2 (73.6, 80.5)	80.2 (76.5, 83.5)
A/Victoria/210/2009 (H3N2)	71.5 (69.3, 73.5)	65.8 (61.9, 69.6)	70.0 (65.9, 73.9)
B/Brisbane/60/2008 (Victoria lineage)	58.1 (55.8, 60.4)	55.4 (51.3, 59.4)	47.5 (43.2, 51.9)
B/Brisbane/3/2007 (Yamagata lineage)	61.7 (59.5, 64.0)	45.6 (41.6, 49.7)	59.1 (54.7, 63.3)

ATP = According-to-protocol; GMT = Geometric mean antibody titer; CI = Confidence Interval.

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

[a] Contained the same composition as FLUARIX (trivalent formulation) manufactured for the 2010-2011 season and an additional influenza type B virus of Yamagata lineage.

[b] Contained the same composition as FLUARIX manufactured for the 2010-2011 season (2 influenza A subtype viruses and an influenza type B virus of Victoria lineage).

[c] Contained the same 2 influenza A subtype viruses as FLUARIX manufactured for the 2010-2011 season and an influenza type B virus of Yamagata lineage.

[d] Seroconversion defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥1:40 or at least a 4-fold increase in serum titers of HI antibodies to ≥1:40.

14.3 Immunological Evaluation of FLUARIX QUADRIVALENT in Children

Trial 2 was a randomized, double-blind, active-controlled, safety, immunogenicity, and non-inferiority trial. In this trial, subjects received FLUARIX QUADRIVALENT (N = 791) or one of two formulations of comparator trivalent influenza vaccine (FLUARIX, TIV-1, N = 819 or TIV-2, N = 801), each containing an influenza type B virus that corresponded to one of the two type B viruses in FLUARIX QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). In children aged 3 through 17 years, immune responses to each of the vaccine antigens were evaluated in sera 28 days following 1 or 2 doses. In the overall population, 52% of subjects were male; 56% were white, 29% were Asian, 12% were black, and 3% were of other racial/ethnic groups.

The immunogenicity endpoints were GMTs adjusted for baseline, and the percentage of subjects who achieved seroconversion, defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥1:40 or at least a 4-fold increase in serum HI titer over baseline to ≥1:40, following vaccination, performed on the According-to-Protocol (ATP) cohort for whom immunogenicity assay results were available after vaccination. FLUARIX QUADRIVALENT was non-inferior to both TIVs based on adjusted GMTs (upper limit of the 2-sided 95% CI for the GMT ratio [TIV/FLUARIX QUADRIVALENT] ≤1.5) and seroconversion rates (upper limit of the 2-sided 95% CI on difference of the TIV minus FLUARIX QUADRIVALENT ≤10%). The antibody response to influenza B strains contained in FLUARIX QUADRIVALENT was higher than the antibody response after vaccination with a TIV containing an influenza B strain from a different lineage. There was no evidence that the addition of the second B strain resulted in immune interference to other strains included in the vaccine (Table 8).

Table 8. FLUARIX QUADRIVALENT: Immune Responses to Each Antigen 28 Days after Last Vaccination in Children Aged 3 through 17 Years (ATP Cohort for Immunogenicity)

		Trivalent Influenza Vaccine (TIV)	
	FLUARIX QUADRIVALENT[a]	**TIV-1 (B Victoria)[b]**	**TIV-2 (B Yamagata)[c]**
GMTs	**N = 791 (95% CI)**	**N = 818 (95% CI)**	**N = 801 (95% CI)**
A/California/7/2009 (H1N1)	386.2 (357.3, 417.4)	433.2 (401.0, 468.0)	422.3 (390.5, 456.5)
A/Victoria/210/2009 (H3N2)	228.8 (215.0, 243.4)	227.3 (213.3, 242.3)	234.0 (219.1, 249.9)
B/Brisbane/60/2008 (Victoria lineage)	244.2 (227.5, 262.1)	245.6 (229.2, 263.2)	88.4 (81.5, 95.8)
B/Brisbane/3/2007 (Yamagata lineage)	569.6 (533.6, 608.1)	224.7 (207.9, 242.9)	643.3 (603.2, 686.1)
Seroconversion[d]	**N = 790 % (95% CI)**	**N = 818 % (95% CI)**	**N = 800 % (95% CI)**
A/California/7/2009 (H1N1)	91.4 (89.2, 93.3)	89.9 (87.6, 91.8)	91.6 (89.5, 93.5)
A/Victoria/210/2009 (H3N2)	72.3 (69.0, 75.4)	70.7 (67.4, 73.8)	71.9 (68.6, 75.0)
B/Brisbane/60/2008 (Victoria lineage)	70.0 (66.7, 73.2)	68.5 (65.2, 71.6)	29.6 (26.5, 32.9)
B/Brisbane/3/2007 (Yamagata lineage)	72.5 (69.3, 75.6)	37.0 (33.7, 40.5)	70.8 (67.5, 73.9)

ATP = According-to-protocol; GMT = Geometric mean antibody titer; CI = Confidence Interval.

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

[a] Contained the same composition as FLUARIX (trivalent formulation) manufactured for the 2010-2011 season and an additional influenza type B virus of Yamagata lineage.

[b] Contained the same composition as FLUARIX manufactured for the 2010-2011 season (2 influenza A subtype viruses and an influenza type B virus of Victoria lineage).

[c] Contained the same 2 influenza A subtype viruses as FLUARIX manufactured for the 2010-2011 season and an influenza B virus of Yamagata lineage.

[d] Seroconversion defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥1:40 or 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

NDC 58160-905-41 Syringe in Package of 10: NDC 58160-905-52

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

Provide the following information to the vaccine recipient or guardian:

- Inform of the potential benefits and risks of immunization with FLUARIX QUADRIVALENT.
- Educate regarding potential side effects, emphasizing that: (1) FLUARIX QUADRIVALENT contains non-infectious killed viruses and cannot cause influenza and (2) FLUARIX QUADRIVALENT is intended to provide protection against illness due to influenza viruses only, and cannot provide protection against all respiratory illness.
- Inform that safety and efficacy have not been established in pregnant women. Register women who receive FLUARIX QUADRIVALENT while pregnant in the pregnancy registry by calling 1-888-452-9622.
- Give the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 prior to each immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).
- Instruct that annual revaccination is recommended.

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