

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**FLULAVAL (Influenza Vaccine)**  
**Suspension for Intramuscular Injection**  
**2015-2016 Formula**  
**Initial U.S. Approval: 2006**

### INDICATIONS AND USAGE

FLULAVAL is a vaccine indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B virus contained in the vaccine. FLULAVAL 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 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. 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 reactions were pain (51%), redness (13%), and/or swelling (11%); the most common solicited systemic adverse events were fatigue (20%), headache (18%), and muscle aches/arthralgia (18%). (6.1)
- In children aged 3 through 17 years, the most common ( $\geq 10\%$ ) solicited local adverse reaction was pain (56%). (6.1)
- In children aged 3 through 4 years, the most common ( $\geq 10\%$ ) solicited systemic adverse events were irritability (25%), drowsiness (19%), and loss of appetite (16%). (6.1)
- In children aged 5 through 17 years, the most common ( $\geq 10\%$ ) solicited systemic adverse events were muscle aches (24%), headache (17%), and fatigue (17%). (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 have not been established in pregnant women or nursing mothers. (8.1, 8.3)
- Register women who receive FLULAVAL 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 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> is indicated for active immunization for the prevention of disease caused by  
4 influenza A subtype viruses and type B virus contained in the vaccine. FLULAVAL is approved  
5 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 are presented in Table 1.

10 **Table 1. FLULAVAL: Dosing**

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

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

#### 15 2.2 Administration Instructions

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

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

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

### 34 **4 CONTRAINDICATIONS**

35 Do not administer FLULAVAL to anyone with a history of severe allergic reactions (e.g.,  
36 anaphylaxis) to any component of the vaccine, including egg protein, or following a previous  
37 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 should be based on careful consideration of the  
42 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. Syncope can be accompanied by transient neurological signs such as visual  
49 disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to  
50 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.

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

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

## 60 **5.5 Limitations of Vaccine Effectiveness**

61 Vaccination with FLULAVAL may not protect all susceptible individuals.

## 62 **5.6 Persons at Risk of Bleeding**

63 As with other intramuscular injections, FLULAVAL should be given with caution in individuals  
64 with bleeding disorders such as hemophilia or on anticoagulant therapy to avoid the risk of  
65 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 could reveal adverse reactions not observed in clinical  
72 trials.

73 In adults who received FLULAVAL, the most common ( $\geq 10\%$ ) solicited local adverse reactions  
74 were pain (51%), redness (13%), and swelling (11%); the most common ( $\geq 10\%$ ) solicited  
75 systemic adverse events were fatigue (20%), headache (18%), and muscle aches/arthralgia  
76 (18%).

77 In children aged 3 through 17 years who received FLULAVAL, the most common ( $\geq 10\%$ )  
78 solicited local adverse reaction was pain (56%). In children aged 3 through 4 years, the most  
79 common ( $\geq 10\%$ ) solicited systemic adverse events were irritability (25%), drowsiness (19%),  
80 and loss of appetite (16%). In children aged 5 through 17 years, the most common ( $\geq 10\%$ )  
81 systemic adverse events were muscle aches (24%), headache (17%), and fatigue (17%).

### 82 FLULAVAL in Adults

83 Safety data was obtained from 3 randomized, controlled trials, one of which was a placebo-  
84 controlled efficacy trial. In these trials, 9,836 subjects were randomized to receive either  
85 FLULAVAL (5,114 subjects in the safety analysis), FLUZONE, a US-licensed trivalent,  
86 inactivated influenza vaccine, manufactured by Sanofi Pasteur SA (894 subjects in the safety  
87 analysis), or placebo (3,828 subjects in the safety analysis), intramuscularly. In these trials,  
88 solicited events were collected for 4 days (i.e., 30 minutes post-vaccination through the next  
89 3 days). Unsolicited adverse events that occurred within 22 days of vaccination (Day 0 to 21)  
90 were recorded based on spontaneous reports or in response to queries about changes in health  
91 status.

92 *Trial 1 (Immunogenicity):* Safety information was collected in a randomized, controlled US  
93 trial. This trial included 1,000 adults aged 18 through 64 years who were randomized to receive  
94 FLULAVAL (N = 721) or a US-licensed trivalent, inactivated influenza vaccine (N = 279).  
95 Among recipients of FLULAVAL, 57% were female; 91% of subjects were white and 9% were

96 of other racial/ethnic groups. The mean age of subjects was 38 years; 80% were aged 18 through  
97 49 years and 20% were aged 50 through 64 years.

98 *Trial 2 (Immunogenicity Non-Inferiority)*: Safety information was collected in a randomized,  
99 double-blind, active-controlled US trial. The trial included 1,225 adults aged  $\geq 50$  years  
100 randomized to receive FLULAVAL (N = 610) or a US-licensed trivalent, inactivated influenza  
101 vaccine (N = 615). In the total population, 57% were female; 95% of subjects were white and 5%  
102 were of other racial/ethnic groups. The mean age of subjects was 66 years; 46% were aged 50  
103 through 64 years, 41% were aged 65 through 79 years, and 13% were aged  $\geq 80$  years.

104 *Trial 3 (Efficacy)*: Safety information was collected in a double-blind, placebo-controlled US  
105 trial. The trial included 7,658 adults aged 18 through 49 years randomized to receive  
106 FLULAVAL (N = 3,807) or placebo (N = 3,851). In the total population, 61% were female; 84%  
107 of subjects were white, 10% black, 2% Asian, and 4% were of other racial/ethnic groups. The  
108 mean age of subjects was 33 years.

109 *Solicited Adverse Events*: Solicited local adverse reactions and systemic adverse events  
110 collected for 4 days (day of vaccination and the next 3 days) are presented in Table 2.

111 **Table 2. FLULAVAL: Incidence of Solicited Local Adverse Reactions and Systemic**  
 112 **Adverse Events within 4 Days<sup>a</sup> of Vaccination in Adults (Total Vaccinated Cohort)**

	Percentage of Subjects Reporting Event					
	Trial 1 <sup>b</sup> Aged 18 through 64 Years		Trial 2 <sup>b</sup> Aged 50 Years and Older		Trial 3 <sup>b</sup> Aged 18 through 49 Years	
	FLULAVAL N = 721	Comparator <sup>c</sup> N = 279	FLULAVAL N = 610	Comparator <sup>c</sup> N = 615	FLULAVAL N = 3,783	Placebo N = 3,828
<b>Local Adverse Reactions</b>						
Pain	24	31	25	32	51	14
Redness	11	10	10	11	13	6
Swelling	10	10	7	9	11	3
<b>Systemic Adverse Events</b>						
Headache	18	17	11	12	18	19
Fatigue	17	15	12	13	20	18
Muscle aches <sup>d</sup>	13	16	11	10	18	10
Fever $\geq 99.5^{\circ}\text{F}$ ( $37.5^{\circ}\text{C}$ )	11	10	1	1	3	1
Malaise	10	10	6	7	9	6
Sore throat	9	9	5	6	9	9
Reddened eyes	6	5	4	7	7	6
Cough	6	7	5	6	8	7
Chills	5	2	3	6	4	4
Chest tightness	3	1	2	2	3	3
Facial swelling	1	1	1	2	1	1

113 Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were  
 114 available.

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

116 <sup>b</sup> Trial 1: NCT01389479; Trial 2: NCT00232947; Trial 3: NCT00216242.

117 <sup>c</sup> US-licensed trivalent, inactivated influenza vaccine (manufactured by Sanofi Pasteur SA).

118 <sup>d</sup> For Trial 2 and Trial 3, includes muscle aches and arthralgia.

119 *Unsolicited Adverse Events:* The incidence of unsolicited adverse events in the 21 days post-  
 120 vaccination was comparable for FLULAVAL and the active comparator in Trial 1 (16% and  
 121 15%, respectively) and in Trial 2 (18% and 21%, respectively). In Trial 3, the incidence of  
 122 unsolicited adverse events was comparable for the groups (21% for FLULAVAL and 19% for  
 123 placebo).

124 Unsolicited adverse events defined as reported with FLULAVAL in >1.0% of subjects are  
125 described as follows: Trial 1: Cough, headache, and pharyngolaryngeal pain; Trial 2: Diarrhea,  
126 headache, and nasopharyngitis; and Trial 3: Pharyngolaryngeal pain, headache, fatigue, cough,  
127 injection site pain, upper respiratory tract infection, musculoskeletal pain, nasopharyngitis,  
128 injection site erythema, and discomfort.

129 *Serious Adverse Events (SAEs)*: In Trial 1, no SAEs were reported. In Trial 2, 3% of subjects  
130 receiving FLULAVAL and 3% of subjects receiving the active comparator reported SAEs. In  
131 Trial 3, 1% of subjects receiving FLULAVAL and 1% of subjects receiving placebo reported  
132 SAEs. In the 3 clinical trials, the rates of SAEs were comparable between groups and none of the  
133 SAEs were considered related to vaccination.

#### 134 FLULAVAL in Children

135 *Trial 4 (Immunogenicity Non-Inferiority)*: An observer-blind, active-controlled US trial  
136 evaluated subjects aged 3 through 17 years who received FLULAVAL (N = 1,055) or  
137 FLUZONE (N = 1,061), a US-licensed trivalent, inactivated influenza vaccine, manufactured by  
138 Sanofi Pasteur SA. In the overall population, 53% were male; 78% of subjects were white, 12%  
139 were black, 2% were Asian, and 8% were of other racial/ethnic groups. The mean age of subjects  
140 was 8 years. Children aged 3 through 8 years with no history of influenza vaccination received  
141 2 doses approximately 28 days apart. Children aged 3 through 8 years with a history of influenza  
142 vaccination and children aged 9 years and older received one dose. Solicited local adverse  
143 reactions and systemic adverse events were collected for 4 days (day of vaccination and the next  
144 3 days) (Table 3).

145 **Table 3. FLULAVAL: Incidence of Solicited Local Adverse Reactions and Systemic**  
 146 **Adverse Events within 4 Days<sup>a</sup> of First Vaccination in Children Aged 3 through 17 Years<sup>b</sup>**  
 147 **(Total Vaccinated Cohort)**

	<b>FLULAVAL</b> %	<b>Active Comparator<sup>c</sup></b> %
<b>Aged 3 through 17 Years</b>		
<b>Local Adverse Reactions</b>	<b>N = 1,042</b>	<b>N = 1,026</b>
Pain	56	53
Redness	4	5
Swelling	4	5
<b>Aged 3 through 4 Years</b>		
<b>Systemic Adverse Events</b>	<b>N = 293</b>	<b>N = 279</b>
Irritability	25	27
Drowsiness	19	19
Loss of appetite	16	13
Fever $\geq 100.4^{\circ}\text{F}$ ( $38.0^{\circ}\text{C}$ )	5	3
<b>Aged 5 through 17 Years</b>		
<b>Systemic Adverse Events</b>	<b>N = 750</b>	<b>N = 747</b>
Muscle aches	24	23
Headache	17	15
Fatigue	17	17
Arthralgia	8	10
Shivering	6	5
Fever $\geq 100.4^{\circ}\text{F}$ ( $38.0^{\circ}\text{C}$ )	5	4

148 Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were  
 149 available.

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

151 <sup>b</sup> Trial 4: NCT00980005.

152 <sup>c</sup> US-licensed trivalent, inactivated influenza vaccine (manufactured by Sanofi Pasteur SA).

153 In children who received a second dose of FLULAVAL or the comparator vaccine, the  
 154 incidences of adverse events following the second dose were generally lower than those  
 155 observed after the first dose.

156 The incidence of unsolicited adverse events that occurred within 28 days (Day 0 to 27) of any  
 157 vaccination reported in subjects who received FLULAVAL (N = 1,055) or FLUZONE  
 158 (N = 1,061) was 40% and 37%, respectively. The unsolicited adverse events that occurred most  
 159 frequently ( $\geq 0.1\%$  of subjects for FLULAVAL) and considered possibly related to vaccination  
 160 included diarrhea, influenza-like illness, injection site hematoma, injection site rash, injection  
 161 site warmth, rash, upper abdominal pain, and vomiting. The rates of SAEs were comparable  
 162 between groups (0.9% and 0.6% for FLULAVAL and the comparator, respectively); none of the



163 SAEs were considered related to vaccination.

## 164 **6.2 Postmarketing Experience**

165 In addition to reports in clinical trials, the following adverse events have been identified during  
166 postapproval use of FLULAVAL. Because these events are reported voluntarily from a  
167 population of uncertain size, it is not always possible to reliably estimate their incidence rate or  
168 establish a causal relationship to the vaccine. Adverse events described here are included  
169 because: a) they represent reactions which are known to occur following immunizations  
170 generally or influenza immunizations specifically; b) they are potentially serious; or c) the  
171 frequency of reporting.

### 172 Blood and Lymphatic System Disorders

173 Lymphadenopathy.

### 174 Eye Disorders

175 Eye pain, photophobia.

### 176 Gastrointestinal Disorders

177 Dysphagia.

### 178 General Disorders and Administration Site Conditions

179 Chest pain, injection site inflammation, asthenia, injection site rash, abnormal gait, injection site  
180 bruising, injection site sterile abscess.

### 181 Immune System Disorders

182 Allergic reactions including anaphylaxis, angioedema.

### 183 Infections and Infestations

184 Rhinitis, laryngitis, cellulitis.

### 185 Musculoskeletal and Connective Tissue Disorders

186 Muscle weakness, arthritis.

### 187 Nervous System Disorders

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

### 190 Psychiatric Disorders

191 Insomnia.

### 192 Respiratory, Thoracic, and Mediastinal Disorders

193 Dyspnea, dysphonia, bronchospasm, throat tightness.

194 Skin and Subcutaneous Tissue Disorders

195 Urticaria, pruritus, sweating.

196 Vascular Disorders

197 Flushing, pallor.

198 **7 DRUG INTERACTIONS**

199 **7.1 Concomitant Administration with Other Vaccines**

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

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

204 **7.2 Immunosuppressive Therapies**

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

208 **8 USE IN SPECIFIC POPULATIONS**

209 **8.1 Pregnancy**

210 Pregnancy Category B. A reproductive and developmental toxicity study has been performed in  
211 female rats at a dose 40-fold the human dose (on a mg/kg basis) and showed no evidence of  
212 impaired female fertility or harm to the fetus due to FLULAVAL. There are, however, no  
213 adequate and well-controlled studies in pregnant women. Because animal reproduction studies  
214 are not always predictive of human response, FLULAVAL should be given to a pregnant woman  
215 only if clearly needed.

216 In a reproductive and developmental toxicity study, the effect of FLULAVAL on embryo-fetal  
217 and pre-weaning development was evaluated in rats. Animals were administered FLULAVAL by  
218 intramuscular injection once prior to gestation, and during the period of organogenesis (gestation  
219 Days 6, 8, 11, and 15), 0.1 mL/dose/rat (approximately 40-fold higher than the projected human  
220 dose on a body weight basis). No adverse effects on mating, female fertility, pregnancy,  
221 parturition, lactation parameters, and embryo-fetal or pre-weaning development were observed.  
222 There were no vaccine-related fetal malformations or other evidence of teratogenesis.

223 Pregnancy Registry

224 GlaxoSmithKline maintains a surveillance registry to collect data on pregnancy outcomes and  
225 newborn health status outcomes following vaccination with FLULAVAL during pregnancy.  
226 Women who receive FLULAVAL during pregnancy should be encouraged to contact  
227 GlaxoSmithKline directly or their healthcare provider should contact GlaxoSmithKline by

228 calling 1-888-452-9622.

### 229 **8.3 Nursing Mothers**

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

### 233 **8.4 Pediatric Use**

234 Safety and effectiveness of FLULAVAL in children younger than 3 years have not been  
235 established.

236 Safety and immunogenicity of FLULAVAL in children aged 3 through 17 years have been  
237 evaluated [*see Adverse Reactions (6.1), Clinical Studies (14)*].

### 238 **8.5 Geriatric Use**

239 In clinical trials, there were 330 subjects aged 65 years and older who received FLULAVAL;  
240 142 of these subjects were aged 75 years and older. Hemagglutination inhibition antibody  
241 responses were lower in geriatric subjects than younger subjects after administration of  
242 FLULAVAL. [*See Clinical Studies (14.2)*.] Solicited adverse events were similar in frequency to  
243 those reported in younger subjects [*see Adverse Reactions (6.1)*].

## 244 **11 DESCRIPTION**

245 FLULAVAL, Influenza Vaccine, for intramuscular injection, is a trivalent, split-virion,  
246 inactivated influenza virus vaccine prepared from virus propagated in the allantoic cavity of  
247 embryonated hens' eggs. Each of the influenza viruses is produced and purified separately. The  
248 virus is inactivated with ultraviolet light treatment followed by formaldehyde treatment, purified  
249 by centrifugation, and disrupted with sodium deoxycholate.

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

253 FLULAVAL has been standardized according to USPHS requirements for the 2015-2016  
254 influenza season and is formulated to contain 45 micrograms (mcg) hemagglutinin (HA) per 0.5-  
255 mL dose in the recommended ratio of 15 mcg HA of each of the following 3 strains:  
256 A/California/7/2009 NYMC X-179A (H1N1), A/Switzerland/9715293/2013 NIB-88 (H3N2),  
257 and B/Phuket/3073/2013.

258 The prefilled syringe is formulated without preservatives and does not contain thimerosal. Each  
259 0.5-mL dose from the multi-dose vial contains 50 mcg thimerosal (<25 mcg mercury);  
260 thimerosal, a mercury derivative, is added as a preservative.

261 Each 0.5-mL dose of either presentation may also contain residual amounts of ovalbumin  
262 ( $\leq 0.3$  mcg), formaldehyde ( $\leq 25$  mcg), sodium deoxycholate ( $\leq 50$  mcg),  $\alpha$ -tocopheryl hydrogen

263 succinate ( $\leq 240$  mcg), and polysorbate 80 ( $\leq 665$  mcg) from the manufacturing process.  
264 Antibiotics are not used in the manufacture of this vaccine.  
265 The tip caps and plungers of the prefilled syringes are not made with natural rubber latex. The  
266 vial stoppers are not made with natural rubber latex.

## 267 **12 CLINICAL PHARMACOLOGY**

### 268 **12.1 Mechanism of Action**

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

272 Specific levels of hemagglutination inhibition (HI) antibody titer post-vaccination with  
273 inactivated influenza virus vaccines have not been correlated with protection from influenza  
274 illness but the antibody titers have been used as a measure of vaccine activity. In some human  
275 challenge studies, antibody titers of  $\geq 1:40$  have been associated with protection from influenza  
276 illness in up to 50% of subjects.<sup>1,2</sup> Antibody against one influenza virus type or subtype confers  
277 little or no protection against another virus. Furthermore, antibody to one antigenic variant of  
278 influenza virus might not protect against a new antigenic variant of the same type or subtype.  
279 Frequent development of antigenic variants through antigenic drift is the virological basis for  
280 seasonal epidemics and the reason for the usual change of one or more new strains in each year's  
281 influenza vaccine. Therefore, inactivated influenza vaccines are standardized to contain the  
282 hemagglutinins of strains (i.e., typically 2 type A and 1 type B), representing the influenza  
283 viruses likely to circulate in the United States in the upcoming winter.

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

## 286 **13 NONCLINICAL TOXICOLOGY**

### 287 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

## 291 **14 CLINICAL STUDIES**

292 The effectiveness of FLULAVAL was demonstrated based on clinical endpoint efficacy data for  
293 FLULAVAL QUADRIVALENT (Influenza Vaccine), clinical endpoint efficacy data for  
294 FLULAVAL, and on an evaluation of serum HI antibody responses to FLULAVAL.  
295 FLULAVAL QUADRIVALENT, an inactivated influenza vaccine that contains the  
296 hemagglutinins of two influenza A subtype viruses and two influenza type B viruses, is  
297 manufactured according to the same process as FLULAVAL.

298 **14.1 Efficacy against Influenza**

299 Efficacy Trial in Children

300 The efficacy of FLULAVAL QUADRIVALENT was evaluated in Trial 5, a randomized,  
301 observer-blind, non-influenza vaccine-controlled trial conducted in 3 countries in Asia, 3 in Latin  
302 America, and 2 in the Middle East/Europe during the 2010-2011 influenza season. Healthy  
303 subjects aged 3 through 8 years were randomized (1:1) to receive FLULAVAL  
304 QUADRIVALENT (N = 2,584), containing A/California/7/2009 (H1N1), A/Victoria/210/2009  
305 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/4/2006 (Yamagata lineage)  
306 influenza strains, or HAVRIX<sup>®</sup> (Hepatitis A Vaccine) (N = 2,584), as a control vaccine. Children  
307 with no history of influenza vaccination received 2 doses of FLULAVAL QUADRIVALENT or  
308 HAVRIX approximately 28 days apart. Children with a history of influenza vaccination received  
309 one dose of FLULAVAL QUADRIVALENT or HAVRIX. In the overall population, 52% were  
310 male; 60% were Asian, 5% were white, and 35% were of other racial/ethnic groups. The mean  
311 age of subjects was 5 years.

312 Efficacy of FLULAVAL QUADRIVALENT was assessed for the prevention of reverse  
313 transcriptase polymerase chain reaction (RT-PCR)-positive influenza A and/or B disease  
314 presenting as influenza-like illness (ILI). ILI was defined as a temperature  $\geq 100^{\circ}\text{F}$  in the  
315 presence of at least one of the following symptoms on the same day: cough, sore throat, runny  
316 nose, or nasal congestion. Subjects with ILI (monitored by passive and active surveillance for  
317 approximately 6 months) had nasal and throat swabs collected and tested for influenza A and/or  
318 B by RT-PCR. All RT-PCR-positive specimens were further tested in cell culture. Vaccine  
319 efficacy was calculated based on the ATP cohort for efficacy (Table 4).

320 **Table 4. FLULAVAL QUADRIVALENT: Influenza Attack Rates and Vaccine Efficacy**  
 321 **against Influenza A and/or B in Children Aged 3 through 8 Years<sup>a</sup> (According-to-Protocol**  
 322 **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	–

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

324 <sup>a</sup> Trial 5: NCT01218308.

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

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

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

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

332 <sup>f</sup> Of 162 culture-confirmed influenza cases, 108 (67%) were antigenically typed (87 matched;  
 333 21 unmatched); 54 (33%) could not be antigenically typed [but were typed by RT-PCR and  
 334 nucleic acid sequence analysis: 5 cases A (H1N1) (5 with HAVRIX), 47 cases A (H3N2) (10  
 335 with FLULAVAL QUADRIVALENT; 37 with HAVRIX), and 2 cases B Victoria (2 with  
 336 HAVRIX)].

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

338 In an exploratory analysis by age, vaccine efficacy against RT-PCR-positive influenza A and/or  
 339 B disease presenting as ILI was evaluated in subjects aged 3 through 4 years and 5 through  
 340 8 years; vaccine efficacy was 35.3% (95% CI: -1.3, 58.6) and 67.7% (95% CI: 49.7, 79.2),

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

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

349 The risk reduction of fever >102.2°F/39.0°C associated with RT-PCR-positive influenza was  
 350 71.0% (95% CI: 44.8, 84.8) based on the ATP cohort for efficacy [FLULAVAL  
 351 QUADRIVALENT (n = 12/2,379); HAVRIX (n = 41/2,398)]. The other pre-specified adverse  
 352 outcomes had too few cases to calculate a risk reduction. The incidence of these adverse  
 353 outcomes is presented in Table 5.

354 **Table 5. FLULAVAL QUADRIVALENT: Incidence of Adverse Outcomes Associated with**  
 355 **RT-PCR-positive Influenza in Children Aged 3 through 8 Years<sup>a</sup> (Total Vaccinated**  
 356 **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

357 <sup>a</sup> Trial 5: NCT01218308.

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

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

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

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

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

365 **Efficacy Trial in Adults**

366 The efficacy of FLULAVAL was evaluated in a randomized, double-blind, placebo-controlled  
 367 trial conducted in the United States during the 2005-2006 and 2006-2007 influenza seasons  
 368 (Trial 3). Efficacy of FLULAVAL was defined as the prevention of culture-confirmed influenza  
 369 A and/or B cases, for vaccine antigenically matched strains, compared with placebo. Healthy  
 370 subjects aged 18 through 49 years were randomized (1:1); a total of 3,783 subjects received  
 371 FLULAVAL and 3,828 subjects received placebo [see *Adverse Reactions (6.1)*]. Subjects were  
 372 monitored for influenza-like illnesses (ILI) starting 2 weeks post-vaccination and for duration of  
 373 approximately 7 months thereafter. Culture-confirmed influenza was assessed by active and  
 374 passive surveillance of ILI. Influenza-like illness was defined as illness sufficiently severe to  
 375 limit daily activity and including cough, and at least one of the following: Fever >99.9°F, nasal  
 376 congestion or runny nose, sore throat, muscle aches or arthralgia, headache, feverishness or  
 377 chills. After an episode of ILI, nose and throat swab samples were collected for analysis; attack  
 378 rates and vaccine efficacy were calculated using the per protocol cohort (Table 6). Of note, the  
 379 1.2% attack rate in the placebo group for culture-confirmed, antigenically matched strains was  
 380 lower than expected, contributing to a wide confidence interval for the estimate of vaccine  
 381 efficacy.

382 **Table 6. FLULAVAL: Influenza Attack Rates and Vaccine Efficacy against Culture-**  
 383 **confirmed Influenza in Adults Aged 18 through 49 Years<sup>a</sup> (Per Protocol Cohort)**

			Influenza Attack Rates	Vaccine Efficacy	
	N <sup>b</sup>	n <sup>c</sup>	% (n/N)	%	97.5% CI Lower Limit
<b>Antigenically Matched Strains</b>					
FLULAVAL	3,714	23	0.6	46.3	9.8 <sup>d</sup>
Placebo	3,768	45	1.2	–	–
<b>All Culture-confirmed Influenza (Matched, Unmatched, and Untyped)</b>					
FLULAVAL	3,714	30	0.8	49.3	20.3
Placebo	3,768	60	1.6	–	–

384 CI = Confidence Interval.

385 <sup>a</sup> Trial 3: NCT00216242.

386 <sup>b</sup> Per Protocol Cohort for efficacy included subjects with no protocol deviations considered to



387       compromise efficacy data.

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

389       <sup>d</sup> Lower limit of the one-sided 97.5% CI for vaccine efficacy against influenza due to  
390       antigenically matched strains was less than the pre-defined success criterion of  $\geq 35\%$ .

## 391   **14.2 Immunological Evaluation**

### 392   Adults

393   Trial 1 was a randomized, blinded, active-controlled US trial performed in healthy adults aged 18  
394   through 64 years (N = 1,000). A total of 721 subjects received FLULAVAL, and 279 received a  
395   US-licensed trivalent, inactivated influenza vaccine, FLUZONE (manufactured by Sanofi  
396   Pasteur SA), intramuscularly; 959 subjects had complete serological data and no major protocol  
397   deviations [*see Adverse Reactions (6.1)*].

398   Analyses of immunogenicity (Table 7) were performed for each hemagglutinin (HA) antigen  
399   contained in the vaccine: 1) assessment of the lower bounds of 2-sided 95% confidence intervals  
400   for the proportion of subjects with HI antibody titers of  $\geq 1:40$  after vaccination, and  
401   2) assessment of the lower bounds of 2-sided 95% confidence intervals for rates of  
402   seroconversion (defined as a 4-fold increase in post-vaccination HI antibody titer from pre-  
403   vaccination titer  $\geq 1:10$ , or an increase in titer from  $< 1:10$  to  $\geq 1:40$ ). The pre-specified success  
404   criteria for HI titer  $\geq 1:40$  was 70% and for seroconversion rate was 40%. The lower limit of the  
405   2-sided 95% CI for the percentage of subjects who achieved an HI titer of  $\geq 1:40$  exceeded the  
406   pre-defined criteria for the A strains. The lower limit of the 2-sided 95% CI for the percentage of  
407   subjects who achieved seroconversion exceeded the pre-defined criteria for all 3 strains.

408 **Table 7. Immune Responses to Each Antigen 21 Days after Vaccination with FLULAVAL<sup>a</sup>**  
 409 **in Adults Aged 18 through 64 Years (Per Protocol Cohort)<sup>b</sup>**

HI titers $\geq$ 1:40	FLULAVAL N = 692 % of Subjects (95% CI)	
	Pre-vaccination	Post-vaccination
A/New Caledonia/20/99 (H1N1)	24.6	96.5 (94.9, 97.8)
A/Wyoming/03/03 (H3N2)	58.7	98.7 (97.6, 99.4)
B/Jiangsu/10/03	5.4	62.9 (59.1, 66.5)
<b>Seroconversion<sup>c</sup> to:</b>		
A/New Caledonia/20/99 (H1N1)	85.6 (82.7, 88.1)	
A/Wyoming/03/03 (H3N2)	79.3 (76.1, 82.3)	
B/Jiangsu/10/03	58.4 (54.6, 62.1)	

410 HI = hemagglutination inhibition; CI = Confidence Interval.

411 <sup>a</sup> Results obtained following vaccination with FLULAVAL manufactured for the 2004–2005  
 412 season.

413 <sup>b</sup> Per Protocol Cohort for immunogenicity included subjects with complete pre- and post-dose  
 414 HI titer data and no major protocol deviations.

415 <sup>c</sup> Seroconversion defined as a 4-fold increase in post-vaccination HI antibody titers from pre-  
 416 vaccination titer  $\geq$ 1:10, or an increase in titer from  $<$ 1:10 to  $\geq$ 1:40.

417 *Trial 2 (Immunogenicity Non-Inferiority)*: In a randomized, double-blind, active-controlled US  
 418 trial, immunological non-inferiority of FLULAVAL was compared with a US-licensed trivalent,  
 419 inactivated influenza vaccine, FLUZONE, manufactured by Sanofi Pasteur SA. A total of 1,225  
 420 adults aged 50 years and older in stable health were randomized to receive FLULAVAL or the  
 421 comparator vaccine intramuscularly [see *Adverse Reactions (6.1)*].

422 Analyses of immunogenicity were performed for each HA antigen contained in the vaccines:  
 423 1) assessment of the lower bounds of 2-sided 95% confidence intervals for the geometric mean  
 424 antibody titer (GMT) ratio (FLULAVAL/comparator), and 2) assessment of the lower bounds of  
 425 2-sided 95% confidence intervals for seroconversion rates (defined as a 4-fold increase in post-  
 426 vaccination HI antibody titer from pre-vaccination titer  $\geq$ 1:10, or an increase in titer from  $<$ 1:10  
 427 to  $\geq$ 1:40). Non-inferiority of FLULAVAL to the comparator vaccine was established for all 6 co-  
 428 primary endpoints (Table 8). Within each age stratum, immunogenicity results were similar  
 429 between the groups.

430 **Table 8. Immune Responses to Each Antigen 21 Days after Vaccination with FLULAVAL**  
 431 **Versus Comparator Influenza Vaccine in Adults Aged 50 Years and Older<sup>a</sup> (Per Protocol**  
 432 **Cohort)<sup>b</sup>**

	<b>FLULAVAL N = 592</b>	<b>Active Comparator<sup>c</sup> N = 595</b>	
<b>GMTs Against</b>	<b>GMT (95% CI)</b>	<b>GMT (95% CI)</b>	<b>GMT Ratio<sup>d</sup> (95% CI)</b>
A/New Caledonia/20/99 (H1N1)	113.4 (104.7, 122.8)	110.2 (101.8, 119.3)	1.03 (0.92, 1.15)
A/New York/55/04 (H3N2)	223.9 (199.5, 251.3)	214.6 (191.3, 240.7)	1.04 (0.89, 1.23)
B/Jiangsu/10/03	82.3 (74.7, 90.6)	97.1 (88.2, 106.8)	0.85 (0.74, 0.97)
<b>Seroconversion<sup>e</sup> to:</b>	<b>% of Subjects (95% CI)</b>	<b>% of Subjects (95% CI)</b>	<b>Difference in Seroconversion Rates<sup>f</sup> (95% CI)</b>
A/New Caledonia/20/99 (H1N1)	34 (30.0, 37.6)	32 (28.3, 35.9)	2 (-3.7, 7.0)
A/New York/55/04 (H3N2)	83 (80.3, 86.3)	82 (78.4, 84.6)	1 (-2.6, 6.1)
B/Jiangsu/10/03	53 (49.0, 57.1)	56 (51.6, 59.6)	-3 (-8.3, 3.1)

433 GMT = Geometric mean antibody titer; CI = Confidence Interval.

434 <sup>a</sup> Results obtained following vaccination with influenza vaccines manufactured for the  
 435 2005-2006 season.

436 <sup>b</sup> Per Protocol Cohort for immunogenicity included subjects with complete pre- and post-dose  
 437 HI titer data and no major protocol deviations.

438 <sup>c</sup> US-licensed trivalent, inactivated influenza vaccine (manufactured by Sanofi Pasteur SA).

439 <sup>d</sup> FLULAVAL met non-inferiority criteria based on GMTs (lower limit of 2-sided 95% CI for  
 440 GMT ratio [FLULAVAL/comparator vaccine]  $\geq 0.67$ ).

441 <sup>e</sup> Seroconversion defined as a 4-fold increase in post-vaccination HI antibody titer from pre-  
 442 vaccination titer  $\geq 1:10$ , or an increase in titer from  $<1:10$  to  $\geq 1:40$ .

443 <sup>f</sup> FLULAVAL met non-inferiority criteria based on seroconversion rates (lower limit of 2-sided  
 444 95% CI for difference of FLULAVAL minus the comparator vaccine  $\geq -10\%$ ).

445 **Children**

446 In Trial 4, the immune response of FLULAVAL (N = 987) was compared to FLUZONE, a

447 US-licensed trivalent, inactivated influenza vaccine (N = 979), manufactured by Sanofi Pasteur  
 448 SA, in an observer-blind, randomized trial in children aged 3 through 17 years. The immune  
 449 responses to each of the antigens contained in FLULAVAL formulated for the 2009-2010 season  
 450 were evaluated in sera obtained after one or 2 doses of FLULAVAL and were compared to those  
 451 following the comparator influenza vaccine [see Adverse Reactions (6.1)].

452 The non-inferiority endpoints were GMTs adjusted for baseline, and the percentage of subjects  
 453 who achieved seroconversion, defined as at least a 4-fold increase in serum HI titer over baseline  
 454 to  $\geq 1:40$ , following vaccination, performed on the According-to-Protocol (ATP) cohort.

455 FLULAVAL was non-inferior to the comparator influenza for all strains based on adjusted  
 456 GMTs and seroconversion rates (Table 9).

457 **Table 9. Immune Responses to Each Antigen 28 Days after Last Vaccination with**  
 458 **FLULAVAL Versus Comparator Influenza Vaccine in Children Aged 3 through 17 Years<sup>a</sup>**  
 459 **(According-to-Protocol Cohort for Immunogenicity)<sup>b</sup>**

	<b>FLULAVAL</b>	<b>Active Comparator<sup>c</sup></b>	
<b>GMTs Against</b>	<b>N = 987</b> <b>(95% CI)</b>	<b>N = 979</b> <b>(95% CI)</b>	<b>GMT Ratio<sup>d</sup></b> <b>(95% CI)</b>
A/Brisbane (H1N1)	320.9 (298.3, 345.2)	329.4 (306.8, 353.7)	1.03 (0.94, 1.13)
A/Uruguay (H3N2)	414.7 (386.5, 444.9)	451.9 (423.8, 481.8)	1.05 (0.96, 1.13)
B/Brisbane	213.7 (198.5, 230.1)	200.2 (186.1, 215.3)	0.93 (0.85, 1.02)
<b>Seroconversion<sup>e</sup> to:</b>	<b>N = 987</b> <b>%</b> <b>(95% CI)</b>	<b>N = 978</b> <b>%</b> <b>(95% CI)</b>	<b>Difference in</b> <b>Seroconversion</b> <b>Rate<sup>f</sup></b> <b>(95% CI)</b>
A/Brisbane (H1N1)	59.8 (56.6, 62.9)	58.2 (55.0, 61.3)	-1.6 (-5.9, 2.8)
A/Uruguay (H3N2)	68.2 (65.2, 71.1)	66.2 (63.1, 69.1)	-2.0 (-6.1, 2.1)
B/Brisbane	81.1 (78.5, 83.5)	78.6 (75.9, 81.2)	-2.4 (-6.0, 1.1)

460 GMT = Geometric mean antibody titer; CI = Confidence Interval.

461 <sup>a</sup> Results obtained following vaccination with influenza vaccines formulated for the 2009-2010  
 462 season.

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

- 465 <sup>c</sup> US-licensed trivalent, inactivated influenza vaccine (Sanofi Pasteur SA).
- 466 <sup>d</sup> FLULAVAL met non-inferiority criteria based on GMTs (upper limit of 2-sided 95% CI for  
467 GMT ratio [comparator vaccine/FLULAVAL] ≤1.5).
- 468 <sup>e</sup> Seroconversion defined as a 4-fold increase in post-vaccination HI antibody titer from pre-  
469 vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40.
- 470 <sup>f</sup> FLULAVAL met non-inferiority criteria based on seroconversion rates (upper limit of 2-sided  
471 95% CI for difference of the comparator vaccine minus FLULAVAL ≤10%).

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## 481 **16 HOW SUPPLIED/STORAGE AND HANDLING**

482 FLULAVAL is available in 0.5-mL single-dose disposable prefilled TIP-LOK syringes  
483 (packaged without needles) and in 5-mL multi-dose vials containing 10 doses (0.5-mL each).  
484 NDC 19515-850-41 Syringe in Package of 10: NDC 19515-850-52  
485 NDC 19515-845-01 Multi-Dose Vial (containing 10 doses) in Package of 1: NDC 19515-845-11  
486 Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has  
487 been frozen. Store in the original package to protect from light. Once entered, a multi-dose vial  
488 should be discarded after 28 days.

## 489 **17 PATIENT COUNSELING INFORMATION**

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

- 491 • Inform of the potential benefits and risks of immunization with FLULAVAL.
- 492 • Educate regarding potential side effects, emphasizing that: (1) FLULAVAL contains non-  
493 infectious killed viruses and cannot cause influenza, and (2) FLULAVAL is intended to  
494 provide protection against illness due to influenza viruses only, and cannot provide  
495 protection against all respiratory illness.
- 496 • Inform that safety and efficacy have not been established in pregnant women. Register  
497 women who receive FLULAVAL while pregnant in the pregnancy registry by calling 1-888-

- 498 452-9622.
- 499 • Give the Vaccine Information Statements, which are required by the National Childhood  
500 Vaccine Injury Act of 1986 prior to each immunization. These materials are available free of  
501 charge at the Centers for Disease Control and Prevention (CDC) website  
502 ([www.cdc.gov/vaccines](http://www.cdc.gov/vaccines)).
- 503 • Instruct that annual revaccination is recommended.
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