

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

FLUARIX QUADRIVALENT (Influenza Vaccine)

Suspension for Intramuscular Injection

2016-2017 Formula

Initial U.S. Approval: 2012

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

For intramuscular injection only. (2)

Age	Vaccination Status	Dose and Schedule
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 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 ($\geq 10\%$) 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 ($\geq 10\%$) 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

- 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/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 aged 3 years
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
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 2 doses ^a (0.5-mL each)
9 years and older	Not applicable	One 0.5-mL dose

12 ^a One dose or 2 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 2 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 (NCT01204671) was a randomized, double-blind (2 arms) and open-label (one arm),
81 active-controlled, safety, and immunogenicity trial. In this trial, subjects received FLUARIX
82 QUADRIVALENT (n = 3,036) or one of 2 formulations of comparator trivalent influenza
83 vaccine (FLUARIX, TIV-1, n = 1,010 or TIV-2, n = 610), each containing an influenza type B
84 virus that corresponded to one of the 2 type B viruses in FLUARIX QUADRIVALENT (a type
85 B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The population was
86 aged 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 %	
	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	0.0	1.7	0.0	2.0	0.0
Swelling	2.1	0.0	2.1	0.0	1.3	0.0
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	0.0	1.2	0.0	1.5	0.0

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

95 ^a Seven 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 Grade 3 pain: Defined as significant pain at rest; prevented normal everyday activities.
 104 Grade 3 redness, swelling: Defined as >100 mm.

105 Grade 3 muscle aches, headache, fatigue, arthralgia, gastrointestinal symptoms, shivering:
 106 Defined as prevented normal activity.

107 Grade 3 fever: Defined as >102.2°F (39.0°C).

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

109 ^h Fever: Defined as ≥99.5°F (37.5°C).

110 Unsolicited events occurring within 21 days of vaccination (Day 0 to 20) were reported in 13%,
 111 14%, and 15% of subjects who received FLUARIX QUADRIVALENT, TIV-1, or TIV-2,
 112 respectively. The unsolicited adverse reactions that occurred most frequently (≥0.1% for
 113 FLUARIX QUADRIVALENT) included dizziness, injection site hematoma, injection site

114 pruritus, and rash. Serious adverse events occurring within 21 days of vaccination were reported
115 in 0.5%, 0.6%, and 0.2% of subjects who received FLUARIX QUADRIVALENT, TIV-1, or
116 TIV-2, respectively.

117 FLUARIX QUADRIVALENT in Children

118 Trial 2 (NCT01196988) was a randomized, double-blind, active-controlled, safety, and
119 immunogenicity trial. In this trial, subjects received FLUARIX QUADRIVALENT (n = 915) or
120 one of 2 formulations of comparator trivalent influenza vaccine (FLUARIX, TIV-1, n = 912 or
121 TIV-2, n = 911), each containing an influenza type B virus that corresponded to one of the 2 type
122 B viruses in FLUARIX QUADRIVALENT (a type B virus of the Victoria lineage or a type B
123 virus of the Yamagata lineage). Subjects were aged 3 through 17 years and 52% were male; 56%
124 were white, 29% were Asian, 12% were black, and 3% were of other racial/ethnic groups.
125 Children aged 3 through 8 years with no history of influenza vaccination received 2 doses
126 approximately 28 days apart. Children aged 3 through 8 years with a history of influenza
127 vaccination and children aged 9 years and older received one dose. Solicited local adverse
128 reactions and systemic adverse events were collected using diary cards for 7 days (day of
129 vaccination and the next 6 days). The frequencies of solicited adverse events are shown in
130 Table 3.

131 **Table 3. FLUARIX QUADRIVALENT: Incidence of Solicited Local Adverse Reactions**
 132 **and Systemic Adverse Events within 7 Days^a after First Vaccination in Children Aged 3**
 133 **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
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	0.0	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	0.0
Fever ^h	6.0	1.1	8.5	0.5	6.1	0.3

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

136 ^a Seven days included day of vaccination and the subsequent 6 days.

137 ^b Trial 2: NCT01196988.

138 ^c Contained the same composition as FLUARIX (trivalent formulation) manufactured for the
 139 2010-2011 season and an additional influenza type B virus of Yamagata lineage.

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

142 ^e Contained the same 2 influenza A subtype viruses as FLUARIX manufactured for the 2010-
 143 2011 season and an influenza type B virus of Yamagata lineage.

144 ^f Grade 3 pain: Defined as cried when limb was moved/spontaneously painful (children
 145 <6 years), or significant pain at rest, prevented normal everyday activities (children ≥6 years).

146 Grade 3 redness, swelling: Defined as >50 mm.

147 Grade 3 drowsiness: Defined as prevented normal activity.
148 Grade 3 irritability: Defined as crying that could not be comforted/prevented normal activity.
149 Grade 3 loss of appetite: Defined as not eating at all.
150 Grade 3 fever: Defined as >102.2°F (39.0°C).
151 Grade 3 fatigue, muscle aches, headache, arthralgia, gastrointestinal symptoms, shivering:
152 Defined as prevented normal activity.
153 ^g Percentage of subjects with any pain by age subgroup: 39%, 38%, and 37% for FLUARIX
154 QUADRIVALENT, TIV-1, and TIV-2, respectively, in children aged 3 through 8 years and
155 52%, 50%, and 46% for FLUARIX QUADRIVALENT, TIV-1, and TIV-2, respectively, in
156 children aged 9 through 17 years.
157 ^h Fever: Defined as ≥99.5°F (37.5°C).
158 ⁱ Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.
159 In children who received a second dose of FLUARIX QUADRIVALENT, TIV-1, or TIV-2, the
160 incidences of adverse events following the second dose were generally lower than those
161 observed after the first dose.
162 Unsolicited adverse events occurring within 28 days of any vaccination were reported in 31%,
163 33%, and 34% of subjects who received FLUARIX QUADRIVALENT, TIV-1, or TIV-2,
164 respectively. The unsolicited adverse reactions that occurred most frequently (≥0.1% for
165 FLUARIX QUADRIVALENT) included injection site pruritus and rash. Serious adverse events
166 occurring within 28 days of any vaccination were reported in 0.1%, 0.1%, and 0.1% of subjects
167 who received FLUARIX QUADRIVALENT, TIV-1, or TIV-2, respectively.

168 FLUARIX (Trivalent Formulation)

169 FLUARIX has been administered to 10,317 adults aged 18 through 64 years, 606 subjects aged
170 65 years and older, and 2,115 children aged 6 months through 17 years in clinical trials. The
171 incidence of solicited adverse events in each age-group is shown in Tables 4 and 5.

172 **Table 4. FLUARIX (Trivalent Formulation): Incidence of Solicited Local Adverse**
 173 **Reactions and Systemic Adverse Events within 4 Days^a of Vaccination in Adults (Total**
 174 **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 %	
	Any	Gr 3 ^d	Any	Gr 3 ^d	Any	Gr 3 ^d	Any	Gr 3 ^d
Local								
Pain	54.7	0.1	12.0	0.0	19.1	0.0	17.6	0.0
Redness	17.5	0.0	10.4	0.0	10.6	0.2	13.1	0.7
Swelling	9.3	0.1	5.7	0.0	6.0	0.0	8.9	0.7
Systemic								
Muscle aches	23.0	0.4	12.0	0.5	7.0	0.3	6.5	0.0
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	0.0	1.7	0.2	2.2	0.0
Fever ^e	1.7	0.0	1.6	0.0	1.7	0.0	0.5	0.0

175 Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were
 176 available. n = number of subjects with diary card completed. Gr 3 = Grade 3.

177 ^a Four days included day of vaccination and the subsequent 3 days.

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

180 ^c Trial 4 was a randomized, single-blind, active-controlled, safety, and immunogenicity trial
 181 (NCT00197288). The active control was FLUZONE[®], a U.S.-licensed trivalent, inactivated
 182 influenza vaccine (Sanofi Pasteur Inc.).

183 ^d Grade 3 pain, muscle aches, fatigue, headache, arthralgia, shivering: Defined as prevented
 184 normal activity.

185 Grade 3 redness, swelling: Defined as >50 mm.

186 Grade 3 fever: Defined as >102.2°F (39.0°C).

187 ^e Fever: Defined as ≥100.4°F (38.0°C) in Trial 3, and ≥99.5°F (37.5°C) in Trial 4.

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

	Aged 3 through 4 Years				Aged 5 through 17 Years			
	FLUARIX		Comparator		FLUARIX		Comparator	
	n = 350		n = 341		n = 1,348		n = 451	
	%		%		%		%	
	Any	Gr 3 ^c	Any	Gr 3 ^c	Any	Gr 3 ^c	Any	Gr 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	0.0	17.7	1.0	16.4	0.7
Swelling	13.7	0.0	13.2	0.0	13.9	1.5	13.3	0.7
Systemic								
Irritability	20.9	0.9	22.0	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

191 Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were
 192 available. n = number of subjects with diary card completed. Gr 3 = Grade 3.

193 ^a Four days included day of vaccination and the subsequent 3 days.

194 ^b Trial 6 was a single-blind, active-controlled, safety, and immunogenicity U.S. trial
 195 (NCT00383123). The active control was FLUZONE, a U.S.-licensed trivalent, inactivated
 196 influenza vaccine (Sanofi Pasteur Inc.).

197 ^c Grade 3 pain, irritability, loss of appetite, drowsiness, muscle aches, fatigue, headache,
 198 arthralgia, shivering: Defined as prevented normal activity.

199 Grade 3 swelling, redness: Defined as >50 mm.

200 Grade 3 fever: Defined as >102.2°F (39.0°C).

201 ^d Fever: Defined as ≥99.5°F (37.5°C).

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

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

206 **6.2 Postmarketing Experience**

207 Beyond those events reported above in the clinical trials for FLUARIX QUADRIVALENT or
 208 FLUARIX, the following adverse events have been spontaneously reported during postapproval

209 use of FLUARIX (trivalent influenza vaccine). This list includes serious events or events which
210 have causal connection to FLUARIX. Because these events are reported voluntarily from a
211 population of uncertain size, it is not always possible to reliably estimate their frequency or
212 establish a causal relationship to the vaccine.

213 Blood and Lymphatic System Disorders

214 Lymphadenopathy.

215 Cardiac Disorders

216 Tachycardia.

217 Ear and Labyrinth Disorders

218 Vertigo.

219 Eye Disorders

220 Conjunctivitis, eye irritation, eye pain, eye redness, eye swelling, eyelid swelling.

221 Gastrointestinal Disorders

222 Abdominal pain or discomfort, swelling of the mouth, throat, and/or tongue.

223 General Disorders and Administration Site Conditions

224 Asthenia, chest pain, feeling hot, injection site mass, injection site reaction, injection site
225 warmth, body aches.

226 Immune System Disorders

227 Anaphylactic reaction including shock, anaphylactoid reaction, hypersensitivity, serum sickness.

228 Infections and Infestations

229 Injection site abscess, injection site cellulitis, pharyngitis, rhinitis, tonsillitis.

230 Nervous System Disorders

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

233 Respiratory, Thoracic, and Mediastinal Disorders

234 Asthma, bronchospasm, dyspnea, respiratory distress, stridor.

235 Skin and Subcutaneous Tissue Disorders

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

238 Vascular Disorders

239 Henoch-Schönlein purpura, vasculitis.

240 **7 DRUG INTERACTIONS**

241 **7.1 Concomitant Vaccine Administration**

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

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

247 **7.2 Immunosuppressive Therapies**

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

251 **8 USE IN SPECIFIC POPULATIONS**

252 **8.1 Pregnancy**

253 Pregnancy Exposure Registry

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

257 Risk Summary

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

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

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

267 Clinical Considerations

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

272 **Data**

273 *Animal Data:* In a developmental toxicity study, female rats were administered FLUARIX
274 QUADRIVALENT by intramuscular injection 4 and 2 weeks prior to mating, on gestation Days
275 3, 8, 11, and 15, and on lactation Day 7. The total dose was 0.2 mL at each occasion (a single
276 human dose is 0.5 mL). No adverse effects on pre-weaning development up to post-natal Day 25
277 were observed. There were no vaccine-related fetal malformations or variations.

278 **8.2 Lactation**

279 **Risk Summary**

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

287 **8.4 Pediatric Use**

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

290 Safety and immunogenicity of FLUARIX QUADRIVALENT in children aged 3 through
291 17 years have been evaluated [*see Adverse Reactions (6.1), Clinical Studies (14.3)*].

292 **8.5 Geriatric Use**

293 In a randomized, double-blind (2 arms) and open-label (one arm), active-controlled trial,
294 immunogenicity and safety were evaluated in a cohort of subjects aged 65 years and older who
295 received FLUARIX QUADRIVALENT (n = 1,517); 469 of these subjects were aged 75 years
296 and older. In subjects aged 65 years and older, the geometric mean antibody titers (GMTs) post-
297 vaccination and seroconversion rates were lower than in younger subjects (aged 18 through
298 64 years) and the frequencies of solicited and unsolicited adverse events were generally lower
299 than in younger subjects.

300 **11 DESCRIPTION**

301 FLUARIX QUADRIVALENT, Influenza Vaccine, for intramuscular injection, is a sterile,
302 colorless, and slightly opalescent suspension. FLUARIX QUADRIVALENT is prepared from
303 influenza viruses propagated in embryonated chicken eggs. Each of the influenza viruses is
304 produced and purified separately. After harvesting the virus-containing fluids, each influenza
305 virus is concentrated and purified by zonal centrifugation using a linear sucrose density gradient
306 solution containing detergent to disrupt the viruses. Following dilution, the vaccine is further
307 purified by diafiltration. Each influenza virus solution is inactivated by the consecutive effects of

308 sodium deoxycholate and formaldehyde leading to the production of a “split virus.” Each split
309 inactivated virus is then suspended in sodium phosphate-buffered isotonic sodium chloride
310 solution. Each vaccine is formulated from the split inactivated virus solutions.

311 FLUARIX QUADRIVALENT has been standardized according to US Public Health Service
312 (USPHS) requirements for the 2016-2017 influenza season and is formulated to contain
313 60 micrograms (mcg) hemagglutinin (HA) per 0.5-mL dose, in the recommended ratio of 15 mcg
314 HA of each of the following 4 influenza virus strains: A/Christchurch/16/2010 (H1N1)
315 NIB-74XP (an A/California/7/2009 (H1N1) pdm09-like virus), A/Hong Kong/4801/2014
316 (H3N2) NYMC X-263B, B/Phuket/3073/2013, and B/Brisbane/60/2008.

317 FLUARIX QUADRIVALENT is formulated without preservatives. FLUARIX
318 QUADRIVALENT does not contain thimerosal. Each 0.5-mL dose also contains octoxynol-10
319 (TRITON® X-100) ≤ 0.115 mg, α -tocopheryl hydrogen succinate ≤ 0.135 mg, and polysorbate 80
320 (Tween 80) ≤ 0.550 mg. Each dose may also contain residual amounts of hydrocortisone
321 ≤ 0.0016 mcg, gentamicin sulfate ≤ 0.15 mcg, ovalbumin ≤ 0.050 mcg, formaldehyde ≤ 5 mcg, and
322 sodium deoxycholate ≤ 65 mcg from the manufacturing process.

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

325 **12 CLINICAL PHARMACOLOGY**

326 **12.1 Mechanism of Action**

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

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

336 Specific levels of hemagglutination-inhibition (HI) antibody titer post-vaccination with
337 inactivated influenza virus vaccines have not been correlated with protection from influenza
338 illness but the HI antibody titers have been used as a measure of vaccine activity. In some human
339 challenge studies, HI antibody titers of $\geq 1:40$ have been associated with protection from
340 influenza illness in up to 50% of subjects.^{1,2} Antibody against one influenza virus type or subtype
341 confers little or no protection against another virus. Furthermore, antibody to one antigenic
342 variant of influenza virus might not protect against a new antigenic variant of the same type or
343 subtype. Frequent development of antigenic variants through antigenic drift is the virological
344 basis for seasonal epidemics and the reason for the usual replacement of one or more influenza

345 viruses in each year's influenza vaccine.
346 Annual revaccination is recommended because immunity declines during the year after
347 vaccination, and because circulating strains of influenza virus change from year to year.

348 **13 NONCLINICAL TOXICOLOGY**

349 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

353 **14 CLINICAL STUDIES**

354 **14.1 Efficacy against Culture-Confirmed Influenza**

355 The efficacy experience with FLUARIX is relevant to FLUARIX QUADRIVALENT because
356 both vaccines are manufactured using the same process and have overlapping compositions [*see*
357 *Description (11)*].

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

371 **Table 6. FLUARIX (Trivalent Formulation): Attack Rates and Vaccine Efficacy against**
 372 **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	–	–	–

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

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

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

379 In a post-hoc, exploratory analysis by age, vaccine efficacy (against culture-confirmed influenza
 380 A and/or B cases, for vaccine antigenically matched strains) in subjects aged 18 through 49 years
 381 was 73.4% (95% CI: 59.3, 82.8) (number of influenza cases: FLUARIX [n = 35/3,602] and
 382 placebo [n = 66/1,810]). In subjects aged 50 through 64 years, vaccine efficacy was 13.8%
 383 (95% CI: -137.0, 66.3) (number of influenza cases: FLUARIX [n = 14/1,501] and placebo
 384 [n = 8/739]). As the trial lacked statistical power to evaluate efficacy within age subgroups, the
 385 clinical significance of these results is unknown.

386 **14.2 Immunological Evaluation of FLUARIX QUADRIVALENT in Adults**

387 Trial 1 was a randomized, double-blind (2 arms) and open-label (one arm), active-controlled,
 388 safety, immunogenicity, and non-inferiority trial. In this trial, subjects received FLUARIX
 389 QUADRIVALENT (n = 1,809) or one of 2 formulations of comparator trivalent influenza
 390 vaccine (FLUARIX, TIV-1, n = 608 or TIV-2, n = 534), each containing an influenza type B
 391 virus that corresponded to one of the 2 type B viruses in FLUARIX QUADRIVALENT (a type
 392 B virus of the Victoria lineage or a type B virus of the Yamagata lineage). Subjects aged
 393 18 years and older (mean age: 58 years) were evaluated for immune responses to each of the
 394 vaccine antigens 21 days following vaccination. In the overall population, 57% of subjects were
 395 female; 69% were white, 27% were Asian, and 4% were of other racial/ethnic groups.

396 The immunogenicity endpoints were GMTs of serum hemagglutination-inhibition (HI)
 397 antibodies adjusted for baseline, and the percentage of subjects who achieved seroconversion,
 398 defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥1:40 or at least a
 399 4-fold increase in serum HI antibody titer over baseline to ≥1:40 following vaccination,
 400 performed on the According-to-Protocol (ATP) cohort for whom immunogenicity assay results

401 were available after vaccination. FLUARIX QUADRIVALENT was non-inferior to both TIVs
 402 based on adjusted GMTs (upper limit of the 2-sided 95% CI for the GMT ratio [TIV/FLUARIX
 403 QUADRIVALENT] ≤ 1.5) and seroconversion rates (upper limit of the 2-sided 95% CI on
 404 difference of the TIV minus FLUARIX QUADRIVALENT $\leq 10\%$). The antibody response to
 405 influenza B strains contained in FLUARIX QUADRIVALENT was higher than the antibody
 406 response after vaccination with a TIV containing an influenza B strain from a different lineage.
 407 There was no evidence that the addition of the second B strain resulted in immune interference to
 408 other strains included in the vaccine (Table 7).

409 **Table 7. FLUARIX QUADRIVALENT: Immune Responses to Each Antigen 21 Days after**
 410 **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)

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

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

414 ^a Contained the same composition as FLUARIX (trivalent formulation) manufactured for the

- 415 2010-2011 season and an additional influenza type B virus of Yamagata lineage.
- 416 ^b Contained the same composition as FLUARIX manufactured for the 2010-2011 season (2
417 influenza A subtype viruses and an influenza type B virus of Victoria lineage).
- 418 ^c Contained the same 2 influenza A subtype viruses as FLUARIX manufactured for the 2010-
419 2011 season and an influenza type B virus of Yamagata lineage.
- 420 ^d Seroconversion defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer
421 \geq 1:40 or at least a 4-fold increase in serum titers of HI antibodies to \geq 1:40.

422 **14.3 Immunological Evaluation of FLUARIX QUADRIVALENT in Children**

423 Trial 2 was a randomized, double-blind, active-controlled, safety, immunogenicity, and non-
424 inferiority trial. In this trial, subjects received FLUARIX QUADRIVALENT (n = 791) or one of
425 2 formulations of comparator trivalent influenza vaccine (FLUARIX, TIV-1, n = 819 or TIV-2,
426 n = 801), each containing an influenza type B virus that corresponded to one of the 2 type B
427 viruses in FLUARIX QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus
428 of the Yamagata lineage). In children aged 3 through 17 years, immune responses to each of the
429 vaccine antigens were evaluated in sera 28 days following 1 or 2 doses. In the overall population,
430 52% of subjects were male; 56% were white, 29% were Asian, 12% were black, and 3% were of
431 other racial/ethnic groups.

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

444 **Table 8. FLUARIX QUADRIVALENT: Immune Responses to Each Antigen 28 Days after**
 445 **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)

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

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

449 ^a Contained the same composition as FLUARIX (trivalent formulation) manufactured for the
 450 2010-2011 season and an additional influenza type B virus of Yamagata lineage.

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

453 ^c Contained the same 2 influenza A subtype viruses as FLUARIX manufactured for the 2010-
 454 2011 season and an influenza B virus of Yamagata lineage.

455 ^d Seroconversion defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer
 456 ≥1:40 or at least a 4-fold increase in serum titers of HI antibodies to ≥1:40.

457 **15 REFERENCES**

- 458 1. Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza
459 vaccination. *Virus Res.* 2004;103:133-138.
- 460 2. Hobson D, Curry RL, Beare AS, et al. The role of serum haemagglutination-inhibiting
461 antibody in protection against challenge infection with influenza A2 and B viruses. *J Hyg*
462 *Camb.* 1972;70:767-777.

463 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

467 **17 PATIENT COUNSELING INFORMATION**

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

- 469 • Inform of the potential benefits and risks of immunization with FLUARIX
470 QUADRIVALENT.
- 471 • Educate regarding potential side effects, emphasizing that: (1) FLUARIX
472 QUADRIVALENT contains non-infectious killed viruses and cannot cause influenza and (2)
473 FLUARIX QUADRIVALENT is intended to provide protection against illness due to
474 influenza viruses only, and cannot provide protection against all respiratory illness.
- 475 • Encourage women exposed to FLUARIX QUADRIVALENT during pregnancy to enroll in
476 the pregnancy registry [*see Use in Specific Populations (8.1)*].
- 477 • Give the Vaccine Information Statements, which are required by the National Childhood
478 Vaccine Injury Act of 1986 prior to each immunization. These materials are available free of
479 charge at the Centers for Disease Control and Prevention (CDC) website
480 (www.cdc.gov/vaccines).
- 481 • Instruct that annual revaccination is recommended.

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