

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

FLULAVAL QUADRIVALENT (Influenza Vaccine)

Suspension for Intramuscular Injection

2016-2017 Formula

Initial U.S. Approval: 2013

RECENT MAJOR CHANGES

Indications and Usage (1)	11/2016
Dosage and Administration (2.1)	11/2016

INDICATIONS AND USAGE

FLULAVAL 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. FLULAVAL QUADRIVALENT is approved for use in persons aged 6 months and older. (1)

DOSAGE AND ADMINISTRATION

For intramuscular injection only. (2)

Age	Vaccination Status	Dose and Schedule
6 months through 8 years	Not previously vaccinated with influenza vaccine	Two doses (0.5-mL each) at least 4 weeks apart (2.1)
	Vaccinated with influenza vaccine in a previous season	One or two 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 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:

- 0.5-mL single-dose prefilled syringes (3)
- 5-mL multi-dose vials containing 10 doses (each dose is 0.5 mL). (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 FLULAVAL QUADRIVALENT should be based on careful consideration of the potential benefits and risks. (5.1)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including FLULAVAL 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 ($\geq 10\%$) solicited local adverse reaction was pain (60%); most common solicited systemic adverse events were muscle aches (26%), headache (22%), fatigue (22%), and arthralgia (15%). (6.1)
- In children aged 6 through 35 months, the most common ($\geq 10\%$) solicited local adverse reaction was pain (40%); most common solicited systemic adverse events were irritability (49%), drowsiness (37%), and loss of appetite (29%). (6.1)
- In children aged 3 through 17 years, the most common ($\geq 10\%$) solicited local adverse reaction was pain (65%). (6.1)
- In children aged 3 through 4 years, the most common ($\geq 10\%$) solicited systemic adverse events were irritability (26%), drowsiness (21%), and loss of appetite (17%). (6.1)
- In children aged 5 through 17 years, the most common ($\geq 10\%$) solicited systemic adverse events were muscle aches (29%), fatigue (22%), headache (22%), arthralgia (13%), 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 FLULAVAL QUADRIVALENT than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2016

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1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

3 FLULAVAL[®] 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.
5 FLULAVAL QUADRIVALENT is approved for use in persons aged 6 months and older.

6 **2 DOSAGE AND ADMINISTRATION**

7 **For intramuscular injection only.**

8 **2.1 Dosage and Schedule**

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

10 **Table 1. FLULAVAL QUADRIVALENT: Dosing**

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

11 ^a 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 For the multi-dose vial, use a sterile needle and sterile syringe to withdraw the 0.5-mL dose from
21 the multi-dose vial and administer intramuscularly. A sterile syringe with a needle bore no larger
22 than 23 gauge is recommended for administration. It is recommended that small syringes
23 (0.5 mL or 1 mL) be used to minimize any product loss. Use a separate sterile needle and syringe
24 for each dose withdrawn from the multi-dose vial.

25 Between uses, return the multi-dose vial to the recommended storage conditions, between 2° and
26 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has been frozen. Once entered, a multi-

27 dose vial, and any residual contents, should be discarded after 28 days.

28 The preferred sites for intramuscular injection are the anterolateral thigh for children aged 6
29 through 11 months and the deltoid muscle of the upper arm for persons aged 12 months and
30 older. Do not inject in the gluteal area or areas where there may be a major nerve trunk.

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

32 **3 DOSAGE FORMS AND STRENGTHS**

33 FLULAVAL QUADRIVALENT is a suspension for injection available in 0.5-mL prefilled
34 TIP-LOK[®] syringes and 5-mL multi-dose vials containing 10 doses (each dose is 0.5 mL).

35 **4 CONTRAINDICATIONS**

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

39 **5 WARNINGS AND PRECAUTIONS**

40 **5.1 Guillain-Barré Syndrome**

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

44 The 1976 swine influenza vaccine was associated with an elevated risk of GBS. Evidence for a
45 causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is
46 probably slightly more than one additional case/one million persons vaccinated.

47 **5.2 Syncope**

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

52 **5.3 Preventing and Managing Allergic Vaccine Reactions**

53 Prior to administration, the healthcare provider should review the immunization history for
54 possible vaccine sensitivity and previous vaccination-related adverse reactions. Appropriate
55 medical treatment and supervision must be available to manage possible anaphylactic reactions
56 following administration of FLULAVAL QUADRIVALENT.

57 **5.4 Altered Immunocompetence**

58 If FLULAVAL QUADRIVALENT is administered to immunosuppressed persons, including
59 individuals receiving immunosuppressive therapy, the immune response may be lower than in

60 immunocompetent persons.

61 **5.5 Limitations of Vaccine Effectiveness**

62 Vaccination with FLULAVAL QUADRIVALENT may not protect all susceptible individuals.

63 **5.6 Persons at Risk of Bleeding**

64 As with other intramuscular injections, FLULAVAL QUADRIVALENT should be given with
65 caution in individuals with bleeding disorders such as hemophilia or on anticoagulant therapy to
66 avoid the risk of hematoma following the injection.

67 **6 ADVERSE REACTIONS**

68 **6.1 Clinical Trials Experience**

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

74 In adults who received FLULAVAL QUADRIVALENT, the most common ($\geq 10\%$) solicited
75 local adverse reaction was pain (60%); the most common ($\geq 10\%$) solicited systemic adverse
76 events were muscle aches (26%), headache (22%), fatigue (22%), and arthralgia (15%).

77 In children aged 6 through 35 months who received FLULAVAL QUADRIVALENT, the most
78 common ($\geq 10\%$) solicited local adverse reaction was pain (40%); the most common ($\geq 10\%$)
79 solicited systemic adverse events were irritability (49%), drowsiness (37%), and loss of appetite
80 (29%).

81 In children aged 3 through 17 years who received FLULAVAL QUADRIVALENT, the most
82 common ($\geq 10\%$) solicited local adverse reaction was pain (65%). In children aged 3 through
83 4 years, the most common ($\geq 10\%$) solicited systemic adverse events were irritability (26%),
84 drowsiness (21%), and loss of appetite (17%). In children aged 5 through 17 years, the most
85 common ($\geq 10\%$) systemic adverse events were muscle aches (29%), fatigue (22%), headache
86 (22%), arthralgia (13%), and gastrointestinal symptoms (10%).

87 FLULAVAL QUADRIVALENT has been administered in 8 clinical trials to 1,384 adults aged
88 18 years and older, 1,965 children aged 6 through 35 months, and 3,516 children aged 3 through
89 17 years.

90 FLULAVAL QUADRIVALENT in Adults

91 Trial 1 (NCT01196975) was a randomized, double-blind, active-controlled, safety and
92 immunogenicity trial. In this trial, subjects received FLULAVAL QUADRIVALENT
93 ($n = 1,272$), or one of two formulations of a comparator trivalent influenza vaccine
94 (FLULAVAL, TIV-1, $n = 213$ or TIV-2, $n = 218$), each containing an influenza type B virus that

105 corresponded to one of the two B viruses in FLULAVAL QUADRIVALENT (a type B virus of
 106 the Victoria lineage or a type B virus of the Yamagata lineage). The population was aged 18
 107 years and older (mean age: 50 years) and 61% were female; 61% of subjects were white, 3%
 108 were black, 1% were Asian, and 35% were of other racial/ethnic groups. Solicited adverse events
 109 were collected for 7 days (day of vaccination and the next 6 days). The incidence of local
 110 adverse reactions and systemic adverse events occurring within 7 days of vaccination in adults
 111 are shown in Table 2.

102 **Table 2. FLULAVAL QUADRIVALENT: Incidence of Solicited Local Adverse Reactions**
 103 **and Systemic Adverse Events within 7 Days^a of Vaccination in Adults Aged 18 Years and**
 104 **Older^b (Total Vaccinated Cohort)**

	FLULAVAL QUADRIVALENT ^c n = 1,260 %		Trivalent Influenza Vaccine (TIV)			
			TIV-1 (B Victoria) ^d n = 208 %		TIV-2 (B Yamagata) ^e n = 216 %	
	Any	Grade 3 ^f	Any	Grade 3 ^f	Any	Grade 3 ^f
Local Adverse Reactions						
Pain	59.5	1.7	44.7	1.0	41.2	1.4
Swelling	2.5	0.0	1.4	0.0	3.7	0.0
Redness	1.7	0.0	2.9	0.0	1.4	0.0
Systemic Adverse Events						
Muscle aches	26.3	0.8	25.0	0.5	18.5	1.4
Headache	21.5	0.9	19.7	0.5	22.7	0.0
Fatigue	21.5	0.8	21.6	1.0	17.1	1.9
Arthralgia	14.8	0.8	16.7	1.0	14.6	2.9
Gastrointestinal symptoms ^g	9.3	0.8	10.1	1.9	6.9	0.5
Shivering	8.8	0.6	7.7	0.5	6.0	0.9
Fever ^h	1.3	0.4	0.5	0.0	1.4	0.5

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

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

108 ^b Trial 1: NCT01196975.

109 ^c Contained two A strains and two B strains, one of Victoria lineage and one of Yamagata
 110 lineage.

111 ^d Contained the same two A strains as FLULAVAL QUADRIVALENT and a B strain of
 112 Victoria lineage.

113 ^e Contained the same two A strains as FLULAVAL QUADRIVALENT and a B strain of
 114 Yamagata lineage.

115 ^f Grade 3 pain: Defined as significant pain at rest; prevented normal everyday activities.
116 Grade 3 swelling, redness: Defined as >100 mm.
117 Grade 3 muscle aches, headache, fatigue, arthralgia, gastrointestinal symptoms, shivering:
118 Defined as prevented normal activity.
119 Grade 3 (or higher) fever: Defined as $\geq 102.2^{\circ}\text{F}$ (39.0°C).
120 ^g Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.
121 ^h Fever: Defined as $\geq 100.4^{\circ}\text{F}$ (38.0°C)

122 Unsolicited adverse events occurring within 21 days of vaccination were reported in 19%, 23%,
123 and 23% of subjects who received FLULAVAL QUADRIVALENT (n = 1,272), TIV-1
124 (B Victoria) (n = 213), or TIV-2 (B Yamagata) (n = 218), respectively. The unsolicited adverse
125 events that occurred most frequently ($\geq 1\%$ for FLULAVAL QUADRIVALENT) included
126 nasopharyngitis, upper respiratory tract infection, headache, cough, and oropharyngeal pain.
127 Serious adverse events occurring within 21 days of vaccination were reported in 0.4%, 0%, and
128 0% of subjects who received FLULAVAL QUADRIVALENT, TIV-1 (B Victoria), or TIV-2
129 (B Yamagata), respectively.

130 FLULAVAL QUADRIVALENT in Children

131 Trial 4 (NCT02242643) was a randomized, observer-blind, active-controlled immunogenicity
132 and safety trial. The trial included subjects aged 6 through 35 months who received FLULAVAL
133 QUADRIVALENT (n = 1,207) or FLUZONE[®] QUADRIVALENT, a U.S.-licensed inactivated
134 influenza vaccine (n = 1,217) used as comparator, manufactured by Sanofi Pasteur Inc. Children
135 with no history of influenza vaccination received 2 doses of FLULAVAL QUADRIVALENT or
136 the comparator vaccine approximately 28 days apart. Children with a history of influenza
137 vaccination received one dose of FLULAVAL QUADRIVALENT or the comparator vaccine. In
138 the overall population, 53% were male; 64% were white, 16% were black, 3% were Asian, and
139 17% were of other racial/ethnic groups. The mean age of subjects was 20 months. Subjects were
140 followed for safety for 6 months; solicited local adverse reactions and systemic adverse events
141 were collected for 7 days (day of vaccination and the next 6 days) postvaccination. The incidence
142 of local adverse reactions and systemic adverse events occurring within 7 days of vaccination in
143 children are shown in Table 3.

144 **Table 3. FLULAVAL QUADRIVALENT: Incidence of Solicited Local Adverse Reactions**
 145 **and Systemic Adverse Events within 7 Days^a of First Vaccination in Children Aged 6**
 146 **through 35 Months^b (Total Vaccinated Cohort)**

	FLULAVAL QUADRIVALENT		Active Comparator ^c	
	%		%	
	Any	Grade 3 ^d	Any	Grade 3 ^d
Local Adverse Reactions	n = 1,151		n = 1,146	
Pain	40.3	2.4	37.4	1.4
Swelling	1.0	0.0	0.4	0.0
Redness	1.3	0.0	1.3	0.0
Systemic Adverse Events	n = 1,155		n = 1,148	
Irritability	49.4	3.8	45.9	3.0
Drowsiness	36.7	2.7	36.9	2.6
Loss of appetite	28.9	1.6	28.6	1.3
Fever ^e	5.6	1.4	5.8	1.0

147 Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were
 148 available (i.e., diary card completed for solicited symptoms). n = number of subjects with diary
 149 card completed.

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

151 ^b Trial 4: NCT02242643.

152 ^c U.S.-licensed quadrivalent, inactivated influenza vaccine (manufactured by Sanofi Pasteur
 153 Inc).

154 ^d Grade 3 pain: Defined as cried when limb was moved/spontaneously painful.

155 Grade 3 swelling, redness: Defined as >100 mm.

156 Grade 3 irritability: Defined as crying that could not be comforted/prevented normal activity.

157 Grade 3 drowsiness: Defined as prevented normal activity.

158 Grade 3 loss of appetite: Defined as not eating at all.

159 Grade 3 (or higher) fever: Defined as >102.2°F (39.0°C).

160 ^e Fever: Defined as ≥100.4°F (38.0°C).

161 In children who received a second dose of FLULAVAL QUADRIVALENT or the comparator
 162 vaccine, the incidences of solicited adverse events following the second dose were generally
 163 similar or lower than those observed after the first dose.

164 Unsolicited adverse events occurring within 28 days of vaccination were reported in 46% and
 165 44% of subjects who received FLULAVAL QUADRIVALENT (n = 1,207) and the comparator
 166 vaccine (n = 1,217), respectively. The unsolicited adverse reactions that occurred most
 167 frequently (≥1%) for FLULAVAL QUADRIVALENT included upper respiratory tract infection,
 168 cough, diarrhea, pyrexia, vomiting, and rash. Serious adverse events occurring during the study
 169 period (approximately 6 months) were reported in 2% of subjects who received FLULAVAL
 170 QUADRIVALENT and in 2% of subjects who received the comparator vaccine. There were no

171 deaths reported during the study period.

172 Trial 2 (NCT01198756) was a randomized, double-blind, active-controlled trial. In this trial,
173 subjects received FLULAVAL QUADRIVALENT (n = 932) or one of two formulations of a
174 comparator trivalent influenza vaccine [FLUARIX[®] (Influenza Vaccine), TIV-1 (B Victoria),
175 n = 929 or TIV-2 (B Yamagata), n = 932], each containing an influenza type B virus that
176 corresponded to one of the two B viruses in FLULAVAL QUADRIVALENT (a type B virus of
177 the Victoria lineage or a type B virus of the Yamagata lineage). The population was aged
178 3 through 17 years (mean age: 9 years) and 53% were male; 65% were white, 13% were Asian,
179 9% were black, and 13% were of other racial/ethnic groups. Children aged 3 through 8 years
180 with no history of influenza vaccination received 2 doses approximately 28 days apart. Children
181 aged 3 through 8 years with a history of influenza vaccination and children aged 9 years and
182 older received one dose. Solicited local adverse reactions and systemic adverse events were
183 collected for 7 days (day of vaccination and the next 6 days). The incidence of local adverse
184 reactions and systemic adverse events occurring within 7 days of vaccination in children are
185 shown in Table 4.

186 **Table 4. FLULAVAL QUADRIVALENT: Incidence of Solicited Local Adverse Reactions**
 187 **and Systemic Adverse Events within 7 Days^a of First Vaccination in Children Aged 3**
 188 **through 17 Years^b (Total Vaccinated Cohort)**

	FLULAVAL 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 Adverse Reactions	n = 913		n = 911		n = 915	
Pain	65.4	3.2	54.6	1.8	55.7	2.4
Swelling	6.2	0.1	3.3	0.0	3.8	0.0
Redness	5.3	0.1	3.2	0.0	3.5	0.0
Aged 3 through 4 Years						
Systemic Adverse Events	n = 185		n = 187		n = 189	
Irritability	25.9	0.5	16.6	0.0	21.7	1.6
Drowsiness	21.1	0.0	19.8	1.6	23.3	0.5
Loss of appetite	17.3	0.0	16.0	1.6	13.2	1.1
Fever ^g	4.9	0.5	5.9	1.1	3.7	1.6
Aged 5 through 17 Years						
Systemic Adverse Events	n = 727		n = 724		n = 725	
Muscle aches	28.5	0.7	24.9	0.6	24.7	1.0
Fatigue	22.1	0.7	23.6	1.8	23.0	1.0
Headache	22.0	1.0	22.1	1.0	20.1	1.2
Arthralgia	12.9	0.4	11.9	0.6	10.5	0.1
Gastrointestinal symptoms ^h	9.6	1.0	9.7	1.0	9.0	0.7
Shivering	7.0	0.4	6.9	1.2	6.9	0.6
Fever ^g	1.9	0.6	3.6	1.1	2.5	0.3

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

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

192 ^b Trial 2: NCT01198756.

193 ^c Contained two A strains and two B strains, one of Victoria lineage and one of Yamagata
 194 lineage.

195 ^d Contained the same two A strains as FLULAVAL QUADRIVALENT and a B strain of
 196 Victoria lineage.

197 ^e Contained the same two A strains as FLULAVAL QUADRIVALENT and a B strain of
 198 Yamagata lineage.

199 ^f Grade 3 pain: Defined as cried when limb was moved/spontaneously painful (children
 200 <5 years), or significant pain at rest, prevented normal everyday activities (children ≥5 years).

201 Grade 3 swelling, redness: Defined as >100 mm.

202 Grade 3 irritability: Defined as crying that could not be comforted/prevented normal activity.
203 Grade 3 drowsiness: Defined as prevented normal activity.
204 Grade 3 loss of appetite: Defined as not eating at all.
205 Grade 3 (or higher) fever: Defined as $\geq 102.2^{\circ}\text{F}$ (39.0°C).
206 Grade 3 muscle aches, fatigue, headache, arthralgia, gastrointestinal symptoms, shivering:
207 Defined as prevented normal activity.
208 ^g Fever: Defined as $\geq 100.4^{\circ}\text{F}$ (38.0°C).
209 ^h Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

210 In children who received a second dose of FLULAVAL QUADRIVALENT, FLUARIX TIV-1
211 (B Victoria), or TIV-2 (B Yamagata), the incidences of adverse events following the second dose
212 were generally lower than those observed after the first dose.

213 Unsolicited adverse events occurring within 28 days of vaccination were reported in 30%, 31%,
214 and 30% of subjects who received FLULAVAL QUADRIVALENT (n = 932), FLUARIX TIV-1
215 (B Victoria) (n = 929), or TIV-2 (B Yamagata) (n = 932), respectively. The unsolicited adverse
216 events that occurred most frequently ($\geq 1\%$ for FLULAVAL QUADRIVALENT) included
217 vomiting, pyrexia, bronchitis, nasopharyngitis, pharyngitis, upper respiratory tract infection,
218 headache, cough, oropharyngeal pain, and rhinorrhea. Serious adverse events occurring within
219 28 days of any vaccination were reported in 0.1%, 0.2%, and 0.2% of subjects who received
220 FLULAVAL QUADRIVALENT, FLUARIX TIV-1 (B Victoria), or TIV-2 (B Yamagata),
221 respectively.

222 Trial 3 (NCT01218308) was a randomized, observer-blind, non-influenza vaccine-controlled
223 trial evaluating the efficacy of FLULAVAL QUADRIVALENT. The trial included subjects aged
224 3 through 8 years who received FLULAVAL QUADRIVALENT (n = 2,584) or HAVRIX[®]
225 (Hepatitis A Vaccine) (n = 2,584) as a control vaccine. Children with no history of influenza
226 vaccination received 2 doses of FLULAVAL QUADRIVALENT or HAVRIX approximately
227 28 days apart (this dosing regimen for HAVRIX is not a U.S.-licensed schedule). Children with a
228 history of influenza vaccination received one dose of FLULAVAL QUADRIVALENT or
229 HAVRIX. In the overall population, 52% were male; 60% were Asian, 5% were white, and 35%
230 were of other racial/ethnic groups. The mean age of subjects was 5 years. Solicited local adverse
231 reactions and systemic adverse events were collected for 7 days (day of vaccination and the next
232 6 days). The incidence of local adverse reactions and systemic adverse events occurring within 7
233 days of vaccination in children are shown in Table 5.

234 **Table 5. FLULAVAL QUADRIVALENT: Incidence of Solicited Local Adverse Reactions**
 235 **and Systemic Adverse Events within 7 Days^a of First Vaccination in Children Aged 3**
 236 **through 8 Years^b (Total Vaccinated Cohort)**

	FLULAVAL QUADRIVALENT		HAVRIX ^c	
	%		%	
	Any	Grade 3 ^d	Any	Grade 3 ^d
Aged 3 through 8 Years				
Local Adverse Reactions	n = 2,546		n = 2,551	
Pain	39.4	0.9	27.8	0.7
Swelling	1.0	0.0	0.3	0.0
Redness	0.4	0.0	0.2	0.0
Aged 3 through 4 Years				
Systemic Adverse Events	n = 898		n = 895	
Loss of appetite	9.0	0.3	8.2	0.4
Irritability	8.1	0.4	7.5	0.1
Drowsiness	7.7	0.4	7.3	0.0
Fever ^e	3.8	1.2	4.4	1.3
Aged 5 through 8 Years				
Systemic Adverse Events	n = 1,648		n = 1,654	
Muscle aches	12.0	0.1	9.7	0.2
Headache	10.5	0.4	10.6	0.8
Fatigue	8.4	0.1	7.1	0.3
Arthralgia	6.3	0.1	4.5	0.1
Gastrointestinal symptoms ^f	5.5	0.2	5.9	0.3
Shivering	3.0	0.1	2.5	0.1
Fever ^e	2.7	0.6	2.7	0.7

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

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

240 ^b Trial 3: NCT01218308.

241 ^c Hepatitis A Vaccine used as a control vaccine.

242 ^d Grade 3 pain: Defined as cried when limb was moved/spontaneously painful (children
 243 <5 years), or significant pain at rest, prevented normal everyday activities (children ≥5 years).

244 Grade 3 swelling, redness: Defined as >100 mm.

245 Grade 3 loss of appetite: Defined as not eating at all.

246 Grade 3 irritability: Defined as crying that could not be comforted/prevented normal activity.

247 Grade 3 drowsiness: Defined as prevented normal activity.

248 Grade 3 (or higher) fever: Defined as ≥102.2°F (39.0°C).

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

251 ^e Fever: Defined as ≥100.4°F (38.0°C).

252 ^f Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.
253 In children who received a second dose of FLULAVAL QUADRIVALENT or HAVRIX, the
254 incidences of adverse events following the second dose were generally lower than those
255 observed after the first dose.

256 The frequency of unsolicited adverse events occurring within 28 days of vaccination was similar
257 in both groups (33% for both FLULAVAL QUADRIVALENT and HAVRIX). The unsolicited
258 adverse events that occurred most frequently ($\geq 1\%$ for FLULAVAL QUADRIVALENT)
259 included diarrhea, pyrexia, gastroenteritis, nasopharyngitis, upper respiratory tract infection,
260 varicella, cough, and rhinorrhea. Serious adverse events occurring within 28 days of any
261 vaccination were reported in 0.7% of subjects who received FLULAVAL QUADRIVALENT
262 and in 0.2% of subjects who received HAVRIX.

263 **6.2 Postmarketing Experience**

264 The following adverse events have been spontaneously reported during postapproval use of
265 FLULAVAL QUADRIVALENT or FLULAVAL (trivalent influenza vaccine). Because these
266 events are reported voluntarily from a population of uncertain size, it is not always possible to
267 reliably estimate their incidence rate or establish a causal relationship to the vaccine. Adverse
268 events were included based on one or more of the following factors: severity, frequency of
269 reporting, or strength of evidence for a causal relationship to FLULAVAL QUADRIVALENT or
270 FLULAVAL.

271 *Blood and Lymphatic System Disorders:* Lymphadenopathy.

272 *Eye Disorders:* Eye pain, photophobia.

273 *Gastrointestinal Disorders:* Dysphagia, vomiting.

274 *General Disorders and Administration Site Conditions:* Chest pain, injection site
275 inflammation, asthenia, injection site rash, influenza-like symptoms, abnormal gait, injection site
276 bruising, injection site sterile abscess.

277 *Immune System Disorders:* Allergic reactions including anaphylaxis, angioedema.

278 *Infections and Infestations:* Rhinitis, laryngitis, cellulitis.

279 *Musculoskeletal and Connective Tissue Disorders:* Muscle weakness, arthritis.

280 *Nervous System Disorders:* Dizziness, paresthesia, hypoesthesia, hypokinesia, tremor,
281 somnolence, syncope, Guillain-Barré syndrome, convulsions/seizures, facial or cranial nerve
282 paralysis, encephalopathy, limb paralysis.

283 *Psychiatric Disorders:* Insomnia.

284 *Respiratory, Thoracic, and Mediastinal Disorders:* Dyspnea, dysphonia, bronchospasm,
285 throat tightness.

286 *Skin and Subcutaneous Tissue Disorders:* Urticaria, localized or generalized rash, pruritus,
287 sweating.

288 *Vascular Disorders:* Flushing, pallor.

289 **7 DRUG INTERACTIONS**

290 **7.1 Concomitant Administration with Other Vaccines**

291 FLULAVAL QUADRIVALENT should not be mixed with any other vaccine in the same
292 syringe or vial.

293 There are insufficient data to assess the concomitant administration of FLULAVAL
294 QUADRIVALENT with other vaccines. When concomitant administration of other vaccines is
295 required, the vaccines should be administered at different injection sites.

296 **7.2 Immunosuppressive Therapies**

297 Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic
298 drugs, and corticosteroids (used in greater than physiologic doses) may reduce the immune
299 response to FLULAVAL QUADRIVALENT.

300 **8 USE IN SPECIFIC POPULATIONS**

301 **8.1 Pregnancy**

302 Pregnancy Exposure Registry

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

306 Risk Summary

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

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

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

316 Clinical Considerations

317 *Disease-Associated Maternal and/or Embryo/Fetal Risk:* Pregnant women infected with
318 seasonal influenza are at increased risk of severe illness associated with influenza infection

319 compared with non-pregnant women. Pregnant women with influenza may be at increased risk
320 for adverse pregnancy outcomes, including preterm labor and delivery.

321 Data

322 *Animal Data:* In a developmental toxicity study, female rats were administered FLULAVAL
323 QUADRIVALENT by intramuscular injection 4 and 2 weeks prior to mating, on gestation Days
324 3, 8, 11, and 15, and on lactation Day 7. The total dose was 0.2 mL at each occasion (a single
325 human dose is 0.5 mL). No adverse effects on pre-weaning development up to post-natal Day 25
326 were observed. There were no vaccine-related fetal malformations or variations.

327 **8.2 Lactation**

328 Risk Summary

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

336 **8.4 Pediatric Use**

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

339 **8.5 Geriatric Use**

340 In a randomized, double-blind, active-controlled trial, immunogenicity and safety were evaluated
341 in a cohort of subjects aged 65 years and older who received FLULAVAL QUADRIVALENT
342 (n = 397); approximately one-third of these subjects were aged 75 years and older. In subjects
343 aged 65 years and older, the geometric mean antibody titers (GMTs) post-vaccination and
344 seroconversion rates were lower than in younger subjects (aged 18 to 64 years) and the
345 frequencies of solicited and unsolicited adverse events were generally lower than in younger
346 subjects [*see Adverse Reactions (6.1), Clinical Studies (14.2)*].

347 **11 DESCRIPTION**

348 FLULAVAL QUADRIVALENT, Influenza Vaccine, for intramuscular injection, is a
349 quadrivalent, split-virion, inactivated influenza virus vaccine prepared from virus propagated in
350 the allantoic cavity of embryonated hens' eggs. Each of the influenza viruses is produced and
351 purified separately. The virus is inactivated with ultraviolet light treatment followed by
352 formaldehyde treatment, purified by centrifugation, and disrupted with sodium deoxycholate.

353 FLULAVAL QUADRIVALENT is a sterile, opalescent, translucent to off-white suspension in a

354 phosphate-buffered saline solution that may sediment slightly. The sediment resuspends upon
355 shaking to form a homogeneous suspension.

356 FLULAVAL QUADRIVALENT has been standardized according to USPHS requirements for
357 the 2016-2017 influenza season and is formulated to contain 60 micrograms (mcg)
358 hemagglutinin (HA) per 0.5-mL dose in the recommended ratio of 15 mcg HA of each of the
359 following 4 viruses (two A strains and two B strains): A/California/7/2009 NYMC X-179A
360 (H1N1), A/Hong Kong/4801/2014 (H3N2) NYMC X-263B, B/Phuket/3073/2013, and
361 B/Brisbane/60/2008.

362 The prefilled syringe is formulated without preservatives and does not contain thimerosal. Each
363 0.5-mL dose from the multi-dose vial contains 50 mcg thimerosal (<25 mcg mercury);
364 thimerosal, a mercury derivative, is added as a preservative.

365 Each 0.5-mL dose of either presentation may also contain residual amounts of ovalbumin
366 (≤ 0.3 mcg), formaldehyde (≤ 25 mcg), sodium deoxycholate (≤ 50 mcg), α -tocopheryl hydrogen
367 succinate (≤ 320 mcg), and polysorbate 80 (≤ 887 mcg) from the manufacturing process.
368 Antibiotics are not used in the manufacture of this vaccine.

369 The tip caps and plungers of the prefilled syringes are not made with natural rubber latex. The
370 vial stoppers are not made with natural rubber latex.

371 **12 CLINICAL PHARMACOLOGY**

372 **12.1 Mechanism of Action**

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

376 Public health authorities recommend influenza vaccine strains annually. Inactivated influenza
377 vaccines are standardized to contain the hemagglutinins of strains representing the influenza
378 viruses likely to circulate in the United States during the influenza season.

379 Specific levels of hemagglutination inhibition (HI) antibody titer post-vaccination with
380 inactivated influenza virus vaccines have not been correlated with protection from influenza
381 illness but the antibody titers have been used as a measure of vaccine activity. In some human
382 challenge studies, antibody titers of $\geq 1:40$ have been associated with protection from influenza
383 illness in up to 50% of subjects.^{1,2} Antibody against one influenza virus type or subtype confers
384 little or no protection against another virus. Furthermore, antibody to one antigenic variant of
385 influenza virus might not protect against a new antigenic variant of the same type or subtype.
386 Frequent development of antigenic variants through antigenic drift is the virological basis for
387 seasonal epidemics and the reason for the usual change of one or more new strains in each year's
388 influenza vaccine.

389 Annual revaccination is recommended because immunity declines during the year after

390 vaccination and because circulating strains of influenza virus change from year to year.

391 **13 NONCLINICAL TOXICOLOGY**

392 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

396 **14 CLINICAL STUDIES**

397 **14.1 Efficacy against Influenza**

398 The efficacy of FLULAVAL QUADRIVALENT was evaluated in Trial 3, a randomized,
399 observer-blind, non-influenza vaccine-controlled trial conducted in 3 countries in Asia, 3 in Latin
400 America, and 2 in the Middle East/Europe during the 2010-2011 influenza season. Healthy
401 subjects aged 3 through 8 years were randomized (1:1) to receive FLULAVAL
402 QUADRIVALENT (n = 2,584), containing A/California/7/2009 (H1N1), A/Victoria/210/2009
403 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/4/2006 (Yamagata lineage)
404 influenza strains, or HAVRIX (n = 2,584), as a control vaccine. Children with no history of
405 influenza vaccination received 2 doses of FLULAVAL QUADRIVALENT or HAVRIX
406 approximately 28 days apart. Children with a history of influenza vaccination received one dose
407 of FLULAVAL QUADRIVALENT or HAVRIX [*see Adverse Reactions (6.1)*]. In the overall
408 population, 52% were male; 60% were Asian, 5% were white, and 35% were of other
409 racial/ethnic groups. The mean age of subjects was 5 years.

410 Efficacy of FLULAVAL QUADRIVALENT was assessed for the prevention of reverse
411 transcriptase polymerase chain reaction (RT-PCR)-positive influenza A and/or B disease
412 presenting as influenza-like illness (ILI). ILI was defined as a temperature $\geq 100^{\circ}\text{F}$ in the
413 presence of at least one of the following symptoms on the same day: cough, sore throat, runny
414 nose, or nasal congestion. Subjects with ILI (monitored by passive and active surveillance for
415 approximately 6 months) had nasal and throat swabs collected and tested for influenza A and/or
416 B by RT-PCR. All RT-PCR-positive specimens were further tested in cell culture. Vaccine
417 efficacy was calculated based on the ATP cohort for efficacy (Table 6).

418 **Table 6. FLULAVAL QUADRIVALENT: Influenza Attack Rates and Vaccine Efficacy**
 419 **against Influenza A and/or B in Children Aged 3 through 8 Years^a (According-to-Protocol**
 420 **Cohort for Efficacy)**

	N ^b	n ^c	Influenza Attack Rate % (n/N)	Vaccine Efficacy % (CI)
All RT-PCR-Positive Influenza				
FLULAVAL QUADRIVALENT	2,379	58	2.4	55.4 ^d (95% CI: 39.1, 67.3)
HAVRIX ^e	2,398	128	5.3	–
All Culture-Confirmed Influenza^f				
FLULAVAL QUADRIVALENT	2,379	50	2.1	55.9 (97.5% CI: 35.4, 69.9)
HAVRIX ^e	2,398	112	4.7	–
Antigenically Matched Culture-Confirmed Influenza				
FLULAVAL QUADRIVALENT	2,379	31	1.3	45.1 ^g (97.5% CI: 9.3, 66.8)
HAVRIX ^e	2,398	56	2.3	–

421 CI = Confidence Interval; RT-PCR = Reverse transcriptase polymerase chain reaction.

422 ^a Trial 3: NCT01218308.

423 ^b According-to-protocol cohort for efficacy included subjects who met all eligibility criteria,
 424 were successfully contacted at least once post-vaccination, and complied with the protocol-
 425 specified efficacy criteria.

426 ^c Number of influenza cases.

427 ^d Vaccine efficacy for FLULAVAL QUADRIVALENT met the pre-defined criterion of >30%
 428 for the lower limit of the 2-sided 95% CI.

429 ^e Hepatitis A Vaccine used as a control vaccine.

430 ^f Of 162 culture-confirmed influenza cases, 108 (67%) were antigenically typed (87 matched;
 431 21 unmatched); 54 (33%) could not be antigenically typed [but were typed by RT-PCR and
 432 nucleic acid sequence analysis: 5 cases A (H1N1) (5 with HAVRIX), 47 cases A (H3N2) (10
 433 with FLULAVAL QUADRIVALENT; 37 with HAVRIX), and 2 cases B Victoria (2 with
 434 HAVRIX)].

435 ^g Since only 67% of cases could be typed, the clinical significance of this result is unknown.

436 In an exploratory analysis by age, vaccine efficacy against RT-PCR-positive influenza A and/or
 437 B disease presenting as ILI was evaluated in subjects aged 3 through 4 years and 5 through
 438 8 years; vaccine efficacy was 35.3% (95% CI: -1.3, 58.6) and 67.7% (95% CI: 49.7, 79.2),
 439 respectively. As the trial lacked statistical power to evaluate efficacy within age subgroups, the
 440 clinical significance of these results is unknown.

441 As a secondary objective in the trial, subjects with RT-PCR-positive influenza A and/or B were

442 prospectively classified based on the presence of adverse outcomes that have been associated
 443 with influenza infection (defined as fever >102.2°F/39.0°C, physician-verified shortness of
 444 breath, pneumonia, wheezing, bronchitis, bronchiolitis, pulmonary congestion, croup, and/or
 445 acute otitis media, and/or physician-diagnosed serious extra-pulmonary complications, including
 446 myositis, encephalitis, seizure and/or myocarditis).

447 The risk reduction of fever >102.2°F/39.0°C associated with RT-PCR-positive influenza was
 448 71.0% (95% CI: 44.8, 84.8) based on the ATP cohort for efficacy [FLULAVAL
 449 QUADRIVALENT (n = 12/2,379); HAVRIX (n = 41/2,398)]. The other pre-specified adverse
 450 outcomes had too few cases to calculate a risk reduction. The incidence of these adverse
 451 outcomes is presented in Table 7.

452 **Table 7. FLULAVAL QUADRIVALENT: Incidence of Adverse Outcomes Associated with**
 453 **RT-PCR-Positive Influenza in Children Aged 3 through 8 Years^a (Total Vaccinated**
 454 **Cohort)^b**

Adverse Outcome ^d	FLULAVAL QUADRIVALENT n = 2,584			HAVRIX ^c n = 2,584		
	Number of Events	Number of Subjects ^e	%	Number of Events	Number of Subjects ^e	%
Fever >102.2°F/39.0°C	16 ^f	15	0.6	51 ^f	50	1.9
Shortness of breath	0	0	0	5	5	0.2
Pneumonia	0	0	0	3	3	0.1
Wheezing	1	1	0	1	1	0
Bronchitis	1	1	0	1	1	0
Pulmonary congestion	0	0	0	1	1	0
Acute otitis media	0	0	0	1	1	0
Bronchiolitis	0	0	0	0	0	0
Croup	0	0	0	0	0	0
Encephalitis	0	0	0	0	0	0
Myocarditis	0	0	0	0	0	0
Myositis	0	0	0	0	0	0
Seizure	0	0	0	0	0	0

455 ^a Trial 3: NCT01218308.

456 ^b Total vaccinated cohort included all vaccinated subjects for whom data were available.

457 ^c Hepatitis A Vaccine used as a control vaccine.

458 ^d In subjects who presented with more than one adverse outcome, each outcome was counted in
 459 the respective category.

460 ^e Number of subjects presenting with at least one event in each group.

461 ^f One subject in each group had sequential influenza due to influenza type A and type B

462 viruses.

463 14.2 Immunological Evaluation

464 Adults

465 Trial 1 was a randomized, double-blind, active-controlled, safety and immunogenicity trial
466 conducted in subjects aged 18 years and older. In this trial, subjects received FLULAVAL
467 QUADRIVALENT (n = 1,246) or one of two formulations of a comparator trivalent influenza
468 vaccine (FLULAVAL, TIV-1, n = 204 or TIV-2, n = 211), each containing an influenza type B
469 virus that corresponded to one of the two B viruses in FLULAVAL QUADRIVALENT (a type
470 B virus of the Victoria lineage or a type B virus of the Yamagata lineage) [see Adverse Reactions
471 (6.1)].

472 Immune responses, specifically hemagglutination inhibition (HI) antibody titers to each virus
473 strain in the vaccine, were evaluated in sera obtained 21 days after administration of
474 FLULAVAL QUADRIVALENT or the comparators. The immunogenicity endpoint was GMTs
475 adjusted for baseline, performed on the According-to-Protocol (ATP) cohort for whom
476 immunogenicity assay results were available after vaccination. FLULAVAL QUADRIVALENT
477 was non-inferior to both TIVs based on adjusted GMTs (Table 8). The antibody response to
478 influenza B strains contained in FLULAVAL QUADRIVALENT was higher than the antibody
479 response after vaccination with a TIV containing an influenza B strain from a different lineage.
480 There was no evidence that the addition of the second B strain resulted in immune interference to
481 other strains included in the vaccine (Table 8).

482 **Table 8. Non-inferiority of FLULAVAL QUADRIVALENT Relative to Trivalent Influenza**
483 **Vaccine (TIV) 21 Days Post-vaccination in Adults Aged 18 Years and Older^a (According-**
484 **to-Protocol Cohort for Immunogenicity)^b**

Geometric Mean Titers Against	FLULAVAL QUADRIVALENT ^c	TIV-1 (B Victoria) ^d	TIV-2 (B Yamagata) ^e
	n = 1,245-1,246 (95% CI)	n = 204 (95% CI)	n = 210-211 (95% CI)
A/California/7/2009 (H1N1)	204.6 ^f (190.4, 219.9)	176.0 (149.1, 207.7)	149.0 (122.9, 180.7)
A/Victoria/210/2009 (H3N2)	125.4 ^f (117.4, 133.9)	147.5 (124.1, 175.2)	141.0 (118.1, 168.3)
B/Brisbane/60/2008 (Victoria lineage)	177.7 ^f (167.8, 188.1)	135.9 (118.1, 156.5)	71.9 (61.3, 84.2)
B/Florida/4/2006 (Yamagata lineage)	399.7 ^f (378.1, 422.6)	176.9 (153.8, 203.5)	306.6 (266.2, 353.3)

485 CI = Confidence Interval.

486 ^a Trial 1: NCT01196975.

487 ^b According-to-protocol cohort for immunogenicity included all evaluable subjects for whom

488 assay results were available after vaccination for at least one trial vaccine antigen.
489 ^c Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Florida/04/2006
490 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage)
491 ^d Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and
492 B/Brisbane/60/2008 (Victoria lineage)
493 ^e Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and
494 B/Florida/04/2006 (Yamagata lineage).
495 ^f Non-inferior to both TIVs based on adjusted GMTs [upper limit of the 2-sided 95% CI for the
496 GMT ratio (TIV/FLULAVAL QUADRIVALENT) ≤ 1.5]; superior to TIV-1 (B Victoria) with
497 respect to the B strain of Yamagata lineage and to TIV-2 (B Yamagata) with respect to the B
498 strain of Victoria lineage based on adjusted GMTs [lower limit of the 2-sided 95% CI for the
499 GMT ratio (FLULAVAL QUADRIVALENT/TIV) > 1.5].

500 Children

501 Trial 4 was a randomized, observer-blind, active-controlled trial in children aged 6 through 35
502 months which was conducted in the United States and Mexico. In this trial, subjects received
503 0.5 mL of FLULAVAL QUADRIVALENT containing 15 mcg HA of each of the four influenza
504 strains included in the vaccine (n = 1,207); or 0.25 mL of control vaccine FLUZONE[®]
505 QUADRIVALENT (Influenza Vaccine) containing 7.5 mcg HA of each of the four influenza
506 strains included in the vaccine (n = 1,217) [*see Adverse Reactions (6.1)*].

507 Immune responses, specifically HI antibody titers to each virus strain in the vaccine, were
508 evaluated in sera obtained 28 days following completion of vaccination regimen. Previously
509 vaccinated children received one dose and previously unvaccinated children (i.e., unprimed
510 individuals) received two doses 4 weeks apart of FLULAVAL QUADRIVALENT or the
511 comparator. The immunogenicity endpoints were GMTs adjusted for baseline, and the
512 percentage of subjects who achieved seroconversion, defined as a pre-vaccination HI titer of $< 1:10$
513 with a post-vaccination titer $\geq 1:40$ or at least a 4-fold increase in serum HI titer over baseline to
514 $\geq 1:40$, following vaccination, performed on the ATP cohort. FLULAVAL QUADRIVALENT
515 was non-inferior to the comparator for all 4 vaccine strains based on adjusted GMTs and
516 seroconversion rates (Table 9).

517 **Table 9. Non-inferiority of FLULAVAL QUADRIVALENT Relative to Comparator**
 518 **Quadrivalent Influenza Vaccine at 28 Days Post-vaccination in Children Aged 6 through**
 519 **35 Months^a (According-to-Protocol Cohort for Immunogenicity)^b**

Adjusted Geometric Mean Titers Against	FLULAVAL QUADRIVALENT^c	Active Comparator^d
	n = 972-974	n = 980
A/California/07/2009 (H1N1)	99.6 ^e	85.1
A/Texas/50/2012 (H3N2)	99.8 ^e	84.6
B/Massachusetts/02/2012 (Yamagata lineage)	258.1 ^e	167.3
B/Brisbane/60/2008 (Victoria lineage)	54.5 ^e	33.7
Seroconversion^f to:	n = 972-974 % (95% CI)	n = 980 % (95% CI)
A/California/07/2009 (H1N1)	73.7 ^e (70.8, 76.4)	67.3 (64.3, 70.3)
A/Texas/50/2012 (H3N2)	76.1 ^e (73.3, 78.8)	69.4 (66.4, 72.3)
B/Massachusetts/02/2012 (Yamagata lineage)	85.5 ^e (83.2, 87.7)	73.8 (70.9, 76.5)
B/Brisbane/60/2008 (Victoria lineage)	64.9 ^e (61.8, 67.9)	48.5 (45.3, 51.6)

520 CI = Confidence Interval.

521 ^a Trial 4: NCT02242643.

522 ^b According-to-protocol cohort for immunogenicity included all evaluable subjects for whom
 523 assay results were available after vaccination for at least one trial vaccine antigen.

524 ^c A 0.5-mL dose containing 15 mcg each of A/California/07/2009 (H1N1), A/Texas/50/2012
 525 (H3N2), B/Massachusetts/02/2012 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria
 526 lineage).

527 ^d A 0.25-mL dose of U.S.-licensed quadrivalent, inactivated influenza vaccine (manufactured
 528 by Sanofi Pasteur Inc.) containing 7.5 mcg each of A/California/07/2009 (H1N1),
 529 A/Texas/50/2012 (H3N2), B/Massachusetts/02/2012 (Yamagata lineage), and
 530 B/Brisbane/60/2008 (Victoria lineage).

531 ^e Non-inferior to the comparator vaccine based on adjusted GMTs [upper limit of the 2-sided
 532 95% CI for the GMT ratio (comparator/FLULAVAL QUADRIVALENT) ≤1.5] and
 533 seroconversion rates (upper limit of the 2-sided 95% CI on difference of comparator vaccine

534 minus FLULAVAL QUADRIVALENT $\leq 10\%$).

535 ^f Seroconversion defined as a 4-fold increase in post-vaccination antibody titer from pre-
536 vaccination titer $\geq 1:10$, or an increase in titer from $< 1:10$ to $\geq 1:40$.

537 Trial 2 was a randomized, double-blind, active-controlled trial conducted in children aged
538 3 through 17 years. In this trial, subjects received FLULAVAL QUADRIVALENT (n = 878), or
539 one of two formulations of a comparator trivalent influenza vaccine (FLUARIX, TIV-1, n = 871
540 or TIV-2 n = 878), each containing an influenza type B virus that corresponded to one of the two
541 B viruses in FLULAVAL QUADRIVALENT (a type B virus of the Victoria lineage or a type B
542 virus of the Yamagata lineage) [*see Adverse Reactions (6.1)*].

543 Immune responses, specifically HI antibody titers to each virus strain in the vaccine, were
544 evaluated in sera obtained 28 days following one or 2 doses of FLULAVAL QUADRIVALENT
545 or the comparators. The immunogenicity endpoints were GMTs adjusted for baseline, and the
546 percentage of subjects who achieved seroconversion, defined as at least a 4-fold increase in
547 serum HI titer over baseline to $\geq 1:40$, following vaccination, performed on the ATP cohort.
548 FLULAVAL QUADRIVALENT was non-inferior to both TIVs based on adjusted GMTs and
549 seroconversion rates (Table 10). The antibody response to influenza B strains contained in
550 FLULAVAL QUADRIVALENT was higher than the antibody response after vaccination with a
551 TIV containing an influenza B strain from a different lineage. There was no evidence that the
552 addition of the second B strain resulted in immune interference to other strains included in the
553 vaccine (Table 10).

554 **Table 10. Non-inferiority of FLULAVAL QUADRIVALENT Relative to Trivalent**
555 **Influenza Vaccine (TIV) at 28 Days Post-vaccination in Children Aged 3 through 17 Years^a**
556 **(According-to-Protocol Cohort for Immunogenicity)^b**

Geometric Mean Titers Against	FLULAVAL QUADRIVALENT^c	TIV-1 (B Victoria)^d	TIV-2 (B Yamagata)^e
	n = 878 (95% CI)	n = 871 (95% CI)	n = 877-878 (95% CI)
A/California/7/2009 (H1N1)	362.7 ^f (335.3, 392.3)	429.1 (396.5, 464.3)	420.2 (388.8, 454.0)
A/Victoria/210/2009 (H3N2)	143.7 ^f (134.2, 153.9)	139.6 (130.5, 149.3)	151.0 (141.0, 161.6)
B/Brisbane/60/2008 (Victoria lineage)	250.5 ^f (230.8, 272.0)	245.4 (226.9, 265.4)	68.1 (61.9, 74.9)
B/Florida/4/2006 (Yamagata lineage)	512.5 ^f (477.6, 549.9)	197.0 (180.7, 214.8)	579.0 (541.2, 619.3)
Seroconversion^g to:	n = 876 % (95% CI)	n = 870 % (95% CI)	n = 876-877 % (95% CI)
A/California/7/2009 (H1N1)	84.4 ^f (81.8, 86.7)	86.8 (84.3, 89.0)	85.5 (83.0, 87.8)
A/Victoria/210/2009 (H3N2)	70.1 ^f (66.9, 73.1)	67.8 (64.6, 70.9)	69.6 (66.5, 72.7)
B/Brisbane/60/2008 (Victoria lineage)	74.5 ^f (71.5, 77.4)	71.5 (68.4, 74.5)	29.9 (26.9, 33.1)
B/Florida/4/2006 (Yamagata lineage)	75.2 ^f (72.2, 78.1)	41.3 (38.0, 44.6)	73.4 (70.4, 76.3)

557 CI = Confidence Interval.

558 ^a Trial 2: NCT01198756.

559 ^b According-to-protocol cohort for immunogenicity included all evaluable subjects for whom
560 assay results were available after vaccination for at least one trial vaccine antigen.

561 ^c Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Florida/04/2006
562 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage).

563 ^d Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and
564 B/Brisbane/60/2008 (Victoria lineage).

565 ^e Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and
566 B/Florida/04/2006 (Yamagata lineage).

567 ^f Non-inferior to both TIVs based on adjusted GMTs [upper limit of the 2-sided 95% CI for the
568 GMT ratio (TIV/FLULAVAL QUADRIVALENT) ≤1.5] and seroconversion rates (upper
569 limit of the 2-sided 95% CI on difference of the TIV minus FLULAVAL QUADRIVALENT
570 ≤10%); superior to TIV-1 (B Victoria) with respect to the B strain of Yamagata lineage and to
571 TIV-2 (B Yamagata) with respect to the B strain of Victoria lineage based on adjusted GMTs

572 [lower limit of the 2-sided 95% CI for the GMT ratio (FLULAVAL
573 QUADRIVALENT/TIV) >1.5] and seroconversion rates (lower limit of the 2-sided 95% CI
574 on difference of FLULAVAL QUADRIVALENT minus the TIV >10%).

575 ^g Seroconversion defined as a 4-fold increase in post-vaccination antibody titer from pre-
576 vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40.

577 **15 REFERENCES**

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- 580 2. Hobson D, Curry RL, Beare AS, et al. The role of serum haemagglutination-inhibiting
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582 *Camb* 1972;70:767-777.

583 **16 HOW SUPPLIED/STORAGE AND HANDLING**

584 FLULAVAL QUADRIVALENT is available in 0.5-mL single-dose disposable prefilled TIP-
585 LOK syringes (packaged without needles) and in 5-mL multi-dose vials containing 10 doses
586 (0.5-mL each).

587 NDC 19515-908-41 Syringe in Package of 10: NDC 19515-908-52

588 NDC 19515-903-01 Multi-Dose Vial (containing 10 doses) in Package of 1: NDC 19515-903-11

589 Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has
590 been frozen. Store in the original package to protect from light. Once entered, a multi-dose vial
591 should be discarded after 28 days.

592 **17 PATIENT COUNSELING INFORMATION**

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

- 594 • Inform of the potential benefits and risks of immunization with FLULAVAL
595 QUADRIVALENT.
- 596 • Educate regarding potential side effects, emphasizing that (1) FLULAVAL
597 QUADRIVALENT contains non-infectious killed viruses and cannot cause influenza, and
598 (2) FLULAVAL QUADRIVALENT is intended to provide protection against illness due to
599 influenza viruses only, and cannot provide protection against all respiratory illness.
- 600 • Encourage women exposed to FLULAVAL QUADRIVALENT during pregnancy to enroll
601 in the pregnancy registry [*see Use in Specific Populations (8.1)*].
- 602 • Give the Vaccine Information Statements, which are required by the National Childhood
603 Vaccine Injury Act of 1986 prior to each immunization. These materials are available free of
604 charge at the Centers for Disease Control and Prevention (CDC) website
605 (www.cdc.gov/vaccines).

606 • Instruct that annual revaccination is recommended.
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