

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

2015-2016 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: XX/201X

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1 FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

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

7 2 DOSAGE AND ADMINISTRATION

8 **For intramuscular injection only.**

9 2.1 Dosage and Schedule

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

11 **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

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

16 2.2 Administration Instructions

17 Shake well before administration. Parenteral drug products should be inspected visually for
18 particulate matter and discoloration prior to administration, whenever solution and container
19 permit. If either of these conditions exists, the vaccine should not be administered.

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

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

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

24 **3 DOSAGE FORMS AND STRENGTHS**

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

27 **4 CONTRAINDICATIONS**

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

31 **5 WARNINGS AND PRECAUTIONS**

32 **5.1 Guillain-Barré Syndrome**

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

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

40 **5.2 Syncope**

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

45 **5.3 Preventing and Managing Allergic Vaccine Reactions**

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

50 **5.4 Altered Immunocompetence**

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

54 **5.5 Limitations of Vaccine Effectiveness**

55 Vaccination with FLUARIX QUADRIVALENT may not protect all susceptible individuals.

56 **5.6 Persons at Risk of Bleeding**

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

60 **6 ADVERSE REACTIONS**

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

64 **6.1 Clinical Trials Experience**

65 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
66 observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical
67 trials of another vaccine, and may not reflect the rates observed in practice. There is the
68 possibility that broad use of FLUARIX QUADRIVALENT could reveal adverse reactions not
69 observed in clinical trials.

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

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

79 **FLUARIX QUADRIVALENT in Adults**

80 Trial 1 was a randomized, double-blind (2 arms) and open-label (one arm), active-controlled,
81 safety, and immunogenicity trial. In this trial, subjects received FLUARIX QUADRIVALENT
82 (N = 3,036) or one of two formulations of comparator trivalent influenza vaccine (FLUARIX,
83 TIV-1, N = 1,010 or TIV-2, N = 610), each containing an influenza type B virus that
84 corresponded to one of the two type B viruses in FLUARIX QUADRIVALENT (a type B virus
85 of the Victoria lineage or a type B virus of the Yamagata lineage). The population was aged
86 18 years and older (mean age: 58 years) and 57% were female; 69% were white, 27% were
87 Asian, and 4% were of other racial/ethnic groups. Solicited events were collected for 7 days (day
88 of vaccination and the next 6 days). The frequencies of solicited adverse events are shown in
89 Table 2.

90 **Table 2. FLUARIX QUADRIVALENT: Incidence of Solicited Local Adverse Reactions**
 91 **and Systemic Adverse Events within 7 Days^a of Vaccination in Adults^b (Total Vaccinated**
 92 **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 $\geq 99.5^{\circ}\text{F}$ (37.5°C)	2	1	2

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

95 ^a 7 days included day of vaccination and the subsequent 6 days.

96 ^b Trial 1: NCT01204671.

97 ^c Contained the same composition as FLUARIX (trivalent formulation) manufactured for the
 98 2010-2011 season and an additional influenza type B virus of Yamagata lineage.

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

101 ^e Contained the same 2 influenza A subtype viruses as FLUARIX manufactured for the 2010-
 102 2011 season and an influenza type B virus of Yamagata lineage.

103 ^f Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

104 Unsolicited events occurring within 21 days of vaccination (Day 0 to 20) were reported in 13%,
 105 14%, and 15% of subjects who received FLUARIX QUADRIVALENT, TIV-1, or TIV-2,
 106 respectively. The unsolicited adverse reactions that occurred most frequently ($\geq 0.1\%$ for
 107 FLUARIX QUADRIVALENT) included dizziness, injection site hematoma, injection site
 108 pruritus, and rash. Serious adverse events occurring within 21 days of vaccination were reported
 109 in 0.5%, 0.6%, and 0.2% of subjects who received FLUARIX QUADRIVALENT, TIV-1, or

110 TIV-2, respectively.

111 FLUARIX QUADRIVALENT in Children

112 Trial 2 was a randomized, double-blind, active-controlled, safety, and immunogenicity trial. In
113 this trial, subjects received FLUARIX QUADRIVALENT (N = 915) or one of two formulations
114 of comparator trivalent influenza vaccine (FLUARIX, TIV-1, N = 912 or TIV-2, N = 911), each
115 containing an influenza type B virus that corresponded to one of the two type B viruses in
116 FLUARIX QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the
117 Yamagata lineage). Subjects were aged 3 through 17 years and 52% were male; 56% were white,
118 29% were Asian, 12% were black, and 3% were of other racial/ethnic groups. Children aged 3
119 through 8 years with no history of influenza vaccination received 2 doses approximately 28 days
120 apart. Children aged 3 through 8 years with a history of influenza vaccination and children aged
121 9 years and older received one dose. Solicited local adverse reactions and systemic adverse
122 events were collected using diary cards for 7 days (day of vaccination and the next 6 days). The
123 frequencies of solicited adverse events are shown in Table 3.

124 **Table 3. FLUARIX QUADRIVALENT: Incidence of Solicited Local Adverse Reactions**
 125 **and Systemic Adverse Events within 7 Days^a after First Vaccination in Children Aged 3**
 126 **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 $\geq 99.5^{\circ}\text{F}$ (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 $\geq 99.5^{\circ}\text{F}$ (37.5°C)	6	9	6

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

129 ^a 7 days included day of vaccination and the subsequent 6 days.

130 ^b Trial 2: NCT01196988.

131 ^c Contained the same composition as FLUARIX (trivalent formulation) manufactured for the
 132 2010-2011 season and an additional influenza type B virus of Yamagata lineage.

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

135 ^e Contained the same 2 influenza A subtype viruses as FLUARIX manufactured for the 2010-
 136 2011 season and an influenza type B virus of Yamagata lineage.

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

138 QUADRIVALENT, TIV-1, and TIV-2, respectively, in children aged 3 through 8 years and
139 52%, 50%, and 46% for FLUARIX QUADRIVALENT, TIV-1, and TIV-2, respectively, in
140 children aged 9 through 17 years.

141 ^g Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

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

145 Unsolicited adverse events occurring within 28 days of any vaccination were reported in 31%,
146 33%, and 34% of subjects who received FLUARIX QUADRIVALENT, TIV-1, or TIV-2,
147 respectively. The unsolicited adverse reactions that occurred most frequently ($\geq 0.1\%$ for
148 FLUARIX QUADRIVALENT) included injection site pruritus and rash. Serious adverse events
149 occurring within 28 days of any vaccination were reported in 0.1%, 0.1%, and 0.1% of subjects
150 who received FLUARIX QUADRIVALENT, TIV-1, or TIV-2, respectively.

151 FLUARIX (Trivalent Formulation)

152 FLUARIX has been administered to 10,317 adults aged 18 through 64 years, 606 subjects aged
153 65 years and older, and 2,115 children aged 6 months through 17 years in clinical trials. The
154 incidence of solicited adverse events in each age group is shown in Tables 4 and 5.

155 **Table 4. FLUARIX (Trivalent Formulation): Incidence of Solicited Local Adverse**
 156 **Reactions and Systemic Adverse Events within 4 Days^a of Vaccination in Adults (Total**
 157 **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

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

160 ^a 4 days included day of vaccination and the subsequent 3 days.

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

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

166 **Table 5. FLUARIX (Trivalent Formulation): Incidence of Solicited Local Adverse**
 167 **Reactions and Systemic Adverse Events within 4 Days^a of First Vaccination in Children**
 168 **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 $\geq 99.5^{\circ}\text{F}$ (37.5°C)	7	8	4	3
Muscle aches	–	–	29	29
Fatigue	–	–	20	19
Headache	–	–	15	16
Arthralgia	–	–	6	6
Shivering	–	–	3	4

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

171 ^a 4 days included day of vaccination and the subsequent 3 days.

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

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

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

179 **6.2 Postmarketing Experience**

180 Beyond those events reported above in the clinical trials for FLUARIX QUADRIVALENT or
 181 FLUARIX, the following adverse events have been spontaneously reported during postapproval
 182 use of FLUARIX (trivalent influenza vaccine). This list includes serious events or events which
 183 have causal connection to FLUARIX. Because these events are reported voluntarily from a
 184 population of uncertain size, it is not always possible to reliably estimate their frequency or
 185 establish a causal relationship to the vaccine.

- 186 Blood and Lymphatic System Disorders
- 187 Lymphadenopathy.
- 188 Cardiac Disorders
- 189 Tachycardia.
- 190 Ear and Labyrinth Disorders
- 191 Vertigo.
- 192 Eye Disorders
- 193 Conjunctivitis, eye irritation, eye pain, eye redness, eye swelling, eyelid swelling.
- 194 Gastrointestinal Disorders
- 195 Abdominal pain or discomfort, swelling of the mouth, throat, and/or tongue.
- 196 General Disorders and Administration Site Conditions
- 197 Asthenia, chest pain, feeling hot, injection site mass, injection site reaction, injection site
198 warmth, body aches.
- 199 Immune System Disorders
- 200 Anaphylactic reaction including shock, anaphylactoid reaction, hypersensitivity, serum sickness.
- 201 Infections and Infestations
- 202 Injection site abscess, injection site cellulitis, pharyngitis, rhinitis, tonsillitis.
- 203 Nervous System Disorders
- 204 Convulsion, encephalomyelitis, facial palsy, facial paresis, Guillain-Barré syndrome,
205 hypoesthesia, myelitis, neuritis, neuropathy, paresthesia, syncope.
- 206 Respiratory, Thoracic, and Mediastinal Disorders
- 207 Asthma, bronchospasm, dyspnea, respiratory distress, stridor.
- 208 Skin and Subcutaneous Tissue Disorders
- 209 Angioedema, erythema, erythema multiforme, facial swelling, pruritus, Stevens-Johnson
210 syndrome, sweating, urticaria.
- 211 Vascular Disorders
- 212 Henoch-Schönlein purpura, vasculitis.
- 213 **7 DRUG INTERACTIONS**
- 214 **7.1 Concomitant Vaccine Administration**
- 215 FLUARIX QUADRIVALENT should not be mixed with any other vaccine in the same syringe

216 or vial.

217 There are insufficient data to assess the concurrent administration of FLUARIX
218 QUADRIVALENT with other vaccines. When concomitant administration of other vaccines is
219 required, the vaccines should be administered at different injection sites.

220 **7.2 Immunosuppressive Therapies**

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

224 **8 USE IN SPECIFIC POPULATIONS**

225 **8.1 Pregnancy**

226 Pregnancy Category B. A reproductive and developmental toxicity study has been performed in
227 female rats at doses approximately 80 times the human dose (on a mg/kg basis) and revealed no
228 evidence of impaired female fertility or harm to the fetus due to FLUARIX QUADRIVALENT.
229 There are, however, no adequate and well-controlled studies in pregnant women. Because animal
230 reproduction studies are not always predictive of human response, FLUARIX
231 QUADRIVALENT should be given to a pregnant woman only if clearly needed.

232 In a reproductive and developmental toxicity study, the effect of FLUARIX QUADRIVALENT
233 on embryo-fetal and pre-weaning development was evaluated in rats. Animals were administered
234 FLUARIX QUADRIVALENT by intramuscular injection twice prior to gestation, during the
235 period of organogenesis (gestation Days 3, 8, 11, and 15), and during lactation (Day 7),
236 0.2 mL/rat/occasion (approximately 80-fold excess relative to the projected human dose on a
237 body weight basis). No adverse effects on mating, female fertility, pregnancy, parturition,
238 lactation parameters, and embryo-fetal or pre-weaning development were observed. There were
239 no vaccine-related fetal malformations or other evidence of teratogenesis.

240 Pregnancy Registry

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

246 **8.3 Nursing Mothers**

247 It is not known whether FLUARIX QUADRIVALENT is excreted in human milk. Because
248 many drugs are excreted in human milk, caution should be exercised when FLUARIX
249 QUADRIVALENT is administered to a nursing woman.

250 **8.4 Pediatric Use**

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

253 Safety and immunogenicity of FLUARIX QUADRIVALENT in children aged 3 through
254 17 years have been evaluated [*see Adverse Reactions (6.1), Clinical Studies (14.3)*].

255 **8.5 Geriatric Use**

256 In a randomized, double-blind (2 arms) and open-label (one arm), active-controlled trial,
257 immunogenicity and safety were evaluated in a cohort of subjects aged 65 years and older who
258 received FLUARIX QUADRIVALENT (N = 1,517); 469 of these subjects were aged 75 years
259 and older. In subjects aged 65 years and older, the geometric mean antibody titers (GMTs) post-
260 vaccination and seroconversion rates were lower than in younger subjects (aged 18 through
261 64 years) and the frequencies of solicited and unsolicited adverse events were generally lower
262 than in younger subjects.

263 **11 DESCRIPTION**

264 FLUARIX QUADRIVALENT, Influenza Vaccine, for intramuscular injection, is a sterile
265 colorless and slightly opalescent suspension. FLUARIX QUADRIVALENT is prepared from
266 influenza viruses propagated in embryonated chicken eggs. Each of the influenza viruses is
267 produced and purified separately. After harvesting the virus-containing fluids, each influenza
268 virus is concentrated and purified by zonal centrifugation using a linear sucrose density gradient
269 solution containing detergent to disrupt the viruses. Following dilution, the vaccine is further
270 purified by diafiltration. Each influenza virus solution is inactivated by the consecutive effects of
271 sodium deoxycholate and formaldehyde leading to the production of a “split virus.” Each split
272 inactivated virus is then suspended in sodium phosphate-buffered isotonic sodium chloride
273 solution. Each vaccine is formulated from the split inactivated virus solutions.

274 FLUARIX QUADRIVALENT has been standardized according to USPHS requirements for the
275 2015-2016 influenza season and is formulated to contain 60 micrograms (mcg) hemagglutinin
276 (HA) per 0.5-mL dose, in the recommended ratio of 15 mcg HA of each of the following
277 4 influenza virus strains: A/Christchurch/16/2010 NIB-74XP (H1N1) (an
278 A/California/7/2009-like virus), A/Switzerland/9715293/2013 NIB-88 (H3N2),
279 B/Phuket/3073/2013, and B/Brisbane/60/2008.

280 FLUARIX QUADRIVALENT is formulated without preservatives. FLUARIX
281 QUADRIVALENT does not contain thimerosal. Each 0.5-mL dose also contains octoxynol-10
282 (TRITON® X-100) ≤0.115 mg, α -tocopheryl hydrogen succinate ≤0.135 mg, and polysorbate 80
283 (Tween 80) ≤0.550 mg. Each dose may also contain residual amounts of hydrocortisone
284 ≤0.0016 mcg, gentamicin sulfate ≤0.15 mcg, ovalbumin ≤0.050 mcg, formaldehyde ≤5 mcg, and
285 sodium deoxycholate ≤65 mcg from the manufacturing process.

286 The tip caps and plungers of the prefilled syringes of FLUARIX QUADRIVALENT are not
287 made with natural rubber latex.

288 **12 CLINICAL PHARMACOLOGY**

289 **12.1 Mechanism of Action**

290 Influenza illness and its complications follow infection with influenza viruses. Global
291 surveillance of influenza identifies yearly antigenic variants. Since 1977, antigenic variants of
292 influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation.

293 Public health authorities give annual influenza vaccine composition recommendations.

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

299 Specific levels of hemagglutination-inhibition (HI) antibody titer post-vaccination with
300 inactivated influenza virus vaccines have not been correlated with protection from influenza
301 illness but the HI antibody titers have been used as a measure of vaccine activity. In some human
302 challenge studies, HI antibody titers of $\geq 1:40$ have been associated with protection from
303 influenza illness in up to 50% of subjects.^{1,2} Antibody against one influenza virus type or subtype
304 confers little or no protection against another virus. Furthermore, antibody to one antigenic
305 variant of influenza virus might not protect against a new antigenic variant of the same type or
306 subtype. Frequent development of antigenic variants through antigenic drift is the virological
307 basis for seasonal epidemics and the reason for the usual replacement of one or more influenza
308 viruses in each year's influenza vaccine.

309 Annual revaccination is recommended because immunity declines during the year after
310 vaccination, and because circulating strains of influenza virus change from year to year.³

311 **13 NONCLINICAL TOXICOLOGY**

312 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

316 **14 CLINICAL STUDIES**

317 **14.1 Efficacy against Culture-confirmed Influenza**

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

320 *Description (11)].*

321 The efficacy of FLUARIX was evaluated in a randomized, double-blind, placebo-controlled trial
 322 conducted in 2 European countries during the 2006-2007 influenza season. Efficacy of
 323 FLUARIX, containing A/New Caledonia/20/1999 (H1N1), A/Wisconsin/67/2005 (H3N2), and
 324 B/Malaysia/2506/2004 influenza virus strains, was defined as the prevention of culture-
 325 confirmed influenza A and/or B cases, for vaccine antigenically matched strains, compared with
 326 placebo. Healthy subjects aged 18 through 64 years (mean age: 40 years) were randomized (2:1)
 327 to receive FLUARIX (N = 5,103) or placebo (N = 2,549) and monitored for influenza-like
 328 illnesses (ILI) starting 2 weeks post-vaccination and lasting for approximately 7 months. In the
 329 overall population, 60% of subjects were female and 99.9% were white. Culture-confirmed
 330 influenza was assessed by active and passive surveillance of ILI. Influenza-like illness was
 331 defined as at least one general symptom (fever $\geq 100^{\circ}\text{F}$ and/or myalgia) and at least one
 332 respiratory symptom (cough and/or sore throat). After an episode of ILI, nose and throat swab
 333 samples were collected for analysis; attack rates and vaccine efficacy were calculated (Table 6).

334 **Table 6. FLUARIX (Trivalent Formulation): Attack Rates and Vaccine Efficacy against**
 335 **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	–	–	–

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

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

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

342 In a post-hoc, exploratory analysis by age, vaccine efficacy (against culture-confirmed influenza
 343 A and/or B cases, for vaccine antigenically matched strains) in subjects aged 18 through 49 years
 344 was 73.4% (95% CI: 59.3, 82.8) [number of influenza cases: FLUARIX (n = 35/3,602) and
 345 placebo (n = 66/1,810)]. In subjects aged 50 through 64 years, vaccine efficacy was 13.8%
 346 (95% CI: -137.0, 66.3) [number of influenza cases: FLUARIX (n = 14/1,501) and placebo
 347 (n = 8/739)]. As the trial lacked statistical power to evaluate efficacy within age subgroups, the
 348 clinical significance of these results is unknown.

349 **14.2 Immunological Evaluation of FLUARIX QUADRIVALENT in Adults**

350 Trial 1 was a randomized, double-blind (2 arms) and open-label (one arm), active-controlled,
351 safety, immunogenicity, and non-inferiority trial. In this trial, subjects received FLUARIX
352 QUADRIVALENT (N = 1,809) or one of two formulations of comparator trivalent influenza
353 vaccine (FLUARIX, TIV-1, N = 608 or TIV-2, N = 534), each containing an influenza type B
354 virus that corresponded to one of the two type B viruses in FLUARIX QUADRIVALENT (a
355 type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). Subjects aged
356 18 years and older (mean age: 58 years) were evaluated for immune responses to each of the
357 vaccine antigens 21 days following vaccination. In the overall population, 57% of subjects were
358 female; 69% were white, 27% were Asian, and 4% were of other racial/ethnic groups.

359 The immunogenicity endpoints were GMTs of serum hemagglutination-inhibition (HI)
360 antibodies adjusted for baseline, and the percentage of subjects who achieved seroconversion,
361 defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer \geq 1:40 or at least a
362 4-fold increase in serum HI antibody titer over baseline to \geq 1:40 following vaccination,
363 performed on the According-to-Protocol (ATP) cohort for whom immunogenicity assay results
364 were available after vaccination. FLUARIX QUADRIVALENT was non-inferior to both TIVs
365 based on adjusted GMTs (upper limit of the 2-sided 95% CI for the GMT ratio [TIV/FLUARIX
366 QUADRIVALENT] \leq 1.5) and seroconversion rates (upper limit of the 2-sided 95% CI on
367 difference of the TIV minus FLUARIX QUADRIVALENT \leq 10%). The antibody response to
368 influenza B strains contained in FLUARIX QUADRIVALENT was higher than the antibody
369 response after vaccination with a TIV containing an influenza B strain from a different lineage.
370 There was no evidence that the addition of the second B strain resulted in immune interference to
371 other strains included in the vaccine (Table 7).

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

	FLUARIX QUADRIVALENT ^a	Trivalent Influenza Vaccine (TIV)	
		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)

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

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

377 ^a Contained the same composition as FLUARIX (trivalent formulation) manufactured for the
 378 2010-2011 season and an additional influenza type B virus of Yamagata lineage.

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

381 ^c Contained the same 2 influenza A subtype viruses as FLUARIX manufactured for the 2010-
 382 2011 season and an influenza type B virus of Yamagata lineage.

383 ^d Seroconversion defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer
 384 ≥1:40 or at least a 4-fold increase in serum titers of HI antibodies to ≥1:40.

385 **14.3 Immunological Evaluation of FLUARIX QUADRIVALENT in Children**

386 Trial 2 was a randomized, double-blind, active-controlled, safety, immunogenicity, and non-
387 inferiority trial. In this trial, subjects received FLUARIX QUADRIVALENT (N = 791) or one of
388 two formulations of comparator trivalent influenza vaccine (FLUARIX, TIV-1, N = 819 or TIV-
389 2, N = 801), each containing an influenza type B virus that corresponded to one of the two type
390 B viruses in FLUARIX QUADRIVALENT (a type B virus of the Victoria lineage or a type B
391 virus of the Yamagata lineage). In children aged 3 through 17 years, immune responses to each
392 of the vaccine antigens were evaluated in sera 28 days following 1 or 2 doses. In the overall
393 population, 52% of subjects were male; 56% were white, 29% were Asian, 12% were black, and
394 3% were of other racial/ethnic groups.

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

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

	FLUARIX QUADRIVALENT ^a	Trivalent Influenza Vaccine (TIV)	
		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)

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

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

412 ^a Contained the same composition as FLUARIX (trivalent formulation) manufactured for the
 413 2010-2011 season and an additional influenza type B virus of Yamagata lineage.

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

416 ^c Contained the same 2 influenza A subtype viruses as FLUARIX manufactured for the 2010-
 417 2011 season and an influenza B virus of Yamagata lineage.

418 ^d Seroconversion defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer
 419 ≥1:40 or at least a 4-fold increase in serum titers of HI antibodies to ≥1:40.

420 **15 REFERENCES**

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429 **16 HOW SUPPLIED/STORAGE AND HANDLING**

430 NDC 58160-903-41 Syringe in Package of 10: NDC 58160-903-52

431 Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has
432 been frozen. Store in the original package to protect from light.

433 **17 PATIENT COUNSELING INFORMATION**

434 Provide the following information to the vaccine recipient or guardian:

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

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