

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 Virus Vaccine)

Suspension for Intramuscular Injection

2013-2014 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
3 through 8 years of age	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 of age 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 in 5-mL multi-dose vials containing ten 0.5-mL doses. (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 3 through 17 years of age, the most common ($\geq 10\%$) solicited local adverse reaction was pain (65%). (6.1)
- In children 3 through 4 years of age, the most common ($\geq 10\%$) solicited systemic adverse events were irritability (26%), drowsiness (21%), and loss of appetite (17%). (6.1)
- In children 5 through 17 years of age, 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

- 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/xxxx

FULL PRESCRIBING INFORMATION: CONTENTS*

1	INDICATIONS AND USAGE
2	DOSAGE AND ADMINISTRATION
2.1	Dosage and Schedule
2.2	Administration Instructions
3	DOSAGE FORMS AND STRENGTHS
4	CONTRAINDICATIONS
5	WARNINGS AND PRECAUTIONS
5.1	Guillain-Barré Syndrome
5.2	Syncope
5.3	Preventing and Managing Allergic Vaccine Reactions
5.4	Altered Immunocompetence
5.5	Limitations of Vaccine Effectiveness
5.6	Persons at Risk of Bleeding
6	ADVERSE REACTIONS
6.1	Clinical Trials Experience
6.2	Postmarketing Experience
7	DRUG INTERACTIONS
7.1	Concomitant Administration With Other Vaccines

7.2	Immunosuppressive Therapies
8	USE IN SPECIFIC POPULATIONS
8.1	Pregnancy
8.3	Nursing Mothers
8.4	Pediatric Use
8.5	Geriatric Use
11	DESCRIPTION
12	CLINICAL PHARMACOLOGY
12.1	Mechanism of Action
13	NONCLINICAL TOXICOLOGY
13.1	Carcinogenesis, Mutagenesis, Impairment of Fertility
14	CLINICAL STUDIES
14.1	Efficacy Against Influenza
14.2	Immunological Evaluation
15	REFERENCES
16	HOW SUPPLIED/STORAGE AND HANDLING
17	PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

1 FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

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

7 2 DOSAGE AND ADMINISTRATION

8 For intramuscular injection only.

9 2.1 Dosage and Schedule

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

11
12 **Table 1. FLULAVAL QUADRIVALENT: Dosing**

Age	Vaccination Status	Dose and Schedule
3 through 8 years of age	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 of age and older	Not applicable	One 0.5-mL dose

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

17 18 2.2 Administration Instructions

19 Shake the multi-dose vial vigorously each time before withdrawing a dose of vaccine.
20 Parenteral drug products should be inspected visually for particulate matter and discoloration
21 prior to administration, whenever solution and container permit. If either of these conditions
22 exists, the vaccine should not be administered.

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

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

30 Between uses, return the multi-dose vial to the recommended storage conditions, between

31 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has been frozen. Once entered, a
32 multi-dose vial, and any residual contents, should be discarded after 28 days.

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

34 **3 DOSAGE FORMS AND STRENGTHS**

35 FLULAVAL QUADRIVALENT is a suspension for injection available in 5-mL multi-
36 dose vials containing ten 0.5-mL doses.

37 **4 CONTRAINDICATIONS**

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

41 **5 WARNINGS AND PRECAUTIONS**

42 **5.1 Guillain-Barré Syndrome**

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

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

49 **5.2 Syncope**

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

55 **5.3 Preventing and Managing Allergic Vaccine Reactions**

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

60 **5.4 Altered Immunocompetence**

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

64 **5.5 Limitations of Vaccine Effectiveness**

65 Vaccination with FLULAVAL QUADRIVALENT may not protect all susceptible
66 individuals.

67 **5.6 Persons at Risk of Bleeding**

68 As with other intramuscular injections, FLULAVAL QUADRIVALENT should be given

69 with caution in individuals with bleeding disorders such as hemophilia or on anticoagulant
70 therapy to avoid the risk of hematoma following the injection.

71 **6 ADVERSE REACTIONS**

72 **6.1 Clinical Trials Experience**

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

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

82 Because clinical trials are conducted under widely varying conditions, adverse reaction
83 rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the
84 clinical trials of another vaccine, and may not reflect the rates observed in practice. There is the
85 possibility that broad use of FLULAVAL QUADRIVALENT could reveal adverse reactions not
86 observed in clinical trials.

87 FLULAVAL QUADRIVALENT has been administered to 1,384 adults 18 years of age
88 and older and 3,516 pediatric subjects 3 through 17 years of age in 4 clinical trials.

89 FLULAVAL QUADRIVALENT in Adults: Study 1 was a randomized, double-blind,
90 active-controlled, safety and immunogenicity study. In this study, subjects received FLULAVAL
91 QUADRIVALENT (N = 1,272), or one of two formulations of a comparator trivalent influenza
92 vaccine (FLULAVAL, TIV-1, N = 213 or TIV-2, N = 218), each containing an influenza type B
93 virus that corresponded to one of the two B viruses in FLULAVAL QUADRIVALENT (a type
94 B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The population was
95 18 years of age and older (mean age 50 years) and 61% were female; 61% of subjects were
96 White, 3% were Black, 1% were Asian, and 35% were of other racial/ethnic groups. Solicited
97 adverse events were collected for 7 days (day of vaccination and the next 6 days). The incidence
98 of local adverse reactions and systemic adverse events occurring within 7 days of vaccination in
99 adults are shown in Table 2.

100

101 **Table 2. FLULAVAL QUADRIVALENT: Incidence of Solicited Local Adverse Reactions**
 102 **and Systemic Adverse Events Within 7 Days^a of Vaccination in Adults 18 Years of Age and**
 103 **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 %
Local Adverse Reactions			
Pain	60	45	41
Swelling	3	1	4
Redness	2	3	1
Systemic Adverse Events			
Muscle aches	26	25	19
Headache	22	20	23
Fatigue	22	22	17
Arthralgia	15	17	15
Gastrointestinal symptoms ^f	9	10	7
Shivering	9	8	6
Fever $\geq 100.4^{\circ}\text{F}$ (38.0°C)	2	1	1

104 Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were
 105 available.

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

107 ^b Study 1: NCT01196975.

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

110 ^d Contained two A strains and a B strain of Victoria lineage.

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

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

113

114 Unsolicited adverse events occurring within 21 days of vaccination were reported in
 115 19%, 23%, and 23% of subjects who received FLULAVAL QUADRIVALENT (N = 1,272),
 116 TIV-1 (B Victoria) (N = 213), or TIV-2 (B Yamagata) (N = 218), respectively. The unsolicited
 117 adverse events that occurred most frequently ($\geq 1\%$ for FLULAVAL QUADRIVALENT)
 118 included nasopharyngitis, upper respiratory tract infection, headache, cough and oropharyngeal
 119 pain. Serious adverse events occurring within 21 days of vaccination were reported in 0.4%, 0%,
 120 and 0% of subjects who received FLULAVAL QUADRIVALENT, TIV-1 (B Victoria), or TIV-
 121 2 (B Yamagata), respectively.

122 FLULAVAL QUADRIVALENT in Children: Study 2 was a randomized, double-blind,
 123 active-controlled study. In this study, subjects received FLULAVAL QUADRIVALENT

124 (N = 932), or one of two formulations of a comparator trivalent influenza vaccine [FLUARIX[®]
 125 (Influenza Virus Vaccine), TIV-1, N = 929 or TIV-2, N = 932], each containing an influenza
 126 type B virus that corresponded to one of the two B viruses in FLULAVAL QUADRIVALENT
 127 (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The population
 128 was 3 through 17 years of age (mean age 9 years) and 53% were male; 65% were White, 13%
 129 were Asian, 9% were Black, and 13% were of other racial/ethnic groups. Children 3 through
 130 8 years of age with no history of influenza vaccination received 2 doses approximately 28 days
 131 apart. Children 3 through 8 years of age with a history of influenza vaccination and children
 132 9 years of age and older received one dose. Solicited local adverse reactions and systemic
 133 adverse events were collected for 7 days (day of vaccination and the next 6 days). The incidence
 134 of local adverse reactions and systemic adverse events occurring within 7 days of vaccination in
 135 children are shown in Table 3.

137 **Table 3. FLULAVAL QUADRIVALENT: Incidence of Solicited Local Adverse Reactions**
 138 **and Systemic Adverse Events Within 7 Days^a of First Vaccination in Children 3 Through**
 139 **17 Years of Age^b (Total Vaccinated Cohort)**

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

140 Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were

141 available.

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

143 ^b Study 2: NCT01198756.

144 ^c Contained two A strains and two B strains, one of Victoria lineage and one of Yamagata
145 lineage.

146 ^d Contained two A strains and a B strain of Victoria lineage.

147 ^e Contained the same two A strains as FLUARIX and a B strain of Yamagata lineage.

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

149

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

153 Unsolicited adverse events occurring within 28 days of vaccination were reported in
154 30%, 31% and 30% of subjects who received FLULAVAL QUADRIVALENT (N = 932),
155 FLUARIX TIV-1 (B Victoria) (N = 929), or TIV-2 (B Yamagata) (N = 932), respectively. The
156 unsolicited adverse events that occurred most frequently ($\geq 1\%$ for FLULAVAL
157 QUADRIVALENT) included vomiting, pyrexia, bronchitis, nasopharyngitis, pharyngitis, upper
158 respiratory tract infection, headache, cough, oropharyngeal pain, and rhinorrhea. Serious adverse
159 events occurring within 28 days of any vaccination were reported in 0.1%, 0.2%, and 0.2% of
160 subjects who received FLULAVAL QUADRIVALENT, FLUARIX TIV-1 (B Victoria), or TIV-
161 2 (B Yamagata), respectively.

162 Study 3 was a randomized, observer-blind, non-influenza vaccine-controlled study
163 evaluating the efficacy of FLULAVAL QUADRIVALENT. The study included subjects 3
164 through 8 years of age who received FLULAVAL QUADRIVALENT (N = 2,584) or HAVRIX[®]
165 (Hepatitis A Vaccine) (N = 2,584), as a control vaccine. Children with no history of influenza
166 vaccination received 2 doses of FLULAVAL QUADRIVALENT or HAVRIX approximately
167 28 days apart. Children with a history of influenza vaccination received one dose of
168 FLULAVAL QUADRIVALENT or HAVRIX. In the overall population, 52% were male; 60%
169 were Asian, 5% were White, and 35% were of other racial/ethnic groups. The mean age of
170 subjects was 5 years. Solicited local adverse reactions and systemic adverse events were
171 collected for 7 days (day of vaccination and the next 6 days). The incidence of local adverse
172 reactions and systemic adverse events occurring within 7 days of vaccination in children are
173 shown in Table 4.

174

175 **Table 4. FLULAVAL QUADRIVALENT: Incidence of Solicited Local Adverse Reactions**
 176 **and Systemic Adverse Events Within 7 Days^a of First Vaccination in Children 3 Through**
 177 **8 Years of Age^b (Total Vaccinated Cohort)**

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

178 Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were
 179 available.

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

181 ^b Study 3: NCT01218308.

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

183 ^d Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

184
 185 In children who received a second dose of FLULAVAL QUADRIVALENT or HAVRIX,
 186 the incidences of adverse events following the second dose were generally lower than those
 187 observed after the first dose.

188 The frequency of unsolicited adverse events occurring within 28 days of vaccination was
 189 similar in both groups (33% for both FLULAVAL QUADRIVALENT and HAVRIX). The
 190 unsolicited adverse events that occurred most frequently (≥1% for FLULAVAL
 191 QUADRIVALENT) included diarrhea, pyrexia, gastroenteritis, nasopharyngitis, upper
 192 respiratory tract infection, varicella, cough, and rhinorrhea. Serious adverse events occurring

193 within 28 days of any vaccination were reported in 0.7% of subjects who received FLULAVAL
194 QUADRIVALENT and in 0.2% of subjects who received HAVRIX.

195 **6.2 Postmarketing Experience**

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

204 Blood and Lymphatic System Disorders: Lymphadenopathy

205 Eye Disorders: Eye pain, photophobia

206 Gastrointestinal Disorders: Dysphagia, vomiting

207 General Disorders and Administration Site Conditions: Chest pain, injection site
208 inflammation, asthenia, injection site rash, influenza-like symptoms, abnormal gait, injection site
209 bruising, injection site sterile abscess

210 Immune System Disorders: Allergic reactions including anaphylaxis, angioedema

211 Infections and Infestations: Rhinitis, laryngitis, cellulitis

212 Musculoskeletal and Connective Tissue Disorders: Muscle weakness, arthritis

213 Nervous System Disorders: Dizziness, paresthesia, hypoesthesia, hypokinesia, tremor,
214 somnolence, syncope, Guillain-Barré syndrome, convulsions/seizures, facial or cranial nerve
215 paralysis, encephalopathy, limb paralysis

216 Psychiatric Disorders: Insomnia

217 Respiratory, Thoracic, and Mediastinal Disorders: Dyspnea, dysphonia,
218 bronchospasm, throat tightness

219 Skin and Subcutaneous Tissue Disorders: Urticaria, localized or generalized rash,
220 pruritus, sweating

221 Vascular Disorders: Flushing, pallor

222 **7 DRUG INTERACTIONS**

223 **7.1 Concomitant Administration With Other Vaccines**

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

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

229 **7.2 Immunosuppressive Therapies**

230 Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents,
231 cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the

232 immune response to FLULAVAL QUADRIVALENT.

233 **8 USE IN SPECIFIC POPULATIONS**

234 **8.1 Pregnancy**

235 Pregnancy Category B

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

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

250 Pregnancy Registry: GlaxoSmithKline maintains a surveillance registry to collect data
251 on pregnancy outcomes and newborn health status outcomes following vaccination with
252 FLULAVAL QUADRIVALENT during pregnancy. Women who receive FLULAVAL
253 QUADRIVALENT during pregnancy should be encouraged to contact GlaxoSmithKline directly
254 or their healthcare provider should contact GlaxoSmithKline by calling 1-888-452-9622.

255 **8.3 Nursing Mothers**

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

259 **8.4 Pediatric Use**

260 Safety and effectiveness of FLULAVAL QUADRIVALENT in children younger than
261 3 years of age have not been established.

262 Safety and immunogenicity of FLULAVAL QUADRIVALENT in children 3 through
263 17 years of age have been evaluated [*see Adverse Reactions (6.1) and Clinical Studies (14.2)*].

264 **8.5 Geriatric Use**

265 In a randomized, double-blind, active-controlled study, immunogenicity and safety were
266 evaluated in a cohort of subjects 65 years of age and older who received FLULAVAL
267 QUADRIVALENT (N = 397); approximately one-third of these subjects were 75 years of age
268 and older. In subjects 65 years of age and older, the geometric mean antibody titers post-
269 vaccination and seroconversion rates were lower than in younger subjects (18 to 64 years of age)
270 and the frequencies of solicited and unsolicited adverse events were generally lower than in

271 younger subjects [see *Adverse Reactions (6.1)* and *Clinical Studies (14.2)*].

272 **11 DESCRIPTION**

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

278 FLULAVAL QUADRIVALENT is a sterile, translucent to whitish opalescent suspension
279 in a phosphate-buffered saline solution that may sediment slightly. The sediment resuspends
280 upon shaking to form a homogeneous suspension.

281 FLULAVAL QUADRIVALENT has been standardized according to USPHS
282 requirements for the 2013-2014 influenza season and is formulated to contain 60 micrograms
283 (mcg) hemagglutinin (HA) per 0.5-mL dose in the recommended ratio of 15 mcg HA of each of
284 the following 4 viruses (two A strains and two B strains): A/California/7/2009 NYMC X-179A
285 (H1N1), A/Texas/50/2012 NYMC X-223A (H3N2) (an A/Victoria/361/2011-like virus),
286 B/Massachusetts/2/2012 NYMC BX-51B, and B/Brisbane/60/2008.

287 Thimerosal, a mercury derivative, is added as a preservative. Each 0.5-mL dose contains
288 50 mcg thimerosal (<25 mcg mercury), α -tocopheryl hydrogen succinate (≤ 320 mcg), and
289 polysorbate 80 (≤ 887 mcg). Each 0.5-mL dose may also contain residual amounts of ovalbumin
290 (≤ 0.3 mcg), formaldehyde (≤ 25 mcg), and sodium deoxycholate (≤ 50 mcg) from the
291 manufacturing process. Antibiotics are not used in the manufacture of this vaccine.

292 The vial stoppers are not made with natural rubber latex.

293 **12 CLINICAL PHARMACOLOGY**

294 **12.1 Mechanism of Action**

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

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

307 Specific levels of hemagglutination inhibition (HI) antibody titer post-vaccination with
308 inactivated influenza virus vaccines have not been correlated with protection from influenza
309 illness but the antibody titers have been used as a measure of vaccine activity. In some human

310 challenge studies, antibody titers of $\geq 1:40$ have been associated with protection from influenza
311 illness in up to 50% of subjects.^{1,2} Antibody against one influenza virus type or subtype confers
312 little or no protection against another virus. Furthermore, antibody to one antigenic variant of
313 influenza virus might not protect against a new antigenic variant of the same type or subtype.
314 Frequent development of antigenic variants through antigenic drift is the virological basis for
315 seasonal epidemics and the reason for the usual change of one or more new strains in each year's
316 influenza vaccine.

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

319 **13 NONCLINICAL TOXICOLOGY**

320 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

324 **14 CLINICAL STUDIES**

325 **14.1 Efficacy Against Influenza**

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

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

344

345 **Table 5. FLULAVAL QUADRIVALENT: Influenza Attack Rates and Vaccine Efficacy**
 346 **Against Influenza A and/or B in Children 3 Through 8 Years of Age^a (According to**
 347 **Protocol 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	–

348 CI = Confidence Interval; RT-PCR = reverse transcriptase polymerase chain reaction.

349 ^a Study 3: NCT01218308.

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

353 ^c Number of influenza cases.

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

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

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

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

363

364 In an exploratory analysis by age, vaccine efficacy against RT-PCR-positive influenza A
 365 and/or B disease presenting as ILI was evaluated in subjects 3 through 4 years of age and 5
 366 through 8 years of age; vaccine efficacy was 35.3% (95% CI: -1.3, 58.6) and 67.7% (95% CI:
 367 49.7, 79.2), respectively. As the study lacked statistical power to evaluate efficacy within age
 368 subgroups, the clinical significance of these results is unknown.

369 As a secondary objective in the study, subjects with RT-PCR-positive influenza A and/or

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

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

380
 381 **Table 6. FLULAVAL QUADRIVALENT: Incidence of Adverse Outcomes Associated With**
 382 **RT-PCR-Positive Influenza in Children 3 Through 8 Years of Age^a (Total Vaccinated**
 383 **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

384 ^a Study 3: NCT01218308.

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

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

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

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

390 ^f One subject in each group had sequential influenza due to influenza type A and type B
 391 viruses.

392

393 **14.2 Immunological Evaluation**

394 Adults: Study 1 was a randomized, double-blind, active-controlled, safety and
395 immunogenicity study conducted in subjects 18 years of age and older. In this study, subjects
396 received FLULAVAL QUADRIVALENT (N = 1,246), or one of two formulations of a
397 comparator trivalent influenza vaccine (FLULAVAL, TIV-1, N = 204 or TIV-2, N = 211), each
398 containing an influenza type B virus that corresponded to one of the two B viruses in
399 FLULAVAL QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the
400 Yamagata lineage) [see Adverse Reactions (6.1)].

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

412

413 **Table 7. Non-inferiority of FLULAVAL QUADRIVALENT Relative to Trivalent Influenza**
414 **Vaccine (TIV) 21 Days Post-Vaccination in Adults 18 Years of Age and Older^a (According**
415 **to Protocol Cohort for Immunogenicity)^b**

	FLULAVAL QUADRIVALENT^c	TIV-1 (B Victoria)^d	TIV-2 (B Yamagata)^e
Geometric Mean Titers Against	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)

416 CI = Confidence Interval.

417 ^a Study 1: NCT01196975.

418 ^b According to protocol cohort for immunogenicity included all evaluable subjects for whom
419 assay results were available after vaccination for at least one study vaccine antigen.

- 420 ^c Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Florida/04/2006
421 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage)
- 422 ^d Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and
423 B/Brisbane/60/2008 (Victoria lineage)
- 424 ^e Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and
425 B/Florida/04/2006 (Yamagata lineage).
- 426 ^f Non-inferior to both TIVs based on adjusted GMTs [upper limit of the 2-sided 95% CI for the
427 GMT ratio (TIV/FLULAVAL QUADRIVALENT) ≤ 1.5]; superior to TIV-1 (B Victoria) with
428 respect to the B strain of Yamagata lineage and to TIV-2 (B Yamagata) with respect to the B
429 strain of Victoria lineage based on adjusted GMTs [lower limit of the 2-sided 95% CI for the
430 GMT ratio (FLULAVAL QUADRIVALENT/TIV) > 1.5].

431

432 Children: Study 2 was a randomized, double-blind, active-controlled study conducted in
433 children 3 through 17 years of age. In this study, subjects received FLULAVAL
434 QUADRIVALENT (N = 878), or one of two formulations of a comparator trivalent influenza
435 vaccine (FLUARIX, TIV-1, N = 871 or TIV-2 N = 878), each containing an influenza type B
436 virus that corresponded to one of the two B viruses in FLULAVAL QUADRIVALENT (a type
437 B virus of the Victoria lineage or a type B virus of the Yamagata lineage) [*see Adverse Reactions*
438 (6.1)].

439 Immune responses, specifically HI antibody titers to each virus strain in the vaccine, were
440 evaluated in sera obtained 28 days following one or 2 doses of FLULAVAL QUADRIVALENT
441 or the comparators. The immunogenicity endpoints were GMTs adjusted for baseline, and the
442 percentage of subjects who achieved seroconversion, defined as at least a 4-fold increase in
443 serum HI titer over baseline to $\geq 1:40$, following vaccination, performed on the ATP cohort.
444 FLULAVAL QUADRIVALENT was non-inferior to both TIVs based on adjusted GMTs and
445 seroconversion rates (Table 8). The antibody response to influenza B strains contained in
446 FLULAVAL QUADRIVALENT was higher than the antibody response after vaccination with a
447 TIV containing an influenza B strain from a different lineage. There was no evidence that the
448 addition of the second B strain resulted in immune interference to other strains included in the
449 vaccine (Table 8).

450

451 **Table 8. Non-inferiority of FLULAVAL QUADRIVALENT Relative to Trivalent Influenza**
 452 **Vaccine (TIV) at 28 Days Post-Vaccination in Children 3 Through 17 Years of Age^a**
 453 **(According to Protocol Cohort for Immunogenicity)^b**

	FLULAVAL QUADRIVALENT^c	TIV-1 (B Victoria)^d	TIV-2 (B Yamagata)^e
Geometric Mean Titers Against	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)

454 CI = Confidence Interval.

455 ^a Study 2: NCT01198756.

456 ^b According to protocol cohort for immunogenicity included all evaluable subjects for whom
 457 assay results were available after vaccination for at least one study vaccine antigen.

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

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

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

464 ^f Non-inferior to both TIVs based on adjusted GMTs [upper limit of the 2-sided 95% CI for the
 465 GMT ratio (TIV/FLULAVAL QUADRIVALENT) ≤1.5] and seroconversion rates (upper
 466 limit of the 2-sided 95% CI on difference of the TIV minus FLULAVAL QUADRIVALENT
 467 ≤10%); superior to TIV-1 (B Victoria) with respect to the B strain of Yamagata lineage and to
 468 TIV-2 (B Yamagata) with respect to the B strain of Victoria lineage based on adjusted GMTs

469 [lower limit of the 2-sided 95% CI for the GMT ratio (FLULAVAL QUADRIVALENT/TIV)
470 >1.5] and seroconversion rates (lower limit of the 2-sided 95% CI on difference of
471 FLULAVAL QUADRIVALENT minus the TIV >10%).

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

474

475 **15 REFERENCES**

- 476 1. Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza
477 vaccination. *Virus Res* 2004;103:133-138.
- 478 2. Hobson D, Curry RL, Beare AS, et al. The role of serum haemagglutination-inhibiting
479 antibody in protection against challenge infection with influenza A2 and B viruses. *J Hyg*
480 *Camb* 1972;70:767-777.
- 481 3. Centers for Disease Control and Prevention. Prevention and control of influenza with
482 vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP).
483 *MMWR* 2010;59(RR-8):1-62.

484 **16 HOW SUPPLIED/STORAGE AND HANDLING**

485 FLULAVAL QUADRIVALENT is supplied in a 5-mL multi-dose vial containing 10
486 doses (0.5 mL each).

487 NDC 19515-895-01 Vial (containing 10 doses) in Package of 1: NDC 19515-895-11

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

491 **17 PATIENT COUNSELING INFORMATION**

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

- 493 • Inform of the potential benefits and risks of immunization with FLULAVAL
494 QUADRIVALENT.
- 495 • Educate regarding potential side effects, emphasizing that (1) FLULAVAL
496 QUADRIVALENT contains non-infectious killed viruses and cannot cause influenza, and
497 (2) FLULAVAL QUADRIVALENT is intended to provide protection against illness due to
498 influenza viruses only, and cannot provide protection against all respiratory illness.
- 499 • Instruct to report any adverse events to their healthcare provider.
- 500 • Inform that safety and efficacy have not been established in pregnant women. Register
501 women who receive FLULAVAL QUADRIVALENT while pregnant in the pregnancy
502 registry by calling 1-888-452-9622.
- 503 • Give the Vaccine Information Statements, which are required by the National Childhood
504 Vaccine Injury Act of 1986 prior to immunization. These materials are available free of
505 charge at the Centers for Disease Control and Prevention (CDC) website
506 (www.cdc.gov/vaccines).

507 • Instruct that annual revaccination is recommended.

508

509 FLUARIX, FLULAVAL, and HAVRIX are registered trademarks of GlaxoSmithKline.

510



511

512 Manufactured by **ID Biomedical Corporation of Quebec**

513 Quebec City, QC, Canada, US License 1739

514 Distributed by **GlaxoSmithKline**

515 Research Triangle Park, NC 27709

516

517 ©2013, GlaxoSmithKline. All rights reserved.

518

519 FVQ:1PI