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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) injectable suspension, for intramuscular use
2018-2019 Formula
Initial U.S. Approval: 2012

RECENT MAJOR CHANGES

Indications and Usage (1)	01/2018
Dosage and Administration (2.1)	01/2018

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 aged 6 months and older. (1)

DOSAGE AND ADMINISTRATION

For intramuscular injection only. (2)

Age	Vaccination Status	Dose and Schedule
6 months 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 2 doses[a] (0.5-mL each) (2.1)
9 years and older	Not applicable	One 0.5-mL dose (2.1)

[a] One dose or 2 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 2 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%) solicited local adverse reaction was pain (36%); the most common systemic adverse reactions were muscle aches (16%), headache (16%), and fatigue (16%). (6.1)
- In children aged 6 through 35 months, the most common (≥10%) solicited local adverse reactions were pain (17%) and redness (13%); the most common systemic adverse reactions were irritability (16%), loss of appetite (14%), and drowsiness (13%). (6.1)
- In children aged 3 through 17 years, the solicited local 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 reactions were drowsiness (17%), irritability (17%), and loss of appetite (16%); in children aged 6 through 17 years, the most common systemic adverse reactions 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

- 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/2018

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 aged 6 months 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
6 months 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 2 doses[a] (0.5-mL each)
9 years and older	Not applicable	One 0.5-mL dose

[a] One dose or 2 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 2 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 sites for intramuscular injection are the anterolateral thigh for children aged 6 through 11 months and the deltoid muscle of the upper arm for persons aged 12 months and older if muscle mass is adequate. 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%) solicited local adverse reaction was pain (36%). The most common (≥10%) systemic adverse reactions were muscle aches (16%), headache (16%), and fatigue (16%).

In children aged 6 through 35 months who received FLUARIX QUADRIVALENT, the most common (≥10%) solicited local adverse reactions were pain (17%) and redness (13%). The most common (≥10%) systemic adverse reactions were irritability (16%), loss of appetite (14%), and drowsiness (13%). In children aged 3 through 17 years who received FLUARIX QUADRIVALENT, solicited local adverse reactions were pain (44%), redness (23%), and swelling (19%). In children aged 3 through 5 years, the most common (≥10%) systemic adverse reactions were drowsiness (17%), irritability (17%), and loss of appetite (16%); in children aged 6 through 17 years, the most common systemic adverse reactions were fatigue (20%), muscle aches (18%), headache (16%), arthralgia (10%), and gastrointestinal symptoms (10%).

<u>FLUARIX QUADRIVALENT in Adults</u>

Trial 1 (NCT01204671) 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 2 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 2 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 reactions are shown in Table 2.

Table 2. FLUARIX QUADRIVALENT: Incidence of Solicited Local Adverse Reactions and Systemic Adverse Reactions 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 %	
Adverse Reaction	**Any**	**Grade 3[f]**	**Any**	**Grade 3[f]**	**Any**	**Grade 3[f]**
Local						
Pain	36.4	0.8	36.8	1.2	31.3	0.5
Redness	1.9	0	1.7	0	2.0	0
Swelling	2.1	0	2.1	0	1.3	0
Systemic						
Muscle aches	16.4	0.5	19.4	0.8	16.1	0.5
Headache	15.9	0.9	16.4	0.8	13.2	0.7
Fatigue	15.8	0.7	18.4	0.6	14.8	0.5
Arthralgia	8.4	0.5	10.4	0.7	9.4	0.3
Gastrointestinal symptoms[g]	6.5	0.4	6.5	0.2	5.9	0.3
Shivering	4.2	0.4	5.0	0.3	4.3	0.2
Fever[h]	1.6	0	1.2	0	1.5	0

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available.
n = Number of subjects with diary card completed.
[a] Seven 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] Grade 3 pain: Defined as significant pain at rest; prevented normal everyday activities.
Grade 3 redness, swelling: Defined as >100 mm.
Grade 3 muscle aches, headache, fatigue, arthralgia, gastrointestinal symptoms, shivering: Defined as prevented normal activity.
Grade 3 fever: Defined as >102.2°F (39.0°C).
[g] Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.
[h] Fever: Defined as ≥99.5°F (37.5°C).

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 7 (NCT01439360) was a randomized, observer-blind, non-influenza vaccine-controlled trial evaluating the efficacy of FLUARIX QUADRIVALENT. In this trial, subjects aged 6 through 35 months received FLUARIX QUADRIVALENT (n = 6,006) or a control vaccine (n = 6,012). The comparator was pneumococcal 13-valent conjugate vaccine [Diphtheria CRM197 Protein] (Wyeth Pharmaceuticals, Inc.) in children younger than 12 months, HAVRIX (Hepatitis A Vaccine) in children 12 months and older with a history of influenza vaccination, or HAVRIX (Dose 1) and a varicella vaccine (U.S. Licensed Manufactured by Merck & Co., Inc. or Non-U.S. Licensed Manufactured by GlaxoSmithKline Biologicals**)** (Dose 2) in those with no history of influenza vaccination. Subjects were aged 6 through 35 months, and one child aged 43 months (mean age: 22 months); 51% were male; 27% were white, 45% were Asian, and 28% were of other racial/ethnic groups. Children aged 12 months and older with no history of influenza vaccination and children younger than 12 months received 2 doses of FLUARIX QUADRIVALENT or the control vaccine approximately 28 days apart. Children aged 12 months and older with a history of influenza vaccination 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 incidences of solicited adverse reactions are shown in Table 3.

Table 3. FLUARIX QUADRIVALENT: Incidence of Solicited Local Adverse Reactions and Systemic Adverse Reactions within 7 Days[a] after First Vaccination in Children Aged 6 through 35 Months[b] (Total Vaccinated Cohort)

Adverse Reaction	FLUARIX QUADRIVALENT %		Non-Influenza Active Comparator[c,d] %	
	Any	Grade 3[e]	Any	Grade 3[e]
Local	**n = 5,899**		**n = 5,896**	
Pain	17.2	0.4	17.8	0.5
Redness	13.1	0	14.1	0
Swelling	7.9	0	8.8	0
Systemic	**n = 5,898**		**n = 5,896**	
Irritability	16.2	0.7	17.5	1.1
Loss of appetite	14.4	1.2	14.8	1.0
Drowsiness	12.5	0.7	14.1	0.9
Fever[f]	6.3	1.3	7.2	1.3

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available.
n = Number of subjects with diary card completed.

[a] Seven days included day of vaccination and the subsequent 6 days.
[b] Trial 7: NCT01439360.
[c] Children younger than 12 months: pneumococcal 13-valent conjugate vaccine [Diphtheria CRM197 Protein] (Wyeth Pharmaceuticals, Inc.).
[d] Children 12 months and older: HAVRIX (Hepatitis A Vaccine) for those with a history of influenza vaccination; or HAVRIX (Dose 1) and a varicella vaccine (U.S. Licensed Manufactured by Merck & Co., Inc. or Non-U.S. Licensed Manufactured by GlaxoSmithKline Biologicals) (Dose 2) for those with no history of influenza vaccination.
[e] Grade 3 pain: Defined as cried when limb was moved/spontaneously painful.
Grade 3 swelling, redness: Defined as >50 mm.
Grade 3 irritability: Defined as crying that could not be comforted/prevented normal activity.
Grade 3 loss of appetite: Defined as not eating at all.
Grade 3 drowsiness: Defined as prevented normal activity.
Grade 3 fever: Defined as >102.2°F (39.0°C).
[f] Fever: Defined as ≥100.4°F (38.0°C).

In children who received a second dose of FLUARIX QUADRIVALENT or the Non-Influenza Active Comparator vaccine, the incidences of solicited adverse reactions following the second dose were generally lower than those observed after the first dose.

Unsolicited adverse events occurring within 28 days of vaccination were reported in 44% and 45% of subjects who received FLUARIX QUADRIVALENT (n = 6,006) and the comparator vaccine (n = 6,012), respectively. Serious adverse events (SAEs) occurring during the study period (6 to 8 months) were reported in 3.6% of subjects who received FLUARIX QUADRIVALENT and in 3.3% of subjects who received the comparator vaccine.

Trial 2 (NCT01196988) was a randomized, double-blind, active-controlled, safety, and immunogenicity trial. In this trial, subjects received FLUARIX QUADRIVALENT (n = 915) or one of 2 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 2 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 reactions are shown in Table 4.

Table 4. FLUARIX QUADRIVALENT: Incidence of Solicited Local Adverse Reactions and Systemic Adverse Reactions 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] %	
	Any	Grade 3[f]	Any	Grade 3[f]	Any	Grade 3[f]
Adverse Reaction	**Aged 3 through 17 Years**					
Local	**n = 903**		**n = 901**		**n = 905**	
Pain[g]	43.7	1.6	42.4	1.8	40.3	0.8
Redness	23.0	1.0	21.3	0.2	20.9	0.7
Swelling	18.5	0.8	17.2	1.1	14.9	0.2
	Aged 3 through 5 Years					
Systemic	**n = 291**		**n = 314**		**n = 279**	
Drowsiness	17.2	1.0	12.4	0.3	13.6	0.7
Irritability	16.8	0.7	13.4	0.3	14.3	0.7
Loss of appetite	15.5	0.3	8.0	0	10.4	0.7
Fever[h]	8.9	0.3	8.9	0.3	8.2	1.1
	Aged 6 through 17 Years					
Systemic	**n = 613**		**n = 588**		**n = 626**	
Fatigue	19.7	1.5	18.5	1.4	15.5	0.5
Muscle aches	17.5	0.7	16.0	1.4	15.8	0.5
Headache	16.3	1.3	19.2	0.7	15.2	0.6
Arthralgia	9.8	0.3	9.4	0.7	7.3	0.2
Gastrointestinal symptoms[i]	9.8	1.0	9.5	0.7	7.2	0.3
Shivering	6.4	0.5	4.4	0.5	5.0	0
Fever[h]	6.0	1.1	8.5	0.5	6.1	0.3

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available.
n = Number of subjects with diary card completed.
[a] Seven 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] Grade 3 pain: Defined as cried when limb was moved/spontaneously painful (children <6 years), or significant pain at rest, prevented normal everyday activities (children ≥6 years).

Grade 3 redness, swelling: Defined as >50 mm.
Grade 3 drowsiness: Defined as prevented normal activity.
Grade 3 irritability: Defined as crying that could not be comforted/prevented normal activity.
Grade 3 loss of appetite: Defined as not eating at all.
Grade 3 fever: Defined as >102.2°F (39.0°C).
Grade 3 fatigue, muscle aches, headache, arthralgia, gastrointestinal symptoms, shivering: Defined as prevented normal activity.

[g] Percentage of subjects with any 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.

[h] Fever: Defined as ≥99.5°F (37.5°C).

[i] 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 reactions 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 reactions in each age-group is shown in Tables 5 and 6.

Table 5. FLUARIX (Trivalent Formulation): Incidence of Solicited Local Adverse Reactions and Systemic Adverse Reactions within 4 Days[a] of Vaccination in Adults (Total Vaccinated Cohort)

Adverse Reaction	Trial 3[b] Aged 18 through 64 Years				Trial 4[c] Aged 65 Years and Older			
	FLUARIX n = 760 %		Placebo n = 192 %		FLUARIX n = 601-602 %		Comparator n = 596 %	
	Any	Grade 3[d]	Any	Grade 3[d]	Any	Grade 3[d]	Any	Grade 3[d]
Local								
Pain	54.7	0.1	12.0	0	19.1	0	17.6	0
Redness	17.5	0	10.4	0	10.6	0.2	13.1	0.7
Swelling	9.3	0.1	5.7	0	6.0	0	8.9	0.7
Systemic								
Muscle aches	23.0	0.4	12.0	0.5	7.0	0.3	6.5	0
Fatigue	19.7	0.4	17.7	1.0	9.0	0.3	9.6	0.7
Headache	19.3	0.1	21.4	1.0	7.5	0.3	7.9	0.3
Arthralgia	6.4	0.1	6.3	0.5	5.5	0.5	5.0	0.2
Shivering	3.3	0.1	2.6	0	1.7	0.2	2.2	0
Fever[e]	1.7	0	1.6	0	1.7	0	0.5	0

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available.
n = Number of subjects with diary card completed.
[a] Four 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 U.S.-licensed trivalent, inactivated influenza vaccine (Sanofi Pasteur Inc.).
[d] Grade 3 pain, muscle aches, fatigue, headache, arthralgia, shivering: Defined as prevented normal activity.
Grade 3 redness, swelling: Defined as >50 mm.
Grade 3 fever: Defined as >102.2°F (39.0°C).
[e] Fever: Defined as ≥100.4°F (38.0°C) in Trial 3, and ≥99.5°F (37.5°C) in Trial 4.

Table 6. FLUARIX (Trivalent Formulation): Incidence of Solicited Local Adverse Reactions and Systemic Adverse Reactions within 4 Days[a] of First Vaccination in Children Aged 3 through 17 Years[b] (Total Vaccinated Cohort)

Adverse Reaction	Aged 3 through 4 Years				Aged 5 through 17 Years			
	FLUARIX n = 350 %		Comparator n = 341 %		FLUARIX n = 1,348 %		Comparator n = 451 %	
	Any	Grade 3[c]	Any	Grade 3[c]	Any	Grade 3[c]	Any	Grade 3[c]
Local								
Pain	34.9	1.7	38.4	1.2	56.2	0.8	56.1	0.7
Redness	22.6	0.3	19.9	0	17.7	1.0	16.4	0.7
Swelling	13.7	0	13.2	0	13.9	1.5	13.3	0.7
Systemic								
Irritability	20.9	0.9	22.0	0	–	–	–	–
Loss of appetite	13.4	0.9	15.0	0.9	–	–	–	–
Drowsiness	13.1	0.6	19.6	0.9	–	–	–	–
Fever[d]	6.6	1.4	7.6	1.5	4.2	0.3	3.3	0.2
Muscle aches	–	–	–	–	28.8	0.4	28.8	0.4
Fatigue	–	–	–	–	19.9	1.0	18.8	1.1
Headache	–	–	–	–	15.1	0.5	16.4	0.9
Arthralgia	–	–	–	–	5.6	0.1	6.2	0.2
Shivering	–	–	–	–	3.1	0.1	3.5	0.2

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available.
n = Number of subjects with diary card completed.
[a] Four days included day of vaccination and the subsequent 3 days.
[b] Trial 6 was a single-blind, active-controlled, safety, and immunogenicity U.S. trial (NCT00383123). The active control was FLUZONE, a U.S.-licensed trivalent, inactivated influenza vaccine (Sanofi Pasteur Inc.).
[c] Grade 3 pain, irritability, loss of appetite, drowsiness, muscle aches, fatigue, headache, arthralgia, shivering: Defined as prevented normal activity.
Grade 3 swelling, redness: Defined as >50 mm.
Grade 3 fever: Defined as >102.2°F (39.0°C).
[d] Fever: Defined as ≥99.5°F (37.5°C).

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

Serious Adverse Reactions: 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 reactions have been identified during postapproval use of FLUARIX

QUADRIVALENT or FLUARIX (trivalent influenza vaccine). Because these reactions 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 drug exposure.

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, influenza-like illness, 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 Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FLUARIX QUADRIVALENT during pregnancy. Healthcare providers are encouraged to register women by calling 1-888-452-9622.

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

There are insufficient data on FLUARIX QUADRIVALENT in pregnant women to inform vaccine-associated risks.

A developmental toxicity study was performed in female rats administered FLUARIX QUADRIVALENT prior to mating and during gestation and lactation periods. The total dose was 0.2 mL at each occasion (a single human dose is 0.5 mL). This study revealed no adverse effects on fetal or pre-weaning development due to FLUARIX QUADRIVALENT *(see Data)*.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk: Pregnant women infected with seasonal influenza are at increased risk of severe illness associated with influenza infection compared with non-pregnant women. Pregnant women with influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

Data

Animal Data: In a developmental toxicity study, female rats were administered FLUARIX

QUADRIVALENT by intramuscular injection 4 and 2 weeks prior to mating, on gestation Days 3, 8, 11, and 15, and on lactation Day 7. The total dose was 0.2 mL at each occasion (a single human dose is 0.5 mL). No adverse effects on pre-weaning development up to post-natal Day 25 were observed. There were no vaccine-related fetal malformations or variations.

8.2 Lactation

Risk Summary

It is not known whether FLUARIX QUADRIVALENT is excreted in human milk. Data are not available to assess the effects of FLUARIX QUADRIVALENT on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FLUARIX QUADRIVALENT and any potential adverse effects on the breastfed child from FLUARIX QUADRIVALENT or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of FLUARIX QUADRIVALENT in children younger than 6 months have not been established.

Safety and effectiveness of FLUARIX QUADRIVALENT in individuals aged 6 months through 17 years have been established *[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 reactions 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 U.S. Public Health Service (USPHS)

requirements for the 2018-2019 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 (2 A strains and 2 B strains): A/Singapore/GP1908/2015 (H1N1) IVR-180 (an A/Michigan/45/2015 [H1N1] pdm09-like virus), A/Singapore/INFIMH-16-0019/2016 (H3N2) NIB-104, B/Maryland/15/2016 NYMC BX-69A (a B/Colorado/06/2017-like virus), and B/Phuket/3073/2013.

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 ≤0.0015 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

FLUARIX QUADRIVALENT has not been evaluated for carcinogenic or mutagenic potential or male infertility in animals. Vaccination of female rats with FLUARIX QUADRIVALENT had no effect on fertility *[see Use in Specific Populations (8.1)]*.

14 CLINICAL STUDIES

14.1 Efficacy against 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 7).

Table 7. FLUARIX (Trivalent Formulation): Attack Rates and Vaccine Efficacy against Culture-Confirmed Influenza A and/or B in Adults (Total Vaccinated Cohort)

	N[b]	n[c]	Attack Rates (n/N)		Vaccine Efficacy	
			%	%	Lower Limit	Upper Limit
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% Confidence Interval (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.

The efficacy of FLUARIX QUADRIVALENT was evaluated in Trial 7, a randomized, observer-blind, non-influenza vaccine-controlled trial conducted in 13 countries in Asia, Europe, and Central America during the 2011-2012 and 2012-2013 Northern Hemisphere influenza seasons, and from 2012 to 2014 during influenza seasons in subtropical countries. Healthy subjects aged 6 through 35 months (mean age: 22 months) were randomized (1:1) to receive FLUARIX QUADRIVALENT (n = 6,006) or a non-influenza control vaccine (n = 6,012). In the overall population, 51% were male; 27% were white, 45% were Asian, and 28% were of other racial/ethnic groups. Children aged 12 months and older with no history of influenza vaccination and children younger than 12 months received 2 doses of FLUARIX QUADRIVALENT or the Non-Influenza Active Comparator vaccine approximately 28 days apart. Children aged 12 months and older with a history of influenza vaccination received one dose.

The influenza virus strain composition of FLUARIX QUADRIVALENT administered in each of the 5 study cohorts followed the World Health Organization (WHO) recommendations (which included 2nd B strain from 2012 onwards) for each influenza season associated with a particular cohort.

Efficacy of FLUARIX QUADRIVALENT was assessed for the prevention of reverse transcriptase polymerase chain reaction (RT-PCR)-confirmed influenza°A and/or B°disease, due to any seasonal

influenza strain, compared with non-influenza control vaccines. Influenza disease included episodes of influenza-like illness (ILI, i.e., fever ≥100.4°F with any of the following: cough, runny nose, nasal congestion, or breathing difficulty) or a consequence of influenza virus infection (acute otitis media or lower respiratory illnesses). Among subjects with RT-PCR-positive influenza A and/or B disease, subjects were further prospectively classified based on the presence of adverse outcomes associated with influenza infection: fever >102.2°F, physician-diagnosed acute otitis media, physician-diagnosed lower respiratory tract illness, physician-diagnosed serious extra-pulmonary complications, hospitalization in the intensive care unit, or supplemental oxygen required for more than 8 hours. Subjects were monitored for influenza disease by passive and active surveillance starting 2 weeks post-vaccination and lasting for approximately 6 months. After an episode of ILI, lower respiratory illness, or acute otitis media, nasal swabs were collected and tested for influenza°A and/or°B by RT-PCR. All RT-PCR-positive specimens were further tested in cell culture and by antigenic characterization to determine whether the viral strains matched those in the vaccine. Vaccine efficacy for subjects with RT-PCR confirmed and culture-confirmed vaccine matching strains (According-to-Protocol (ATP) cohort for efficacy – time to event) is presented in Table 8.

Table 8. Attack Rates and Vaccine Efficacy against Influenza A and/or B in Children Aged 6 through 35 Months[a] (ATP Cohort for Efficacy – Time to Event)

			Attack Rates (n/N)	Vaccine Efficacy		
	N[b]	n[c]	%	%	Lower Limit	Upper Limit
All RT-PCR-Confirmed Influenza						
FLUARIX QUADRIVALENT	5,707	344	6.03	49.8	41.8[d]	56.8
Non-Influenza Comparator[e,f]	5,697	662	11.62	-	-	-
All Culture-Confirmed Influenza						
FLUARIX QUADRIVALENT	5,707	303	5.31	51.2	44.1[g]	57.6
Non-Influenza Comparator[e,f]	5,697	602	10.57	-	-	-
All Antigenically Matched Culture-Confirmed Influenza						
FLUARIX QUADRIVALENT	5,707	88	1.54	60.1	49.1[h]	69.0
Non-Influenza Comparator[e,f]	5,697	216	3.79	-	-	-

ATP = According-to-Protocol; RT-PCR = Reverse Transcriptase Polymerase Chain Reaction.

[a] Trial 7: NCT01439360.

[b] Number of subjects in the ATP cohort for efficacy – time to event, which included subjects who met all eligibility criteria, who were followed for efficacy and complied with the study protocol until the influenza-like episode.

[c] Number of subjects who reported at least one case in the reporting period.

[d] Vaccine efficacy for FLUARIX QUADRIVALENT met the pre-defined criterion for the lower limit of the 2-sided 97.5% CI (>15% for all influenza).

[e] Children younger than 12 months: pneumococcal 13-valent conjugate vaccine [Diphtheria CRM197 Protein] (Wyeth Pharmaceuticals, Inc.).

[f] Children 12 months and older: HAVRIX (Hepatitis A Vaccine) for those with a history of influenza vaccination; or HAVRIX (Dose 1) and a varicella vaccine (U.S. Licensed Manufactured by Merck & Co., Inc. or Non-U.S. Licensed Manufactured by GlaxoSmithKline Biologicals) (Dose 2) for those with no history of influenza vaccination.

[g] Vaccine efficacy for FLUARIX QUADRIVALENT met the pre-defined criterion of >10% for the lower limit of the 2-sided 95% CI.

[h] Vaccine efficacy for FLUARIX QUADRIVALENT met the pre-defined criterion of >15% for the lower limit of the 2-sided 95% CI.

The vaccine efficacy against RT-PCR-confirmed influenza associated with adverse outcomes was 64.6% (97.5% CI 53.2%, 73.5%). The vaccine efficacy against RT-PCR-confirmed influenza associated with adverse outcomes due to A/H1N1, A/H3N2, B/Victoria, and B/Yamagata was 71.4% (95% CI 48.5%, 85.2%), 51.3% (95% CI 32.7%, 65.2%), 86.7% (95% CI 52.8%, 97.9%), and 68.9% (95% CI 50.6%, 81.2%), respectively.

For RT-PCR-confirmed influenza cases associated with adverse outcomes, the incidence of the specified adverse outcomes are presented in Table 9.

Table 9. Incidence of Adverse Outcomes Associated with RT-PCR-Positive Influenza in Children Aged 6 through 35 Months[a] (ATP Cohort for Efficacy- Time to Event)[b]

Influenza-Associated Symptom[e]	FLUARIX QUADRIVALENT n = 5,707			Non-Influenza Active Comparator[c,d] n = 5,697		
	Number of Events	Number of Subjects[f]	%	Number of Events	Number of Subjects[f]	%
Fever >102.2^{0}F/39^{0}C	62	61	1.1	184	183	3.2
Acute otitis media (AOM)[g]	5	5	0.1	15	15	0.3
Physician-diagnosed lower respiratory tract illness[h]	28	28	0.5	62	61	1.1
Physician-diagnosed serious extra-pulmonary complications[i]	2	2	0	3	3	0.1
Hospitalization in the intensive care unit	0	0	0	0	0	0
Supplemental oxygen required for more than 8 hours	0	0	0	0	0	0

ATP = According-to-Protocol; RT-PCR = Reverse transcriptase polymerase chain reaction.

[a] Trial 7: NCT01439360.
[b] Number of subjects in the ATP cohort for efficacy – time to event, which included subjects who met all eligibility criteria, who were followed for efficacy and complied with the study protocol until the influenza-like episode.
[c] Children younger than 12 months: pneumococcal 13-valent conjugate vaccine [Diphtheria CRM197 Protein] (Wyeth Pharmaceuticals, Inc.).
[d] Children 12 months and older: HAVRIX (Hepatitis A Vaccine) for those with a history of influenza vaccination; or HAVRIX (Dose 1) and a varicella vaccine (U.S. Licensed Manufactured by Merck & Co., Inc. or Non-U.S. Licensed Manufactured by GlaxoSmithKline Biologicals) (Dose 2) for those with no history of influenza vaccination.
[e] Subjects who experienced more than one adverse outcome, each outcome was counted in the respective category.
[f] Number of subjects with at least one event in a given category.
[g] Analyses considered AOM cases confirmed by otoscopy.
[h] Pneumonia, lower respiratory tract infection, bronchiolitis, bronchitis, or croup infection as per final diagnosis by physician.
[i] Includes myositis, encephalitis or other neurologic condition including seizure, myocarditis/pericarditis or other serious medical condition as per final diagnosis by physician.

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 2 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 2 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 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 10).

Table 10. 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]**
Geometric Mean Antibody Titer	**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; 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 7 was a randomized, observer-blind, non-influenza vaccine-controlled trial evaluating the efficacy of FLUARIX QUADRIVALENT. In this trial, subjects aged 6 through 35 months received FLUARIX QUADRIVALENT (n = 6,006) or a non-influenza control vaccine (n = 6,012). Immune responses to each of the vaccine antigens were evaluated in sera 28 days following 1 or 2 doses in a subgroup of subjects (n = 753 for FLUARIX QUADRIVALENT, n = 579 for control in the ATP cohort for immunogenicity).

Immunogenicity endpoints (GMTs and the percentage of subjects who achieved seroconversion) were analyzed based on the ATP cohort for whom immunogenicity assay results were available after vaccination. Antibody responses for all 4 influenza strains are presented in Table 11.

Table 11. FLUARIX QUADRIVALENT: Immune Responses to Each Antigen 28 Days after Last Vaccination in Children Aged 6 through 35 Months[a] (ATP Cohort for Immunogenicity)

	FLUARIX QUADRIVALENT	**Non-Influenza Active Comparator[b,c]**
Geometric Mean Antibody Titer	**n = 750-753 (95% CI)**	**n = 578-579 (95% CI)**
A (H1N1)	165.3 (148.6, 183.8)	12.6 (11.1, 14.3)
A (H3N2)	132.1 (119.1, 146.5)	14.7 (12.9, 16.7)
B (Victoria lineage)	92.6 (82.3, 104.1)	9.2 (8.4, 10.1)
B (Yamagata lineage)	121.4 (110.1, 133.8)	7.6 (7.0, 8.3)
Seroconversion[d]	**n = 742-746 % (95% CI)**	**n = 566-568 % (95% CI)**
A (H1N1)	80.2 (77.2, 83.0)	3.5 (2.2, 5.4)
A (H3N2)	68.8 (65.3, 72.1)	4.2 (2.7, 6.2)
B (Victoria lineage)	69.3 (65.8, 72.6)	0.9 (0.3, 2.0)
B (Yamagata lineage)	81.2 (78.2, 84.0)	2.3 (1.2, 3.9)

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 trial vaccine antigen.

[a] Trial 7: NCT01439360.

[b] Children younger than 12 months: pneumococcal 13-valent conjugate vaccine [Diphtheria CRM197 Protein] (Wyeth Pharmaceuticals, Inc.).

[c] Children 12 months and older: HAVRIX (Hepatitis A Vaccine) for those with a history of influenza vaccination; or HAVRIX (Dose 1) and a varicella vaccine (U.S. Licensed Manufactured by Merck & Co., Inc. or Non-U.S. Licensed Manufactured by GlaxoSmithKline Biologicals) (Dose 2) for those with no history of influenza vaccination.

[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.

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 2 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 2 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 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 12).

Table 12. 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]**
Geometric Mean Antibody Titer	**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; 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC 58160-898-41 Syringe in Package of 10: NDC 58160-898-52

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.
- Encourage women exposed to FLUARIX QUADRIVALENT during pregnancy to enroll in the pregnancy registry *[see Use in Specific Populations (8.1)]*.
- 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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