

## 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

2015-2016 Formula

Initial U.S. Approval: 2013

#### 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 3 years of age and older. (1)

#### DOSAGE AND ADMINISTRATION

For intramuscular injection only. (2)

Age	Vaccination Status	Dose and Schedule
Aged 3 through 8 years	Not previously vaccinated with influenza vaccine	Two doses (0.5-mL each) at least 4 weeks apart (2.1)
	Vaccinated with influenza vaccine in a previous season	One or two doses <sup>a</sup> (0.5-mL each) (2.1)
Aged 9 years and older	Not applicable	One 0.5-mL dose (2.1)

<sup>a</sup> One dose or two doses (0.5-mL each) depending on vaccination history as per the annual Advisory Committee on Immunization Practices (ACIP) recommendation on prevention and control of influenza with vaccines. If two doses, administer each 0.5-mL dose at least 4 weeks apart. (2.1)

#### DOSAGE FORMS AND STRENGTHS

Suspension for injection in 0.5-mL single-dose prefilled syringes and 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 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](http://www.vaers.hhs.gov).

#### USE IN SPECIFIC POPULATIONS

- Safety and effectiveness of FLULAVAL QUADRIVALENT have not been established in pregnant women or nursing mothers. (8.1, 8.3)
- Register women who receive FLULAVAL QUADRIVALENT while pregnant in the pregnancy registry by calling 1-888-452-9622. (8.1)
- Geriatric Use: Antibody responses were lower in geriatric subjects who received FLULAVAL QUADRIVALENT than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: XX/201X

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1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

3 FLULAVAL<sup>®</sup> 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 3 years of age and older.

6 **2 DOSAGE AND ADMINISTRATION**

7 **For intramuscular injection only.**

8 **2.1 Dosage and Schedule**

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

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

<b>Age</b>	<b>Vaccination Status</b>	<b>Dose and Schedule</b>
Aged 3 through 8 years	Not previously vaccinated with influenza vaccine	Two doses (0.5-mL each) at least 4 weeks apart
	Vaccinated with influenza vaccine in a previous season	One or two doses <sup>a</sup> (0.5-mL each)
Aged 9 years and older	Not applicable	One 0.5-mL dose

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

15 **2.2 Administration Instructions**

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

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

20 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 site for intramuscular injection is the deltoid muscle of the upper arm. Do not  
29 inject in the gluteal area or areas where there may be a major nerve trunk.  
30 Do not administer this product intravenously, intradermally, or subcutaneously.

### 31 **3 DOSAGE FORMS AND STRENGTHS**

32 FLULAVAL QUADRIVALENT is a suspension for injection available in 0.5-mL prefilled  
33 TIP-LOK<sup>®</sup> syringes and 5-mL multi-dose vials containing 10 doses (each dose is 0.5 mL).

### 34 **4 CONTRAINDICATIONS**

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

### 38 **5 WARNINGS AND PRECAUTIONS**

#### 39 **5.1 Guillain-Barré Syndrome**

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

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

#### 46 **5.2 Syncope**

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

#### 51 **5.3 Preventing and Managing Allergic Vaccine Reactions**

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

#### 56 **5.4 Altered Immunocompetence**

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

60 **5.5 Limitations of Vaccine Effectiveness**

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

62 **5.6 Persons at Risk of Bleeding**

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

66 **6 ADVERSE REACTIONS**

67 **6.1 Clinical Trials Experience**

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

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

76 In children aged 3 through 17 years who received FLULAVAL QUADRIVALENT, the most  
77 common ( $\geq 10\%$ ) solicited local adverse reaction was pain (65%). In children aged 3 through  
78 4 years, the most common ( $\geq 10\%$ ) solicited systemic adverse events were irritability (26%),  
79 drowsiness (21%), and loss of appetite (17%). In children aged 5 through 17 years, the most  
80 common ( $\geq 10\%$ ) systemic adverse events were muscle aches (29%), fatigue (22%), headache  
81 (22%), arthralgia (13%), and gastrointestinal symptoms (10%).

82 FLULAVAL QUADRIVALENT has been administered to 1,384 adults aged 18 years and older  
83 and 3,516 pediatric subjects aged 3 through 17 years in 4 clinical trials.

84 **FLULAVAL QUADRIVALENT in Adults**

85 Trial 1 was a randomized, double-blind, active-controlled, safety and immunogenicity trial. In  
86 this trial, subjects received FLULAVAL QUADRIVALENT (N = 1,272), or one of two  
87 formulations of a comparator trivalent influenza vaccine (FLULAVAL, TIV-1, N = 213 or TIV-  
88 2, N = 218), each containing an influenza type B virus that corresponded to one of the two B  
89 viruses in FLULAVAL QUADRIVALENT (a type B virus of the Victoria lineage or a type B  
90 virus of the Yamagata lineage). The population was aged 18 years and older (mean age:  
91 50 years) and 61% were female; 61% of subjects were white, 3% were black, 1% were Asian,  
92 and 35% were of other racial/ethnic groups. Solicited adverse events were collected for 7 days  
93 (day of vaccination and the next 6 days). The incidence of local adverse reactions and systemic  
94 adverse events occurring within 7 days of vaccination in adults are shown in Table 2.

95 **Table 2. FLULAVAL QUADRIVALENT: Incidence of Solicited Local Adverse Reactions**  
 96 **and Systemic Adverse Events within 7 Days<sup>a</sup> of Vaccination in Adults Aged 18 Years and**  
 97 **Older<sup>b</sup> (Total Vaccinated Cohort)**

	FLULAVAL QUADRIVALENT <sup>c</sup> N = 1,260 %	Trivalent Influenza Vaccine (TIV)	
		TIV-1 (B Victoria) <sup>d</sup> N = 208 %	TIV-2 (B Yamagata) <sup>e</sup> N = 216 %
<b>Local Adverse Reactions</b>			
Pain	60	45	41
Swelling	3	1	4
Redness	2	3	1
<b>Systemic Adverse Events</b>			
Muscle aches	26	25	19
Headache	22	20	23
Fatigue	22	22	17
Arthralgia	15	17	15
Gastrointestinal symptoms <sup>f</sup>	9	10	7
Shivering	9	8	6
Fever ≥100.4°F (38.0°C)	2	1	1

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

100 <sup>a</sup> 7 days included day of vaccination and the subsequent 6 days.

101 <sup>b</sup> Trial 1: NCT01196975.

102 <sup>c</sup> Contained two A strains and two B strains, one of Victoria lineage and one of Yamagata  
 103 lineage.

104 <sup>d</sup> Contained two A strains and a B strain of Victoria lineage.

105 <sup>e</sup> Contained the same two A strains as FLULAVAL and a B strain of Yamagata lineage.

106 <sup>f</sup> Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

107 Unsolicited adverse events occurring within 21 days of vaccination were reported in 19%, 23%,  
 108 and 23% of subjects who received FLULAVAL QUADRIVALENT (N = 1,272), TIV-1  
 109 (B Victoria) (N = 213), or TIV-2 (B Yamagata) (N = 218), respectively. The unsolicited adverse  
 110 events that occurred most frequently (≥1% for FLULAVAL QUADRIVALENT) included  
 111 nasopharyngitis, upper respiratory tract infection, headache, cough and oropharyngeal pain.  
 112 Serious adverse events occurring within 21 days of vaccination were reported in 0.4%, 0%, and  
 113 0% of subjects who received FLULAVAL QUADRIVALENT, TIV-1 (B Victoria), or TIV-2  
 114 (B Yamagata), respectively.

115 FLULAVAL QUADRIVALENT in Children

116 Trial 2 was a randomized, double-blind, active-controlled trial. In this trial, subjects received  
117 FLULAVAL QUADRIVALENT (N = 932), or one of two formulations of a comparator trivalent  
118 influenza vaccine [FLUARIX<sup>®</sup> (Influenza Vaccine), TIV-1, N = 929 or TIV-2, N = 932], each  
119 containing an influenza type B virus that corresponded to one of the two B viruses in  
120 FLULAVAL QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the  
121 Yamagata lineage). The population was aged 3 through 17 years (mean age: 9 years) and 53%  
122 were male; 65% were white, 13% were Asian, 9% were black, and 13% were of other  
123 racial/ethnic groups. Children aged 3 through 8 years with no history of influenza vaccination  
124 received 2 doses approximately 28 days apart. Children aged 3 through 8 years with a history of  
125 influenza vaccination and children aged 9 years and older received one dose. Solicited local  
126 adverse reactions and systemic adverse events were collected for 7 days (day of vaccination and  
127 the next 6 days). The incidence of local adverse reactions and systemic adverse events occurring  
128 within 7 days of vaccination in children are shown in Table 3.

129 **Table 3. FLULAVAL QUADRIVALENT: Incidence of Solicited Local Adverse Reactions**  
 130 **and Systemic Adverse Events within 7 Days<sup>a</sup> of First Vaccination in Children Aged 3**  
 131 **through 17 Years<sup>b</sup> (Total Vaccinated Cohort)**

	FLULAVAL QUADRIVALENT <sup>c</sup> %	Trivalent Influenza Vaccine (TIV)	
		TIV-1 (B Victoria) <sup>d</sup> %	TIV-2 (B Yamagata) <sup>e</sup> %
<b>Aged 3 through 17 Years</b>			
<b>Local Adverse Reactions</b>	<b>N = 913</b>	<b>N = 911</b>	<b>N = 915</b>
Pain	65	55	56
Swelling	6	3	4
Redness	5	3	4
<b>Aged 3 through 4 Years</b>			
<b>Systemic Adverse Events</b>	<b>N = 185</b>	<b>N = 187</b>	<b>N = 189</b>
Irritability	26	17	22
Drowsiness	21	20	23
Loss of appetite	17	16	13
Fever ≥100.4°F (38.0°C)	5	6	4
<b>Aged 5 through 17 Years</b>			
<b>Systemic Adverse Events</b>	<b>N = 727</b>	<b>N = 724</b>	<b>N = 725</b>
Muscle aches	29	25	25
Fatigue	22	24	23
Headache	22	22	20
Arthralgia	13	12	11
Gastrointestinal symptoms <sup>f</sup>	10	10	9
Shivering	7	7	7
Fever ≥100.4°F (38.0°C)	2	4	3

132 Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were  
 133 available.

134 <sup>a</sup> 7 days included day of vaccination and the subsequent 6 days.

135 <sup>b</sup> Trial 2: NCT01198756.

136 <sup>c</sup> Contained two A strains and two B strains, one of Victoria lineage and one of Yamagata  
 137 lineage.

138 <sup>d</sup> Contained two A strains and a B strain of Victoria lineage.

139 <sup>e</sup> Contained the same two A strains as FLUARIX and a B strain of Yamagata lineage.

140 <sup>f</sup> Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

141 In children who received a second dose of FLULAVAL QUADRIVALENT, FLUARIX TIV-1  
 142 (B Victoria), or TIV-2 (B Yamagata), the incidences of adverse events following the second dose

143 were generally lower than those observed after the first dose.

144 Unsolicited adverse events occurring within 28 days of vaccination were reported in 30%, 31%  
145 and 30% of subjects who received FLULAVAL QUADRIVALENT (N = 932), FLUARIX TIV-  
146 1 (B Victoria) (N = 929), or TIV-2 (B Yamagata) (N = 932), respectively. The unsolicited  
147 adverse events that occurred most frequently ( $\geq 1\%$  for FLULAVAL QUADRIVALENT)  
148 included vomiting, pyrexia, bronchitis, nasopharyngitis, pharyngitis, upper respiratory tract  
149 infection, headache, cough, oropharyngeal pain, and rhinorrhea. Serious adverse events  
150 occurring within 28 days of any vaccination were reported in 0.1%, 0.2%, and 0.2% of subjects  
151 who received FLULAVAL QUADRIVALENT, FLUARIX TIV-1 (B Victoria), or TIV-2  
152 (B Yamagata), respectively.

153 Trial 3 was a randomized, observer-blind, non-influenza vaccine-controlled trial evaluating the  
154 efficacy of FLULAVAL QUADRIVALENT. The trial included subjects aged 3 through 8 years  
155 who received FLULAVAL QUADRIVALENT (N = 2,584) or HAVRIX<sup>®</sup> (Hepatitis A Vaccine)  
156 (N = 2,584), as a control vaccine. Children with no history of influenza vaccination received  
157 2 doses of FLULAVAL QUADRIVALENT or HAVRIX approximately 28 days apart. Children  
158 with a history of influenza vaccination received one dose of FLULAVAL QUADRIVALENT or  
159 HAVRIX. In the overall population, 52% were male; 60% were Asian, 5% were white, and 35%  
160 were of other racial/ethnic groups. The mean age of subjects was 5 years. Solicited local adverse  
161 reactions and systemic adverse events were collected for 7 days (day of vaccination and the next  
162 6 days). The incidence of local adverse reactions and systemic adverse events occurring within 7  
163 days of vaccination in children are shown in Table 4.



164 **Table 4. FLULAVAL QUADRIVALENT: Incidence of Solicited Local Adverse Reactions**  
 165 **and Systemic Adverse Events within 7 Days<sup>a</sup> of First Vaccination in Children Aged 3**  
 166 **through 8 Years<sup>b</sup> (Total Vaccinated Cohort)**

	<b>FLULAVAL QUADRIVALENT %</b>	<b>HAVRIX<sup>c</sup> %</b>
<b>Aged 3 through 8 Years</b>		
<b>Local Adverse Reactions</b>	<b>N = 2,546</b>	<b>N = 2,551</b>
Pain	39	28
Swelling	1	0.3
Redness	0.4	0.2
<b>Aged 3 through 4 Years</b>		
<b>Systemic Adverse Events</b>	<b>N = 898</b>	<b>N = 895</b>
Loss of appetite	9	8
Irritability	8	8
Drowsiness	8	7
Fever ≥100.4°F (38.0°C)	4	4
<b>Aged 5 through 8 Years</b>		
<b>Systemic Adverse Events</b>	<b>N = 1,648</b>	<b>N = 1,654</b>
Muscle aches	12	10
Headache	11	11
Fatigue	8	7
Arthralgia	6	5
Gastrointestinal symptoms <sup>d</sup>	6	6
Shivering	3	3
Fever ≥100.4°F (38.0°C)	3	3

167 Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were  
 168 available.

169 <sup>a</sup> 7 days included day of vaccination and the subsequent 6 days.

170 <sup>b</sup> Trial 3: NCT01218308.

171 <sup>c</sup> Hepatitis A Vaccine used as a control vaccine.

172 <sup>d</sup> Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

173 In children who received a second dose of FLULAVAL QUADRIVALENT or HAVRIX, the  
 174 incidences of adverse events following the second dose were generally lower than those  
 175 observed after the first dose.

176 The frequency of unsolicited adverse events occurring within 28 days of vaccination was similar  
 177 in both groups (33% for both FLULAVAL QUADRIVALENT and HAVRIX). The unsolicited  
 178 adverse events that occurred most frequently (≥1% for FLULAVAL QUADRIVALENT)

179 included diarrhea, pyrexia, gastroenteritis, nasopharyngitis, upper respiratory tract infection,  
180 varicella, cough, and rhinorrhea. Serious adverse events occurring within 28 days of any  
181 vaccination were reported in 0.7% of subjects who received FLULAVAL QUADRIVALENT  
182 and in 0.2% of subjects who received HAVRIX.

## 183 **6.2 Postmarketing Experience**

184 There are no postmarketing data available for FLULAVAL QUADRIVALENT. The following  
185 adverse events have been spontaneously reported during postapproval use of FLULAVAL  
186 (trivalent influenza vaccine). Because these events are reported voluntarily from a population of  
187 uncertain size, it is not always possible to reliably estimate their incidence rate or establish a  
188 causal relationship to the vaccine. Adverse events described here are included because: a) they  
189 represent reactions which are known to occur following immunizations generally or influenza  
190 immunizations specifically; b) they are potentially serious; or c) the frequency of reporting.

### 191 Blood and Lymphatic System Disorders

192 Lymphadenopathy.

### 193 Eye Disorders

194 Eye pain, photophobia.

### 195 Gastrointestinal Disorders

196 Dysphagia, vomiting.

### 197 General Disorders and Administration Site Conditions

198 Chest pain, injection site inflammation, asthenia, injection site rash, influenza-like symptoms,  
199 abnormal gait, injection site bruising, injection site sterile abscess.

### 200 Immune System Disorders

201 Allergic reactions including anaphylaxis, angioedema.

### 202 Infections and Infestations

203 Rhinitis, laryngitis, cellulitis.

### 204 Musculoskeletal and Connective Tissue Disorders

205 Muscle weakness, arthritis.

### 206 Nervous System Disorders

207 Dizziness, paresthesia, hypoesthesia, hypokinesia, tremor, somnolence, syncope, Guillain-Barré  
208 syndrome, convulsions/seizures, facial or cranial nerve paralysis, encephalopathy, limb paralysis.

### 209 Psychiatric Disorders

210 Insomnia.

211 Respiratory, Thoracic, and Mediastinal Disorders

212 Dyspnea, dysphonia, bronchospasm, throat tightness.

213 Skin and Subcutaneous Tissue Disorders

214 Urticaria, localized or generalized rash, pruritus, sweating.

215 Vascular Disorders

216 Flushing, pallor.

217 **7 DRUG INTERACTIONS**

218 **7.1 Concomitant Administration with Other Vaccines**

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

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

224 **7.2 Immunosuppressive Therapies**

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

228 **8 USE IN SPECIFIC POPULATIONS**

229 **8.1 Pregnancy**

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

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

244 Pregnancy Registry

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

250 **8.3 Nursing Mothers**

251 It is not known whether FLULAVAL QUADRIVALENT is excreted in human milk. Because  
252 many drugs are excreted in human milk, caution should be exercised when FLULAVAL  
253 QUADRIVALENT is administered to a nursing woman.

254 **8.4 Pediatric Use**

255 Safety and effectiveness of FLULAVAL QUADRIVALENT in children younger than 3 years  
256 have not been established.

257 Safety and immunogenicity of FLULAVAL QUADRIVALENT in children aged 3 through  
258 17 years have been evaluated [*see Adverse Reactions (6.1), Clinical Studies (14.2)*].

259 **8.5 Geriatric Use**

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

267 **11 DESCRIPTION**

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

273 FLULAVAL QUADRIVALENT is a sterile, opalescent, translucent to off-white suspension in a  
274 phosphate-buffered saline solution that may sediment slightly. The sediment resuspends upon  
275 shaking to form a homogeneous suspension.

276 FLULAVAL QUADRIVALENT has been standardized according to USPHS requirements for  
277 the 2015-2016 influenza season and is formulated to contain 60 micrograms (mcg)  
278 hemagglutinin (HA) per 0.5-mL dose in the recommended ratio of 15 mcg HA of each of the  
279 following 4 viruses (two A strains and two B strains): A/California/7/2009 NYMC X-179A

280 (H1N1), A/Switzerland/9715293/2013 NIB-88 (H3N2), B/Phuket/3073/2013, and  
281 B/Brisbane/60/2008.

282 The prefilled syringe is formulated without preservatives and does not contain thimerosal. Each  
283 0.5-mL dose from the multi-dose vial contains 50 mcg thimerosal (<25 mcg mercury);  
284 thimerosal, a mercury derivative, is added as a preservative.

285 Each 0.5-mL dose of either presentation may also contain residual amounts of ovalbumin  
286 ( $\leq 0.3$  mcg), formaldehyde ( $\leq 25$  mcg), sodium deoxycholate ( $\leq 50$  mcg),  $\alpha$ -tocopheryl hydrogen  
287 succinate ( $\leq 320$  mcg) and polysorbate 80 ( $\leq 887$  mcg) from the manufacturing process.

288 Antibiotics are not used in the manufacture of this vaccine.

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

## 291 **12 CLINICAL PHARMACOLOGY**

### 292 **12.1 Mechanism of Action**

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

296 Public health authorities recommend influenza vaccine strains annually. Inactivated influenza  
297 vaccines are standardized to contain the hemagglutinins of strains representing the influenza  
298 viruses likely to circulate in the United States during the influenza season. Two B strain lineages  
299 (Victoria and Yamagata) are of public health importance because they have co-circulated since  
300 2001. FLULAVAL (trivalent influenza vaccine) contains only two influenza A subtype viruses  
301 and one influenza type B virus. In 6 of the last 11 seasons, the most predominant circulating  
302 influenza B lineage was not included in the annual trivalent vaccine. Quadrivalent vaccines, such  
303 as FLULAVAL QUADRIVALENT, contain two influenza A subtype viruses and two influenza  
304 type B viruses (one of the Victoria lineage and one of the Yamagata lineage).

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

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

316 vaccination, and because circulating strains of influenza virus change from year to year.<sup>3</sup>

## 317 **13 NONCLINICAL TOXICOLOGY**

### 318 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

319 FLULAVAL QUADRIVALENT has not been evaluated for carcinogenic or mutagenic  
320 potential. Vaccination of female rats with FLULAVAL QUADRIVALENT, at doses shown to  
321 be immunogenic in the rat, had no effect on fertility.

## 322 **14 CLINICAL STUDIES**

### 323 **14.1 Efficacy against Influenza**

324 The efficacy of FLULAVAL QUADRIVALENT was evaluated in Trial 3, a randomized,  
325 observer-blind, non-influenza vaccine-controlled trial conducted in 3 countries in Asia, 3 in Latin  
326 America, and 2 in the Middle East/Europe during the 2010-2011 influenza season. Healthy  
327 subjects aged 3 through 8 years were randomized (1:1) to receive FLULAVAL  
328 QUADRIVALENT (N = 2,584), containing A/California/7/2009 (H1N1), A/Victoria/210/2009  
329 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/4/2006 (Yamagata lineage)  
330 influenza strains, or HAVRIX (N = 2,584), as a control vaccine. Children with no history of  
331 influenza vaccination received 2 doses of FLULAVAL QUADRIVALENT or HAVRIX  
332 approximately 28 days apart. Children with a history of influenza vaccination received one dose  
333 of FLULAVAL QUADRIVALENT or HAVRIX [*see Adverse Reactions (6.1)*].

334 Efficacy of FLULAVAL QUADRIVALENT was assessed for the prevention of reverse  
335 transcriptase polymerase chain reaction (RT-PCR)-positive influenza A and/or B disease  
336 presenting as influenza-like illness (ILI). ILI was defined as a temperature  $\geq 100^{\circ}\text{F}$  in the  
337 presence of at least one of the following symptoms on the same day: cough, sore throat, runny  
338 nose, or nasal congestion. Subjects with ILI (monitored by passive and active surveillance for  
339 approximately 6 months) had nasal and throat swabs collected and tested for influenza A and/or  
340 B by RT-PCR. All RT-PCR-positive specimens were further tested in cell culture. Vaccine  
341 efficacy was calculated based on the ATP cohort for efficacy (Table 5).

342 **Table 5. FLULAVAL QUADRIVALENT: Influenza Attack Rates and Vaccine Efficacy**  
 343 **against Influenza A and/or B in Children Aged 3 through 8 Years<sup>a</sup> (According-to-Protocol**  
 344 **Cohort for Efficacy)**

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

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

346 <sup>a</sup> Trial 3: NCT01218308.

347 <sup>b</sup> According-to-protocol cohort for efficacy included subjects who met all eligibility criteria,  
 348 were successfully contacted at least once post-vaccination, and complied with the protocol-  
 349 specified efficacy criteria.

350 <sup>c</sup> Number of influenza cases.

351 <sup>d</sup> Vaccine efficacy for FLULAVAL QUADRIVALENT met the pre-defined criterion of >30%  
 352 for the lower limit of the 2-sided 95% CI.

353 <sup>e</sup> Hepatitis A Vaccine used as a control vaccine.

354 <sup>f</sup> Of 162 culture-confirmed influenza cases, 108 (67%) were antigenically typed (87 matched;  
 355 21 unmatched); 54 (33%) could not be antigenically typed [but were typed by RT-PCR and  
 356 nucleic acid sequence analysis: 5 cases A (H1N1) (5 with HAVRIX), 47 cases A (H3N2) (10  
 357 with FLULAVAL QUADRIVALENT; 37 with HAVRIX), and 2 cases B Victoria (2 with  
 358 HAVRIX)].

359 <sup>g</sup> Since only 67% of cases could be typed, the clinical significance of this result is unknown.

360 In an exploratory analysis by age, vaccine efficacy against RT-PCR-positive influenza A and/or  
 361 B disease presenting as ILI was evaluated in subjects aged 3 through 4 years and 5 through  
 362 8 years; vaccine efficacy was 35.3% (95% CI: -1.3, 58.6) and 67.7% (95% CI: 49.7, 79.2),

363 respectively. As the trial lacked statistical power to evaluate efficacy within age subgroups, the  
 364 clinical significance of these results is unknown.

365 As a secondary objective in the trial, subjects with RT-PCR-positive influenza A and/or B were  
 366 prospectively classified based on the presence of adverse outcomes that have been associated  
 367 with influenza infection (defined as fever >102.2°F/39.0°C, physician-verified shortness of  
 368 breath, pneumonia, wheezing, bronchitis, bronchiolitis, pulmonary congestion, croup and/or  
 369 acute otitis media, and/or physician-diagnosed serious extra-pulmonary complications, including  
 370 myositis, encephalitis, seizure and/or myocarditis).

371 The risk reduction of fever >102.2°F/39.0°C associated with RT-PCR-positive influenza was  
 372 71.0% (95% CI: 44.8, 84.8) based on the ATP cohort for efficacy [FLULAVAL  
 373 QUADRIVALENT (n = 12/2,379); HAVRIX (n = 41/2,398)]. The other pre-specified adverse  
 374 outcomes had too few cases to calculate a risk reduction. The incidence of these adverse  
 375 outcomes is presented in Table 6.

376 **Table 6. FLULAVAL QUADRIVALENT: Incidence of Adverse Outcomes Associated with**  
 377 **RT-PCR-positive Influenza in Children Aged 3 through 8 Years<sup>a</sup> (Total Vaccinated**  
 378 **Cohort)<sup>b</sup>**

Adverse Outcome <sup>d</sup>	FLULAVAL QUADRIVALENT N = 2,584			HAVRIX <sup>c</sup> N = 2,584		
	Number of Events	Number of Subjects <sup>e</sup>	%	Number of Events	Number of Subjects <sup>e</sup>	%
Fever >102.2°F/39.0°C	16 <sup>f</sup>	15	0.6	51 <sup>f</sup>	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

379 <sup>a</sup> Trial 3: NCT01218308.

380 <sup>b</sup> Total vaccinated cohort included all vaccinated subjects for whom data were available.

381 <sup>c</sup> Hepatitis A Vaccine used as a control vaccine.



382 <sup>d</sup> In subjects who presented with more than one adverse outcome, each outcome was counted in  
383 the respective category.

384 <sup>e</sup> Number of subjects presenting with at least one event in each group.

385 <sup>f</sup> One subject in each group had sequential influenza due to influenza type A and type B  
386 viruses.

## 387 **14.2 Immunological Evaluation**

### 388 Adults

389 Trial 1 was a randomized, double-blind, active-controlled, safety and immunogenicity trial  
390 conducted in subjects aged 18 years and older. In this trial, subjects received FLULAVAL  
391 QUADRIVALENT (N = 1,246), or one of two formulations of a comparator trivalent influenza  
392 vaccine (FLULAVAL, TIV-1, N = 204 or TIV-2, N = 211), each containing an influenza type B  
393 virus that corresponded to one of the two B viruses in FLULAVAL QUADRIVALENT (a type  
394 B virus of the Victoria lineage or a type B virus of the Yamagata lineage) [*see Adverse Reactions*  
395 (6.1)].

396 Immune responses, specifically hemagglutination inhibition (HI) antibody titers to each virus  
397 strain in the vaccine, were evaluated in sera obtained 21 days after administration of  
398 FLULAVAL QUADRIVALENT or the comparators. The immunogenicity endpoint was GMTs  
399 adjusted for baseline, performed on the According-to-Protocol (ATP) cohort for whom  
400 immunogenicity assay results were available after vaccination. FLULAVAL QUADRIVALENT  
401 was non-inferior to both TIVs based on adjusted GMTs (Table 7). The antibody response to  
402 influenza B strains contained in FLULAVAL QUADRIVALENT was higher than the antibody  
403 response after vaccination with a TIV containing an influenza B strain from a different lineage.  
404 There was no evidence that the addition of the second B strain resulted in immune interference to  
405 other strains included in the vaccine (Table 7).

406 **Table 7. Non-inferiority of FLULAVAL QUADRIVALENT Relative to Trivalent Influenza**  
 407 **Vaccine (TIV) 21 Days Post-vaccination in Adults Aged 18 Years and Older<sup>a</sup> (According-**  
 408 **to-Protocol Cohort for Immunogenicity)<sup>b</sup>**

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

409 CI = Confidence Interval.

410 <sup>a</sup> Trial 1: NCT01196975.

411 <sup>b</sup> According-to-protocol cohort for immunogenicity included all evaluable subjects for whom  
 412 assay results were available after vaccination for at least one trial vaccine antigen.

413 <sup>c</sup> Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Florida/04/2006  
 414 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage)

415 <sup>d</sup> Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and  
 416 B/Brisbane/60/2008 (Victoria lineage)

417 <sup>e</sup> Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and  
 418 B/Florida/04/2006 (Yamagata lineage).

419 <sup>f</sup> Non-inferior to both TIVs based on adjusted GMTs [upper limit of the 2-sided 95% CI for the  
 420 GMT ratio (TIV/FLULAVAL QUADRIVALENT)  $\leq 1.5$ ]; superior to TIV-1 (B Victoria) with  
 421 respect to the B strain of Yamagata lineage and to TIV-2 (B Yamagata) with respect to the B  
 422 strain of Victoria lineage based on adjusted GMTs [lower limit of the 2-sided 95% CI for the  
 423 GMT ratio (FLULAVAL QUADRIVALENT/TIV)  $> 1.5$ ].

#### 424 Children

425 Trial 2 was a randomized, double-blind, active-controlled trial conducted in children aged  
 426 3 through 17 years. In this trial, subjects received FLULAVAL QUADRIVALENT (N = 878), or  
 427 one of two formulations of a comparator trivalent influenza vaccine (FLUARIX, TIV-1, N = 871  
 428 or TIV-2 N = 878), each containing an influenza type B virus that corresponded to one of the two  
 429 B viruses in FLULAVAL QUADRIVALENT (a type B virus of the Victoria lineage or a type B

430 virus of the Yamagata lineage) [see Adverse Reactions (6.1)].

431 Immune responses, specifically HI antibody titers to each virus strain in the vaccine, were

432 evaluated in sera obtained 28 days following one or 2 doses of FLULAVAL QUADRIVALENT

433 or the comparators. The immunogenicity endpoints were GMTs adjusted for baseline, and the

434 percentage of subjects who achieved seroconversion, defined as at least a 4-fold increase in

435 serum HI titer over baseline to  $\geq 1:40$ , following vaccination, performed on the ATP cohort.

436 FLULAVAL QUADRIVALENT was non-inferior to both TIVs based on adjusted GMTs and

437 seroconversion rates (Table 8). The antibody response to influenza B strains contained in

438 FLULAVAL QUADRIVALENT was higher than the antibody response after vaccination with a

439 TIV containing an influenza B strain from a different lineage. There was no evidence that the

440 addition of the second B strain resulted in immune interference to other strains included in the

441 vaccine (Table 8).

442 **Table 8. Non-inferiority of FLULAVAL QUADRIVALENT Relative to Trivalent Influenza**

443 **Vaccine (TIV) at 28 Days Post-vaccination in Children Aged 3 through 17 Years<sup>a</sup>**

444 **(According-to-Protocol Cohort for Immunogenicity)<sup>b</sup>**

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

445 CI = Confidence Interval.

- 446 <sup>a</sup> Trial 2: NCT01198756.
- 447 <sup>b</sup> According-to-protocol cohort for immunogenicity included all evaluable subjects for whom  
448 assay results were available after vaccination for at least one trial vaccine antigen.
- 449 <sup>c</sup> Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Florida/04/2006  
450 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage).
- 451 <sup>d</sup> Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and  
452 B/Brisbane/60/2008 (Victoria lineage).
- 453 <sup>e</sup> Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and  
454 B/Florida/04/2006 (Yamagata lineage).
- 455 <sup>f</sup> Non-inferior to both TIVs based on adjusted GMTs [upper limit of the 2-sided 95% CI for the  
456 GMT ratio (TIV/FLULAVAL QUADRIVALENT)  $\leq 1.5$ ] and seroconversion rates (upper  
457 limit of the 2-sided 95% CI on difference of the TIV minus FLULAVAL QUADRIVALENT  
458  $\leq 10\%$ ); superior to TIV-1 (B Victoria) with respect to the B strain of Yamagata lineage and to  
459 TIV-2 (B Yamagata) with respect to the B strain of Victoria lineage based on adjusted GMTs  
460 [lower limit of the 2-sided 95% CI for the GMT ratio (FLULAVAL QUADRIVALENT/TIV)  
461  $> 1.5$ ] and seroconversion rates (lower limit of the 2-sided 95% CI on difference of  
462 FLULAVAL QUADRIVALENT minus the TIV  $> 10\%$ ).
- 463 <sup>g</sup> Seroconversion defined as a 4-fold increase in post-vaccination antibody titer from pre-  
464 vaccination titer  $\geq 1:10$ , or an increase in titer from  $< 1:10$  to  $\geq 1:40$ .

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## 474 **16 HOW SUPPLIED/STORAGE AND HANDLING**

475 FLULAVAL QUADRIVALENT is available in 0.5-mL single-dose disposable prefilled TIP-  
476 LOK syringes (packaged without needles) and in 5-mL multi-dose vials containing 10 doses  
477 (0.5 mL each).

478 NDC 19515-901-41 Syringe in Package of 10: NDC 19515-901-52

479 NDC 19515-898-01 Multi-Dose Vial (containing 10 doses) in Package of 1: NDC 19515-898-11

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

## 483 **17 PATIENT COUNSELING INFORMATION**

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

- 485 • Inform of the potential benefits and risks of immunization with FLULAVAL  
486 QUADRIVALENT.
- 487 • Educate regarding potential side effects, emphasizing that (1) FLULAVAL  
488 QUADRIVALENT contains non-infectious killed viruses and cannot cause influenza, and  
489 (2) FLULAVAL QUADRIVALENT is intended to provide protection against illness due to  
490 influenza viruses only, and cannot provide protection against all respiratory illness.
- 491 • Inform that safety and efficacy have not been established in pregnant women. Register  
492 women who receive FLULAVAL QUADRIVALENT while pregnant in the pregnancy  
493 registry by calling 1-888-452-9622.
- 494 • Give the Vaccine Information Statements, which are required by the National Childhood  
495 Vaccine Injury Act of 1986 prior to each immunization. These materials are available free of  
496 charge at the Centers for Disease Control and Prevention (CDC) website  
497 ([www.cdc.gov/vaccines](http://www.cdc.gov/vaccines)).
- 498 • Instruct that annual revaccination is recommended.

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