

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**FLUARIX (Influenza Vaccine)  
Suspension for Intramuscular Injection  
2015-2016 Formula  
Initial U.S. Approval: 2005**

### INDICATIONS AND USAGE

FLUARIX is a vaccine indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B virus contained in the vaccine. FLUARIX 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 <sup>a</sup> (0.5-mL each) (2.1)
Aged 9 years and older	Not applicable	One 0.5-mL dose (2.1)

<sup>a</sup> 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 should be based on potential benefits and risks. (5.1)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including FLUARIX. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.2)

### ADVERSE REACTIONS

- In adults, the most common ( $\geq 10\%$ ) local and general adverse events were pain and redness at the injection site, muscle aches, fatigue, and headache. (6.1)
- In children aged 5 years through 17 years, the most common ( $\geq 10\%$ ) local and general adverse events were similar to those in adults but also included swelling at the injection site. (6.1)
- In children aged 3 years through 4 years, the most common ( $\geq 10\%$ ) local and general adverse events were pain, redness, and swelling at the injection site, irritability, loss of appetite, and drowsiness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or [www.vaers.hhs.gov](http://www.vaers.hhs.gov).

### USE IN SPECIFIC POPULATIONS

- Safety and effectiveness of FLUARIX have not been established in pregnant women or nursing mothers. (8.1, 8.3)
- Register women who receive FLUARIX while pregnant in the pregnancy registry by calling 1-888-452-9622. (8.1)
- In a clinical trial of children younger than 3 years, antibody titers were lower after FLUARIX than after an active comparator. (8.4)
- Geriatric Use: Antibody responses were lower in geriatric subjects who received FLUARIX 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<sup>®</sup> is indicated for active immunization for the prevention of disease caused by  
4 influenza A subtype viruses and type B virus contained in the vaccine [see Description (11)].  
5 FLUARIX is approved for use in persons 3 years of age and older.

6 **2 DOSAGE AND ADMINISTRATION**

7 **For intramuscular injection only.**

8 **2.1 Dosage and Schedule**

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

10 **Table 1. FLUARIX: 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 <sup>a</sup> (0.5-mL each)
Aged 9 years and older	Not applicable	One 0.5-mL dose

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

15 **2.2 Administration Instructions**

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

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

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

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

23 **3 DOSAGE FORMS AND STRENGTHS**

24 FLUARIX is a suspension for injection. Each 0.5-mL dose is supplied in single-dose prefilled  
25 TIP-LOK<sup>®</sup> syringes.

26 **4 CONTRAINDICATIONS**

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

30 **5 WARNINGS AND PRECAUTIONS**

31 **5.1 Guillain-Barré Syndrome**

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

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

39 **5.2 Syncope**

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

44 **5.3 Preventing and Managing Allergic Vaccine Reactions**

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

49 **5.4 Altered Immunocompetence**

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

53 **5.5 Limitations of Vaccine Effectiveness**

54 Vaccination with FLUARIX may not protect all susceptible individuals.

55 **5.6 Persons at Risk of Bleeding**

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

59 **6 ADVERSE REACTIONS**

60 **6.1 Clinical Trials Experience**

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

66 Adults

67 In adults, the most common ( $\geq 10\%$ ) local adverse reactions and general adverse events observed  
68 with FLUARIX were pain and redness at the injection site, muscle aches, fatigue, and headache.

69 FLUARIX has been administered to 10,317 adults aged 18 through 64 years and 606 subjects  
70 aged 65 years and older in 4 clinical trials.

71 One of the 4 clinical trials was a randomized, double-blind, placebo-controlled trial that  
72 evaluated a total of 952 subjects: FLUARIX (N = 760) and placebo (N = 192). The population  
73 was aged 18 through 64 years (mean: 39.1), 54% were female and 80% were white. Solicited  
74 events were collected for 4 days (day of vaccination and the next 3 days) (Table 2). Unsolicited  
75 events that occurred within 21 days of vaccination (Day 0 to 20) were recorded using diary cards  
76 supplemented by spontaneous reports and a medical history as reported by subjects.

77 **Table 2. Incidence of Solicited Local Adverse Reactions or General Adverse Events within**  
78 **4 Days<sup>a</sup> of Vaccination in Adults Aged 18 through 64 Years<sup>b</sup> (Total Vaccinated Cohort)**

	<b>FLUARIX</b> N = 760 %	<b>Placebo</b> N = 192 %
<b>Local Adverse Reactions</b>		
Pain	55	12
Redness	18	10
Swelling	9	6
<b>General Adverse Events</b>		
Muscle aches	23	12
Fatigue	20	18
Headache	19	21
Arthralgia	6	6
Shivering	3	3
Fever $\geq 100.4^\circ\text{F}$ ( $38.0^\circ\text{C}$ )	2	2

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

81 <sup>a</sup> 4 days included day of vaccination and the subsequent 3 days.

82 <sup>b</sup> NCT00100399.

83 Unsolicited adverse events that occurred in  $\geq 1\%$  of recipients of FLUARIX and at a rate greater  
84 than placebo included upper respiratory tract infection (3.9% versus 2.6%), nasopharyngitis  
85 (2.5% versus 1.6%), nasal congestion (2.2% versus 2.1%), diarrhea (1.6% versus 0%), influenza-  
86 like illness (1.6% versus 0.5%), vomiting (1.4% versus 0%), and dysmenorrhea (1.3% versus  
87 1.0%).

88 A randomized, single-blind, active-controlled US trial evaluated subjects randomized to receive  
89 FLUARIX (N = 917) or FLUZONE<sup>®</sup> (N = 910), a US-licensed trivalent, inactivated influenza  
90 vaccine (Sanofi Pasteur SA) stratified by age: 18 through 64 years and 65 years and older. In the  
91 overall population, 59% of subjects were female and 91% were white. Solicited events were  
92 collected using diary cards for 4 days (day of vaccination and the next 3 days) (Table 3).  
93 Unsolicited events that occurred within 21 days of vaccination (Day 0 to 20) were recorded using  
94 diary cards.  
95

96 **Table 3. Incidence of Solicited Local Adverse Reactions or General Adverse Events in**  
 97 **Adults within 4 Days<sup>a</sup> of Vaccination with FLUARIX or Comparator Influenza Vaccine by**  
 98 **Age Group<sup>b</sup> (Total Vaccinated Cohort)**

	Aged 18 through 64 Years		Aged 65 Years and Older	
	FLUARIX N = 315 %	Comparator Influenza Vaccine N = 314 %	FLUARIX N = 601-602 %	Comparator Influenza Vaccine N = 596 %
<b>Local Adverse Reactions</b>				
Pain	48	53	19	18
Redness	13	16	11	13
Swelling	9	11	6	9
<b>General Adverse Events</b>				
Fatigue	21	18	9	10
Headache	20	21	8	8
Muscle aches	16	13	7	7
Arthralgia	9	9	6	5
Shivering	3	5	2	2
Fever $\geq 99.5^{\circ}\text{F}$ ( $37.5^{\circ}\text{C}$ )	3	1	2	1

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

101 <sup>a</sup> 4 days included day of vaccination and the subsequent 3 days.

102 <sup>b</sup> NCT00197288.

103 Unsolicited adverse events that occurred in  $\geq 1\%$  of all recipients of FLUARIX or the comparator  
 104 influenza vaccine in the 21-day post-vaccination period included headache (2.8% versus 2.3%),  
 105 back pain (1.5% versus 0.4%), pain in extremity (1.2% versus 0.7%), pharyngolaryngeal pain  
 106 (1.2% versus 0.9%), cough (1.1% versus 0.9%), fatigue (1.1% versus 0.7%), nasopharyngitis  
 107 (1.0% versus 1.3%), nausea (0.4% versus 1.0%), arthralgia (0.3% versus 1.0%), and injection  
 108 site pruritus (0.2% versus 1.0%).

109 A double-blind, placebo-controlled trial in subjects aged 18 through 64 years randomized (2:1) to  
 110 receive FLUARIX (N = 5,103) or placebo (N = 2,549) was conducted to evaluate the efficacy of  
 111 FLUARIX. In the total population, 60% were female and 99.9% were white. In a subset  
 112 (FLUARIX [N = 305] and placebo [N = 155]), unsolicited events that occurred within 21 days of  
 113 vaccination (Day 0 to 20) were recorded on diary cards. The percentage of subjects reporting at  
 114 least one unsolicited event was similar among the groups (24.3% for FLUARIX and 22.6% for  
 115 placebo). Unsolicited adverse events that occurred in  $\geq 1\%$  of recipients of FLUARIX and at a

116 rate greater than placebo included injection site pain (5.2% versus 1.3%), dysmenorrhea (1.3%  
117 versus 0.6%), and migraine (1.0% versus 0.0%).

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

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

123 *Infections and Infestations:* Rhinitis.

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

125 *Skin and Subcutaneous Tissue Disorders:* Sweating.

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

## 128 Children

129 In children aged 5 years through 17 years, the most common ( $\geq 10\%$ ) local and general adverse  
130 events were similar to those in adults but also included swelling at the injection site. In children  
131 aged 3 years through 4 years, the most common ( $\geq 10\%$ ) local and general adverse events  
132 included pain, redness, and swelling at the injection site, irritability, loss of appetite, and  
133 drowsiness.

134 A single-blind, active-controlled US trial evaluated subjects aged 6 months through 17 years who  
135 received FLUARIX (N = 2,081) or FLUZONE (N = 1,173), a US-licensed trivalent, inactivated  
136 influenza vaccine (Sanofi Pasteur SA) (Trial 005). Children aged 6 months through 8 years with  
137 no history of influenza vaccination received 2 doses approximately 28 days apart. Children aged  
138 6 months through 8 years with a history of influenza vaccination and children aged 9 years and  
139 older received 1 dose. Children aged 6 months through 35 months received 0.25 mL of  
140 FLUARIX or comparator influenza vaccine, and children aged 3 years and older received 0.5 mL  
141 of FLUARIX or comparator influenza vaccine.

142 Trial subjects were aged 6 months through 17 years and 49% were female; 68% were white, 18%  
143 were black, 3% were Asian, and 11% were of other racial/ethnic groups.

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

148 The frequencies of solicited adverse events for children aged 3 years through 4 years and for  
149 children aged 5 years through 17 years were similar for FLUARIX and the comparator vaccine  
150 (Table 4).

151 **Table 4. Incidence of Solicited Local Adverse Reactions or General Adverse Events within**  
 152 **4 Days<sup>a</sup> of First Vaccination with FLUARIX or Comparator Influenza Vaccine by Age**  
 153 **Group in Children Aged 3 through 17 Years<sup>b</sup>**

	Aged 3 through 4 Years		Aged 5 through 17 Years	
	FLUARIX N = 350 %	Comparator Influenza Vaccine N = 341 %	FLUARIX N = 1,348 %	Comparator Influenza Vaccine N = 451 %
<b>Local Adverse Reactions</b>				
Pain	35	38	56	56
Redness	23	20	18	16
Swelling	14	13	14	13
<b>General Adverse Events</b>				
Irritability	21	22	–	–
Loss of appetite	13	15	–	–
Drowsiness	13	20	–	–
Fever ≥99.5°F (37.5°C)	7	8	4	3
Muscle aches	–	–	29	29
Fatigue	–	–	20	19
Headache	–	–	15	16
Arthralgia	–	–	6	6
Shivering	–	–	3	4

154 <sup>a</sup> 4 days included day of vaccination and the subsequent 3 days.

155 <sup>b</sup> NCT00383123.

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

158 Unsolicited adverse events that occurred in ≥1% of recipients of FLUARIX aged 6 months  
 159 through 17 years included upper respiratory tract infection (5.5%), pyrexia (4.8%), cough  
 160 (4.7%), vomiting (3.2%), headache (2.8%), rhinorrhea (2.7%), diarrhea (2.5%),  
 161 pharyngolaryngeal pain (2.4%), nasopharyngitis (2.3%), otitis media (2.0%), nasal congestion  
 162 (1.8%), upper abdominal pain (1.4%), and upper respiratory tract congestion (1.0%). The  
 163 incidences of these events were similar in recipients of the comparator vaccine.

## 164 **6.2 Postmarketing Experience**

165 Worldwide voluntary reports of adverse events received for FLUARIX since market introduction  
 166 of this vaccine are listed below. This list includes serious events or events which have causal  
 167 connection to FLUARIX. Because these events are reported voluntarily from a population of  
 168 uncertain size, it is not always possible to reliably estimate their frequency or establish a causal



- 169 relationship to the vaccine.
- 170 **Blood and Lymphatic System Disorders**
- 171 Lymphadenopathy.
- 172 **Cardiac Disorders**
- 173 Tachycardia.
- 174 **Ear and Labyrinth Disorders**
- 175 Vertigo.
- 176 **Eye Disorders**
- 177 Conjunctivitis, eye irritation, eye pain, eye redness, eye swelling, eyelid swelling.
- 178 **Gastrointestinal Disorders**
- 179 Abdominal pain or discomfort, nausea, swelling of the mouth, throat, and/or tongue.
- 180 **General Disorders and Administration Site Conditions**
- 181 Asthenia, chest pain, chills, feeling hot, injection site mass, injection site reaction, injection site  
182 warmth, body aches.
- 183 **Immune System Disorders**
- 184 Anaphylactic reaction including shock, anaphylactoid reaction, hypersensitivity, serum sickness.
- 185 **Infections and Infestations**
- 186 Injection site abscess, injection site cellulitis, pharyngitis, rhinitis, tonsillitis.
- 187 **Musculoskeletal and Connective Tissue Disorders**
- 188 Pain in extremity.
- 189 **Nervous System Disorders**
- 190 Convulsion, dizziness, encephalomyelitis, facial palsy, facial paresis, Guillain-Barré syndrome,  
191 hypoesthesia, myelitis, neuritis, neuropathy, paresthesia, syncope.
- 192 **Respiratory, Thoracic, and Mediastinal Disorders**
- 193 Asthma, bronchospasm, cough, dyspnea, respiratory distress, stridor.
- 194 **Skin and Subcutaneous Tissue Disorders**
- 195 Angioedema, erythema, erythema multiforme, facial swelling, pruritus, rash, Stevens-Johnson  
196 syndrome, urticaria.
- 197 **Vascular Disorders**
- 198 Henoch-Schönlein purpura, vasculitis.

199 **7 DRUG INTERACTIONS**

200 **7.1 Concomitant Vaccine Administration**

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

202 There are insufficient data to assess the concurrent administration of FLUARIX with other  
203 vaccines. When concomitant administration of other vaccines is required, the vaccines should be  
204 administered at different injection sites.

205 **7.2 Immunosuppressive Therapies**

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

209 **8 USE IN SPECIFIC POPULATIONS**

210 **8.1 Pregnancy**

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

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

224 Pregnancy Registry

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

230 **8.3 Nursing Mothers**

231 It is not known whether FLUARIX is excreted in human milk. Because many drugs are excreted  
232 in human milk, caution should be exercised when FLUARIX is administered to a nursing  
233 woman.

234 **8.4 Pediatric Use**

235 The immune response to FLUARIX has been evaluated in children aged 6 months through  
236 4 years. In a randomized, controlled trial, serum hemagglutination-inhibition (HI) antibody titers  
237 were lower in children aged 6 months through 35 months compared with a US-licensed vaccine.  
238 Based on these data, FLUARIX is not approved for use in children younger than 3 years.  
239 Immune responses in children aged 3 years through 4 years receiving FLUARIX or a US-  
240 licensed vaccine have been evaluated [see *Clinical Studies (14.2)*]. Safety has been evaluated in  
241 children aged 6 months through 17 years. The frequencies of solicited and unsolicited adverse  
242 events for children aged 3 years through 4 years and for children aged 5 years through 17 years  
243 were similar for FLUARIX and the comparator vaccine [see *Adverse Reactions (6.1)*].

244 **8.5 Geriatric Use**

245 A randomized, single-blind, active-controlled trial evaluated immunological non-inferiority in a  
246 cohort of subjects aged 65 years and older who received FLUARIX (N = 606) or another  
247 US-licensed trivalent, inactivated influenza vaccine (N = 604) (Sanofi Pasteur SA). In subjects  
248 receiving FLUARIX or the comparator vaccine, geometric mean antibody titers (GMTs) post-  
249 vaccination were lower in geriatric subjects than in younger subjects (aged 18 through 64 years).  
250 FLUARIX was non-inferior to the comparator vaccine for each of the 3 influenza strains based  
251 on mean antibody titers and seroconversion rates. [See *Clinical Studies (14.2)*.] Solicited local  
252 and general adverse events were similar for FLUARIX and the comparator vaccine among  
253 geriatric subjects (Table 3). For both vaccines, the frequency of solicited events in subjects aged  
254 65 years and older was lower than in younger subjects (Table 3). [See *Adverse Reactions (6.1)*.]

255 **11 DESCRIPTION**

256 FLUARIX, Influenza Vaccine, for intramuscular injection, is a sterile colorless and slightly  
257 opalescent suspension. FLUARIX is a vaccine prepared from influenza viruses propagated in  
258 embryonated chicken eggs. Each of the influenza viruses is produced and purified separately.  
259 After harvesting the virus-containing fluids, each influenza virus is concentrated and purified by  
260 zonal centrifugation using a linear sucrose density gradient solution containing detergent to  
261 disrupt the viruses. Following dilution, the vaccine is further purified by diafiltration. Each  
262 influenza virus solution is inactivated by the consecutive effects of sodium deoxycholate and  
263 formaldehyde leading to the production of a “split virus.” Each split inactivated virus is then  
264 suspended in sodium phosphate-buffered isotonic sodium chloride solution. The vaccine is  
265 formulated from the 3 split inactivated virus solutions.

266 FLUARIX has been standardized according to USPHS requirements for the 2015-2016 influenza  
267 season and is formulated to contain 45 micrograms (mcg) hemagglutinin (HA) per 0.5-mL dose,  
268 in the recommended ratio of 15 mcg HA of each of the following 3 strains:

- 269 A/Christchurch/16/2010 NIB-74XP (H1N1) (an A/California/7/2009-like virus),  
270 A/Switzerland/9715293/2013 NIB-88 (H3N2), and B/Phuket/3073/2013.

271 FLUARIX is formulated without preservatives. FLUARIX does not contain thimerosal. Each  
272 0.5-mL dose also contains octoxynol-10 (TRITON<sup>®</sup> X-100) ≤0.085 mg, α-tocopheryl hydrogen  
273 succinate ≤0.1 mg, and polysorbate 80 (Tween 80) ≤0.415 mg. Each dose may also contain  
274 residual amounts of hydrocortisone ≤0.0016 mcg, gentamicin sulfate ≤0.15 mcg, ovalbumin  
275 ≤0.05 mcg, formaldehyde ≤5 mcg, and sodium deoxycholate ≤50 mcg from the manufacturing  
276 process.

277 The tip caps and plungers of the prefilled syringes of FLUARIX are not made with natural  
278 rubber latex.

## 279 **12 CLINICAL PHARMACOLOGY**

### 280 **12.1 Mechanism of Action**

281 Influenza illness and its complications follow infection with influenza viruses. Global  
282 surveillance of influenza identifies yearly antigenic variants. For example, since 1977, antigenic  
283 variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global  
284 circulation.

285 Specific levels of hemagglutination-inhibition (HI) antibody titer post-vaccination with  
286 inactivated influenza virus vaccines have not been correlated with protection from influenza  
287 illness but the HI antibody titers have been used as a measure of vaccine activity. In some human  
288 challenge trials, HI antibody titers of ≥1:40 have been associated with protection from influenza  
289 illness in up to 50% of subjects.<sup>1,2</sup> Antibody against one influenza virus type or subtype confers  
290 little or no protection against another virus. Furthermore, antibody to one antigenic variant of  
291 influenza virus might not protect against a new antigenic variant of the same type or subtype.  
292 Frequent development of antigenic variants through antigenic drift is the virological basis for  
293 seasonal epidemics and the reason for the usual incorporation of one or more new strains in each  
294 year's influenza vaccine. Therefore, inactivated influenza vaccines are standardized to contain  
295 the hemagglutinins of strains (i.e., typically 2 type A and 1 type B), representing the influenza  
296 viruses likely to circulate in the United States in the upcoming winter.

297 Annual revaccination is recommended because immunity declines during the year after  
298 vaccination, and because circulating strains of influenza virus change from year to year.<sup>3</sup>

## 299 **13 NONCLINICAL TOXICOLOGY**

### 300 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

303 **14 CLINICAL STUDIES**

304 **14.1 Efficacy against Culture-confirmed Influenza**

305 The efficacy of FLUARIX was evaluated in a randomized, double-blind, placebo-controlled trial  
 306 conducted in 2 European countries during the 2006-2007 influenza season. Efficacy of  
 307 FLUARIX, containing A/New Caledonia/20/1999 (H1N1), A/Wisconsin/67/2005 (H3N2), and  
 308 B/Malaysia/2506/2004 influenza strains, was defined as the prevention of culture-confirmed  
 309 influenza A and/or B cases, for vaccine antigenically matched strains, compared with placebo.  
 310 Healthy subjects aged 18 through 64 years (mean: 39.9 years) were randomized (2:1) to receive  
 311 FLUARIX (N = 5,103) or placebo (N = 2,549) and monitored for influenza-like illnesses (ILI)  
 312 starting 2 weeks post-vaccination and lasting for approximately 7 months. In the overall  
 313 population, 60% of subjects were female and 99.9% were white. Culture-confirmed influenza  
 314 was assessed by active and passive surveillance of ILI. Influenza-like illness was defined as at  
 315 least one general symptom (fever  $\geq 100^{\circ}\text{F}$  and/or myalgia) and at least one respiratory symptom  
 316 (cough and/or sore throat). After an episode of ILI, nose and throat swab samples were collected  
 317 for analysis; attack rates and vaccine efficacy were calculated (Table 5).

318 **Table 5. Attack Rates and Vaccine Efficacy against Culture-confirmed Influenza A and/or**  
 319 **B in Adults Aged 18 through 64 Years<sup>a</sup> (Total Vaccinated Cohort)**

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

320 <sup>a</sup> NCT00363870.

321 <sup>b</sup> There were no vaccine matched culture-confirmed cases of A/New Caledonia/20/1999  
 322 (H1N1) or B/Malaysia/2506/2004 influenza strains with FLUARIX or placebo.

323 <sup>c</sup> Vaccine efficacy for FLUARIX exceeded a pre-defined threshold of 35% for the lower limit  
 324 of the 2-sided 95% CI.

325 <sup>d</sup> Of the 22 additional cases, 18 were unmatched and 4 were untyped; 15 of the 22 cases were A  
 326 (H3N2) (11 cases with FLUARIX and 4 cases with placebo).

327 In a post-hoc, exploratory analysis by age, vaccine efficacy (against culture-confirmed influenza  
 328 A and/or B cases, for vaccine antigenically matched strains) in subjects aged 18 through 49 years  
 329 was 73.4% (95% CI: 59.3, 82.8) [number of influenza cases: FLUARIX (n = 35/3,602) and  
 330 placebo (n = 66/1,810)]. In subjects aged 50 through 64 years, vaccine efficacy was 13.8%

331 (95% CI: -137.0, 66.3) [number of influenza cases: FLUARIX (n = 14/1,501) and placebo  
332 (n = 8/739)]. As the trial lacked statistical power to evaluate efficacy within age subgroups, the  
333 clinical significance of these results is unknown.

## 334 **14.2 Immunological Evaluation**

### 335 Adults

336 In a randomized, double-blind, placebo-controlled trial conducted in healthy subjects aged 18  
337 through 64 years (mean: 39.1 years) in the United States, the immune responses to each of the  
338 antigens contained in FLUARIX were evaluated in sera obtained 21 days after administration of  
339 FLUARIX (N = 745) and were compared to those following administration of a placebo vaccine  
340 (N = 190). In the overall population, 54% of subjects were female and 80% were white. For each  
341 of the influenza antigens, the percentage of subjects who achieved seroconversion, defined as at  
342 least a 4-fold increase in serum hemagglutination-inhibition (HI) titer over baseline to  $\geq 1:40$   
343 following vaccination, and the percentage of subjects who achieved HI titers of  $\geq 1:40$  are  
344 presented in Table 6. The lower limit of the 2-sided 95% CI for the percentage of subjects who  
345 achieved seroconversion or an HI titer of  $\geq 1:40$  exceeded the pre-defined lower limits of 40%  
346 and 70%, respectively.

347 **Table 6. Rates with HI Titers  $\geq 1:40$  and Rates of Seroconversion to Each Antigen following**  
 348 **FLUARIX or Placebo (21 Days after Vaccination) in Adults Aged 18 through 64 Years<sup>a</sup>**  
 349 **(ATP Cohort)**

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

350 HI = Hemagglutination-inhibition; ATP = According-to-protocol; CI = Confidence Interval.

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

353 <sup>a</sup> NCT00100399.

354 <sup>b</sup> Results obtained following vaccination with FLUARIX manufactured for the 2004-2005  
 355 season.

356 <sup>c</sup> Seroconversion defined as at least a 4-fold increase in serum titers of HI antibodies to  $\geq 1:40$ .

357 *Non-Inferiority Trial:* In a randomized, single-blind, active-controlled US trial, immunological  
 358 non-inferiority of FLUARIX (N = 923) was compared with FLUZONE (N = 922), a US-licensed  
 359 trivalent, inactivated influenza vaccine (Sanofi Pasteur SA). Subjects aged 18 through 64 years  
 360 and 65 years and older were evaluated for immune responses to each of the vaccine antigens  
 361 21 days following vaccination [see *Use in Specific Populations (8.5)*]. In the overall population,  
 362 59% of subjects were female and 91% were white. The co-primary immunogenicity endpoints  
 363 were GMTs of serum HI antibodies and the percentage of subjects who achieved seroconversion,  
 364 defined as at least a 4-fold increase in serum HI titer over baseline to  $\geq 1:40$ , following  
 365 vaccination. The primary immunogenicity analyses were performed on the According-to-

366 Protocol (ATP) cohort which included all eligible and evaluable subjects with results of at least  
 367 one serological assay. For each of the influenza antigens, the GMTs and the percentage of  
 368 subjects who achieved seroconversion are presented in Table 7. FLUARIX was non-inferior to  
 369 the comparator influenza vaccine based on antibody GMTs (upper limit of the 2-sided 95% CI  
 370 for the GMT ratio [comparator influenza vaccine/FLUARIX]  $\leq 1.5$ ) and seroconversion rates  
 371 (upper limit of the 2-sided 95% CI on difference of the comparator influenza vaccine minus  
 372 FLUARIX  $\leq 10\%$ ).

373 **Table 7. Immune Responses 21 Days after Vaccination with FLUARIX Compared with**  
 374 **Comparator Influenza Vaccine in Adults Aged 18 Years and Older<sup>a</sup> (ATP Cohort)**

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

375 Comparator influenza vaccine manufactured by Sanofi Pasteur SA.

376 ATP = According-to-protocol; GMT = Geometric mean antibody titer; CI = Confidence Interval;  
 377 H1 = A/New Caledonia/20/99 (H1N1); H3 = A/New York/55/2004 (H3N2) for FLUARIX  
 378 and A/California/7/2004 (H3N2) for comparator influenza vaccine; B = B/Jiangsu/10/2003.

379 ATP cohort included all eligible and evaluable subjects with results of at least one serological  
 380 assay.

381 <sup>a</sup> NCT00197288.

382 <sup>b</sup> Seroconversion defined as at least a 4-fold increase in serum titers of HI antibodies to  $\geq 1:40$ .



383 Children

384 The immune response of FLUARIX was compared to FLUZONE, a US-licensed trivalent,  
385 inactivated influenza vaccine (Sanofi Pasteur SA), in a single-blind, randomized trial in a subset  
386 of children aged 6 months through 4 years (Trial 005). The immune responses to each of the  
387 antigens contained in FLUARIX formulated for the 2006-2007 season were evaluated in sera  
388 obtained after 1 or 2 doses of FLUARIX (N = 426) and were compared to those following  
389 administration of the comparator influenza vaccine (N = 445). Further details on the clinical trial  
390 design and demographic information have been previously described [*see Adverse Reactions*  
391 (6.1)].

392 Non-inferiority of the immune response for FLUARIX to comparator influenza vaccine for  
393 subjects aged 6 months through 4 years was not demonstrated mainly due to lower antibody  
394 response to FLUARIX compared to the comparator influenza vaccine in subjects aged 6 months  
395 through 35 months. In subjects aged 3 years through 4 years, FLUARIX met at least one of the  
396 pre-specified criteria for demonstration of non-inferiority (GMT and seroconversion rate) for the  
397 influenza A strains but not for the influenza B strain. Seroconversion rates and the percentage of  
398 subjects with HI titers  $\geq 1:40$  were analyzed as secondary endpoints. In subjects aged 3 years  
399 through 4 years, the lower limit of the 95% Confidence Interval of the seroconversion rate for  
400 FLUARIX or the comparator influenza vaccine exceeded 40% for all 3 strains; also in this age  
401 group, the lower limit of the 95% Confidence Interval of the rate with HI titer  $\geq 1:40$  for  
402 FLUARIX or the comparator influenza vaccine exceeded 70% for both A strains (Table 8).

403 **Table 8. Rates with HI Titers  $\geq 1:40$  and Rates of Seroconversion to Each Antigen following**  
 404 **FLUARIX or Comparator Influenza Vaccine in Children Aged 3 through 4 Years<sup>a</sup> (ATP**  
 405 **Cohort)**

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

406 HI = Hemagglutination inhibition; ATP = According-to-protocol; CI = Confidence Interval.

407 <sup>a</sup> NCT00383123.

408 <sup>b</sup> Results obtained following vaccination with FLUARIX manufactured for the 2006–2007  
 409 season.

410 <sup>c</sup> US-licensed trivalent, inactivated influenza vaccine (Sanofi Pasteur SA) without preservative  
 411 manufactured for the 2006-2007 season.

412 <sup>d</sup> Seroconversion defined as at least a 4-fold increase in serum titers of HI antibodies to  $\geq 1:40$ .

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## 422 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

425 NDC 58160-883-41 Syringe in Package of 10: NDC 58160-883-52

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

## 428 **17 PATIENT COUNSELING INFORMATION**

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

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

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