

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**Fluzone (Influenza Vaccine)**  
**Suspension for Intramuscular Injection**  
**2015-2016 Formula**  
**Initial US Approval 1980**

### INDICATIONS AND USAGE

Fluzone is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B virus contained in the vaccine. (1)

Fluzone is approved for use in persons 6 months of age and older. (1)

### DOSAGE AND ADMINISTRATION

- For intramuscular use only

Age	Dose	Schedule
6 months through 35 months	One or two doses <sup>a</sup> , 0.25 mL each	If 2 doses, administer at least 1 month apart
36 months through 8 years	One or two doses <sup>a</sup> , 0.5 mL each	If 2 doses, administer at least 1 month apart
9 years and older	One dose, 0.5 mL	-

<sup>a</sup>1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines

"-" Indicates information is not applicable

### DOSAGE FORMS AND STRENGTHS

Suspension for injection supplied in multi-dose vial, 5 mL. (3)

### CONTRAINDICATIONS

Severe allergic reaction to any component of the vaccine, including egg protein, or after previous dose of any influenza vaccine. (4)

### WARNINGS AND PRECAUTIONS

- If Guillain-Barré syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give Fluzone should be based on careful consideration of the potential benefits and risks. (5.1)

### ADVERSE REACTIONS

- In children 6 months through 8 years of age, the most common injection-site reactions were pain or tenderness (>50%) and redness (>25%); the most common solicited systemic adverse events were irritability and drowsiness (>25% of children 6 months through 35 months) and myalgia (>20% of children 3 years through 8 years). (6.1)
- In adults 18 through 64 years of age, the most common injection-site reaction was pain (>50%); the most common solicited systemic adverse events were headache and myalgia (>30%). (6.1)
- In adults ≥65 years of age, the most common injection-site reaction was pain (>20%); the most common solicited systemic adverse events were headache, myalgia, and malaise (>10%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 at 1-800-822-2463 (1-800-VACCINE) 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 Fluzone has not been established in pregnant women. (8.1)
- Antibody responses to Fluzone are lower in persons ≥65 years of age than in younger adults. (8.5)

See 17 PATIENT COUNSELING INFORMATION and FDA - approved patient labeling.

Revised: XXXX XXXX

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

1 **FULL PRESCRIBING INFORMATION:**

2 **1 INDICATIONS AND USAGE**

3 Fluzone® is a vaccine indicated for active immunization for the prevention of influenza disease  
4 caused by influenza A subtype viruses and type B virus contained in the vaccine.

5

6 Fluzone is approved for use in persons 6 months of age and older.

7

8 **2 DOSAGE AND ADMINISTRATION**

- 9 • **For intramuscular use only**

10 **2.1 Dose and Schedule**

11 The dose and schedule for Fluzone are presented in [Table 1](#).

12 **Table 1: Dose and Schedule for Fluzone**

<b>Age</b>	<b>Dose</b>	<b>Schedule</b>
6 months through 35 months	One or two doses <sup>a</sup> , 0.25 mL each	If 2 doses, administer at least 1 month apart
36 months through 8 years	One or two doses <sup>a</sup> , 0.5 mL each	If 2 doses, administer at least 1 month apart
9 years and older	One dose, 0.5 mL	-

13 <sup>a</sup>1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual  
14 recommendations on prevention and control of influenza with vaccines

15 "-" Indicates information is not applicable

16

17 **2.2 Administration**

18 Inspect Fluzone visually for particulate matter and/or discoloration prior to administration. If

19 either of these conditions exist, the vaccine should not be administered.

20

21 Before administering a dose of vaccine, shake the prefilled syringe or multi-dose vial. Withdraw a  
22 single dose of vaccine using a sterile needle and syringe. Use a separate sterile needle and syringe  
23 for each dose withdrawn from the multi-dose vial.

24

25 The preferred sites for intramuscular injection are the anterolateral aspect of the thigh in infants 6  
26 months through 11 months of age, the anterolateral aspect of the thigh (or the deltoid muscle if  
27 muscle mass is adequate) in persons  $\geq 12$  months through 35 months of age, or the deltoid muscle  
28 in persons  $\geq 36$  months of age. The vaccine should not be injected into the gluteal area or areas  
29 where there may be a major nerve trunk.

30

31 Do not administer this product intravenously or subcutaneously.

32

33 Fluzone should not be combined through reconstitution or mixed with any other vaccine.

34

### 35 **3 DOSAGE FORMS AND STRENGTHS**

36 Fluzone is a suspension for injection.

37

38 Fluzone is supplied in 1 presentation:

39 1) Multi-dose vial, 5 mL, for persons 6 months of age and older.

40

### 41 **4 CONTRAINDICATIONS**

42 A severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine [see *Description*  
43 (11)], including egg protein, or to a previous dose of any influenza vaccine is a contraindication to  
44 administration of Fluzone.

45

## 46 **5 WARNINGS AND PRECAUTIONS**

### 47 **5.1 Guillain-Barré Syndrome**

48 The 1976 swine influenza vaccine was associated with an elevated risk of Guillain-Barré  
49 syndrome (GBS). Evidence for a causal relation of GBS with other influenza vaccines is  
50 inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case per 1  
51 million persons vaccinated. (1) If GBS has occurred within 6 weeks following previous influenza  
52 vaccination, the decision to give Fluzone should be based on careful consideration of the potential  
53 benefits and risks.

54

### 55 **5.2 Preventing and Managing Allergic Reactions**

56 Appropriate medical treatment and supervision must be available to manage possible anaphylactic  
57 reactions following administration of the vaccine.

58

### 59 **5.3 Altered Immunocompetence**

60 If Fluzone is administered to immunocompromised persons, including those receiving  
61 immunosuppressive therapy, the expected immune response may not be obtained.

62

### 63 **5.4 Limitations of Vaccine Effectiveness**

64 Vaccination with Fluzone may not protect all recipients.

65

## 66 **6 ADVERSE REACTIONS**

### 67 **6.1 Clinical Trials Experience**

68 Because clinical trials are conducted under widely varying conditions, adverse event rates  
69 observed in the clinical trial(s) of a vaccine cannot be directly compared to rates in the clinical  
70 trial(s) of another vaccine and may not reflect the rates observed in practice.

71

#### 72 **Children 6 Months through 8 Years of Age**

73 In a multi-center study conducted in the US, children 6 months through 35 months of age received  
74 two 0.25 mL doses of Fluzone, and children 3 years through 8 years of age received two 0.5 mL  
75 doses of Fluzone, irrespective of previous influenza vaccination history. The two doses (2006-  
76 2007 formulation) were administered 26 to 30 days apart. The safety analysis set included 97  
77 children 6 months through 35 months of age and 163 children 3 years through 8 years of age.  
78 [Table 2](#) and [Table 3](#) summarize solicited injection site reactions and systemic adverse events  
79 reported within 7 days post-vaccination via diary cards.

80 **Table 2: Frequency of Solicited Injection Site Reactions and Systemic Adverse Events**  
81 **Within 7 Days After Vaccination with Fluzone, Children 6 Through 35 Months of Age**

	Dose 1 (N <sup>a</sup> =90-92) Percentage			Dose 2 (N <sup>a</sup> =86-87) Percentage		
	Any	Moderate <sup>b</sup>	Severe <sup>c</sup>	Any	Moderate <sup>b</sup>	Severe <sup>c</sup>
<b>Injection-Site Tenderness</b>	47.3	8.8	0.0	56.3	3.4	1.1
<b>Injection-Site Erythema</b>	29.3	0.0	0.0	32.2	1.1	0.0
<b>Injection-Site Swelling</b>	16.7	0.0	0.0	14.9	0.0	0.0
<b>Injection-Site Induration</b>	14.4	0.0	0.0	16.1	0.0	0.0
<b>Injection-Site Ecchymosis</b>	14.4	1.1	0.0	14.9	2.3	0.0
<b>Fever<sup>d</sup> (≥100.4°F)</b>	11.0	4.4	0.0	10.3	3.4	1.1
<b>Vomiting</b>	6.6	1.1	0.0	8.1	5.8	0.0
<b>Crying Abnormal</b>	31.9	11.0	0.0	18.6	7.0	2.3
<b>Drowsiness</b>	26.4	1.1	0.0	26.7	4.7	0.0
<b>Appetite Lost</b>	23.1	8.8	0.0	19.8	5.8	1.2
<b>Irritability</b>	42.9	19.8	1.1	34.9	17.4	4.7

82 <sup>a</sup> N is the number of vaccinated participants with available data for the events listed

83 <sup>b</sup> Moderate - Injection-site tenderness: cries and protests when injection site is touched; Injection-site erythema,  
84 Injection-site swelling, Injection-site induration, and Injection-site ecchymosis: ≥2.5 cm to <5 cm; Fever: >101.3°F  
85 to ≤103.1°F; Vomiting: 2 to 5 episodes per 24 hours; Crying abnormal: 1 to 3 hours; Drowsiness: not interested in  
86 surroundings or did not wake up for a meal; Appetite lost: missed 1 or 2 feeds completely; Irritability: requiring  
87 increased attention

88 <sup>c</sup> Severe - Injection-site tenderness: cries when injected limb is moved or the movement of the injected limb is  
89 reduced; Injection-site erythema, Injection-site swelling, Injection-site induration, and Injection-site ecchymosis: ≥5  
90 cm; Fever: >103.1°F; Vomiting: ≥6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal: >3  
91 hours; Drowsiness: sleeping most of the time or difficulty to wake up; Appetite lost: refuses ≥3 feeds or refuses  
92 most feeds; Irritability: inconsolable

93 <sup>d</sup> Fever - The percentage of temperature measurements that were taken by rectal, axillary, or oral routes, or not  
94 recorded were 69.2%, 17.6%, 13.2%, and 0.0%, respectively, for Dose 1; and 69.0%, 13.8%, 16.1%, and 1.1%,  
95 respectively, for Dose 2

96

97 **Table 3: Frequency of Solicited Injection Site Reactions and Systemic Adverse Events**  
98 **Within 7 Days After Vaccination with Fluzone, Children 3 Through 8 Years of Age**

	Dose 1 (N <sup>a</sup> =150-151) Percentage			Dose 2 (N <sup>a</sup> =144-145) Percentage		
	Any	Moderate <sup>b</sup>	Severe <sup>c</sup>	Any	Moderate <sup>b</sup>	Severe <sup>c</sup>
<b>Injection-Site Pain</b>	59.3	8.0	0.0	62.1	9.7	0.7
<b>Injection-Site Erythema</b>	27.8	3.3	0.7	27.6	2.1	0.7
<b>Injection-Site Swelling</b>	19.9	5.3	0.0	14.5	2.8	0.0
<b>Injection-Site Induration</b>	16.6	2.0	0.0	11.7	1.4	0.0
<b>Injection-Site Ecchymosis</b>	12.6	0.7	0.7	15.2	0.7	0.0
<b>Injection-Site Pruritus</b>	7.3	-	-	13.2	-	-
<b>Fever<sup>d</sup> (≥99.5°F)</b>	11.9	2.6	2.0	9.7	1.4	1.4
<b>Headache</b>	16.7	2.0	0.7	11.8	1.4	1.4
<b>Malaise</b>	20.0	2.7	1.3	14.6	4.2	0.7
<b>Myalgia</b>	28.0	5.3	0.0	17.4	4.2	0.0

99 <sup>a</sup> N is the number of vaccinated participants with available data for the events listed

100 <sup>b</sup> Moderate - Injection-site pain: sufficiently discomforting to interfere with normal behavior or activities; Injection-  
101 site erythema, Injection-site swelling, Injection-site induration, and Injection-site ecchymosis: ≥2.5 cm to <5 cm;  
102 Fever: >100.4°F to ≤102.2°F; Headache, Malaise, and Myalgia: interferes with daily activities

103 <sup>c</sup> Severe - Injection-site pain: incapacitating, unable to perform usual activities, may have/or required medical care or  
104 absenteeism; Injection-site erythema, Injection-site swelling, Injection-site induration, and Injection-site  
105 ecchymosis: ≥5 cm; Fever: >102.2°F; Headache, Malaise, and Myalgia: prevents daily activities

106 <sup>d</sup> Fever - The percentage of temperature measurements that were taken by oral or axillary routes, or not recorded were  
107 93.4%, 6.6%, and 0.0%, respectively, for Dose 1; and 93.1%, 6.2%, and 0.7%, respectively, for Dose 2

108 "-" Indicates information was not collected

109

110 During the period from the first vaccination through 6 months following the second vaccination,  
111 there were no serious adverse events considered to be caused by vaccination and no deaths  
112 reported in this study.

113

#### 114 **Adults**

115 Adults 18 through 64 years of age received Fluzone (2008-2009 formulation) in a multi-center  
116 trial conducted in the US. The safety analysis set included 1421 Fluzone recipients. [Table 4](#)

117 summarizes solicited injection-site reactions and systemic adverse events reported within 7 days  
118 post-vaccination via diary cards.

119 **Table 4: Frequency of Solicited Injection-Site Reactions and Systemic Adverse Events**  
120 **Within 7 Days After Vaccination with Fluzone, Adults 18 Through 64 Years of Age**

	(N <sup>a</sup> =1392-1394) Percentage		
	Any	Grade 2 <sup>b</sup>	Grade 3 <sup>c</sup>
<b>Injection-Site Erythema</b>	13.2	2.1	0.9
<b>Injection-Site Induration</b>	10.0	2.3	0.5
<b>Injection-Site Swelling</b>	8.4	2.1	0.9
<b>Injection-Site Pain</b>	53.7	5.8	0.8
<b>Injection-Site Pruritus</b>	9.3	0.4	0.0
<b>Injection-Site Ecchymosis</b>	6.2	1.1	0.4
<b>Headache</b>	30.3	6.5	1.6
<b>Myalgia</b>	30.8	5.5	1.4
<b>Malaise</b>	22.2	5.5	1.8
<b>Shivering</b>	6.2	1.1	0.6
<b>Fever<sup>d</sup> (≥99.5°F)</b>	2.6	0.4	0.2

121 <sup>a</sup> N is the number of vaccinated participants with available data for the events listed

122 <sup>b</sup> Grade 2 - Injection-site erythema, Injection-site induration, Injection-site swelling, and Injection-site ecchymosis: ≥  
123 2.5 cm to <5 cm; Injection-site pain and Injection-site pruritus: sufficiently discomforting to interfere with normal  
124 behavior or activities; Fever: >100.4°F to ≤102.2°F; Headache, Myalgia, Malaise, and Shivering: interferes with  
125 daily activities

126 <sup>c</sup> Grade 3 - Injection-site erythema, Injection-site induration, Injection-site swelling, and Injection-site ecchymosis: ≥5  
127 cm; Injection-site pain: incapacitating, unable to perform usual activities; Injection-site pruritus: incapacitating,  
128 unable to perform usual activities, may have/or required medical care or absenteeism; Fever: >102.2°F; Headache,  
129 Myalgia, Malaise, and Shivering: prevents daily activities

130 <sup>d</sup> Fever - The percentage of temperature measurements that were taken by oral or axillary routes, or not recorded were  
131 99.6%, 0.0%, and 0.4%, respectively

132

133 Within 28 days and 6 months post-vaccination, a serious adverse event was reported by 5 (0.4%)

134 and 20 (1.4%) Fluzone recipients, respectively. No serious adverse event was considered to be

135 caused by vaccination. No deaths were reported during the 6 months post-vaccination.

136



137 **Geriatric Adults**

138 Adults 65 years of age and older received Fluzone (2006-2007 formulation) in a multi-center,  
139 double-blind trial conducted in the US. The safety analysis set included 1260 Fluzone recipients.

140

141 **Table 5** summarizes solicited injection-site reactions and systemic adverse events reported within  
142 7 days post-vaccination via diary cards. Onset was usually within the first 3 days after vaccination  
143 and a majority of the reactions resolved within 3 days.

144 **Table 5: Frequency of Solicited Injection-Site Reactions and Systemic Adverse Events**  
145 **Within 7 Days After Vaccination with Fluzone, Adults 65 Years of Age and Older**

	N <sup>a</sup> =1258-1260 Percentage		
	Any	Moderate <sup>b</sup>	Severe <sup>c</sup>
<b>Injection-Site Pain</b>	24.3	1.7	0.2
<b>Injection-Site Erythema</b>	10.8	0.8	0.6
<b>Injection-Site Swelling</b>	5.8	1.3	0.6
<b>Myalgia</b>	18.3	3.2	0.2
<b>Malaise</b>	14.0	3.7	0.6
<b>Headache</b>	14.4	2.5	0.3
<b>Fever<sup>d</sup> (≥99.5°F)</b>	2.3	0.2	0.1

146 <sup>a</sup> N is the number of vaccinated participants with available data for the events listed

147 <sup>b</sup> Moderate - Injection-site pain: sufficiently discomforting to interfere with normal behavior or activities; Injection-  
148 site erythema and Injection-site swelling: ≥2.5 cm to <5 cm; Fever: >100.4°F to ≤102.2°F; Myalgia, Malaise, and  
149 Headache: interferes with daily activities

150 <sup>c</sup> Severe - Injection-site pain: incapacitating, unable to perform usual activities; Injection-site erythema and Injection-  
151 site swelling: ≥5 cm; Fever: >102.2°F; Myalgia, Malaise, and Headache: prevents daily activities

152 <sup>d</sup> Fever - The percentage of temperature measurements that were taken by oral route or not recorded were 98.6% and  
153 1.4%, respectively

154

155 Within 6 months post-vaccination, 93 (7.4%) Fluzone recipients experienced a serious adverse  
156 event (N=1260). No deaths were reported within 28 days post-vaccination. A total of 7 deaths  
157 were reported during the period Day 29-180 post-vaccination: 7 (0.6%) among Fluzone recipients

158 (N=1260). The majority of these participants had a medical history of cardiac, hepatic, neoplastic,  
159 renal, and/or respiratory diseases. No deaths were considered to be caused by vaccination.

160

## 161 **6.2 Post-Marketing Experience**

162 The following events have been spontaneously reported during the post-approval use of Fluzone.

163 Because these events are reported voluntarily from a population of uncertain size, it is not always  
164 possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

165 Adverse events were included based on one or more of the following factors: severity, frequency  
166 of reporting, or strength of evidence for a causal relationship to Fluzone.

167

- 168 • *Blood and Lymphatic System Disorders*: Thrombocytopenia, lymphadenopathy
- 169 • *Immune System Disorders*: Anaphylaxis, other allergic/hypersensitivity reactions (including  
170 urticaria, angioedema)
- 171 • *Eye Disorders*: Ocular hyperemia
- 172 • *Nervous System Disorders*: Guillain-Barré syndrome (GBS), convulsions, febrile  
173 convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy  
174 (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination),  
175 dizziness, paresthesia
- 176 • *Vascular Disorders*: Vasculitis, vasodilatation/flushing
- 177 • *Respiratory, Thoracic and Mediastinal Disorders*: Dyspnea, pharyngitis, rhinitis, cough,  
178 wheezing, throat tightness
- 179 • *Skin and Subcutaneous Tissue Disorders*: Stevens-Johnson syndrome

180 • *General Disorders and Administration Site Conditions*: Pruritus, asthenia/fatigue, pain in  
181 extremities, chest pain

182 • *Gastrointestinal Disorders*: Vomiting

183

## 184 **7 DRUG INTERACTIONS**

185 Data evaluating the concomitant administration of Fluzone with other vaccines are not available.

186

## 187 **8 USE IN SPECIFIC POPULATIONS**

### 188 **8.1 Pregnancy**

189 Pregnancy Category C: Animal reproduction studies have not been conducted with Fluzone. It is  
190 also not known whether Fluzone can cause fetal harm when administered to a pregnant woman or  
191 can affect reproduction capacity. Fluzone should be given to a pregnant woman only if clearly  
192 needed.

193

### 194 **8.3 Nursing Mothers**

195 It is not known whether Fluzone is excreted in human milk. Because many drugs are excreted in  
196 human milk, caution should be exercised when Fluzone is administered to a nursing woman.

197

### 198 **8.4 Pediatric Use**

199 Safety and effectiveness of Fluzone in children below the age of 6 months have not been  
200 established. Safety and immunogenicity of Fluzone were evaluated in children 6 months through  
201 8 years of age. [See *Adverse Reactions (6.1) and Clinical Studies (14.3)*.] Efficacy of Fluzone was  
202 evaluated in children 6 through 24 months of age. [See *Clinical Studies (14.1)*.]

203 **8.5 Geriatric Use**

204 Safety and immunogenicity of Fluzone were evaluated in adults 65 years of age and older. [See  
205 *Adverse Reactions (6.1) and Clinical Studies (14.3).*] Antibody responses to Fluzone are lower in  
206 persons  $\geq 65$  years of age than in younger adults.

207

208 **11 DESCRIPTION**

209 Fluzone (Influenza Vaccine) for intramuscular injection is an inactivated influenza vaccine,  
210 prepared from influenza viruses propagated in embryonated chicken eggs. The virus-containing  
211 allantoic fluid is harvested and inactivated with formaldehyde. Influenza virus is concentrated and  
212 purified in a linear sucrose density gradient solution using a continuous flow centrifuge. The virus  
213 is then chemically disrupted using a non-ionic surfactant, octylphenol ethoxylate (Triton® X-100),  
214 producing a “split virus”. The split virus is further purified and then suspended in sodium  
215 phosphate-buffered isotonic sodium chloride solution.

216

217 Fluzone suspension for injection is clear and slightly opalescent in color.

218

219 Antibiotics are not used in the manufacture of Fluzone.

220

221 No presentation of Fluzone is made with natural rubber latex.

222

223 Fluzone is standardized according to United States Public Health Service requirements and is  
224 formulated to contain HA of each of the following three influenza strains recommended for the  
225 2015-2016 influenza season: A/California/07/2009 X-179A (H1N1),

226 A/Switzerland/9715293/2013 NIB-88 (H3N2), and B/Phuket/3073/2013 (B Yamagata lineage).  
 227 The amounts of HA and other ingredients per dose of vaccine are listed in Table 6. The 0.5 mL  
 228 single-dose, pre-filled syringe presentation is manufactured and formulated without thimerosal or  
 229 any other preservative. The 5 mL multi-dose vial presentation contains thimerosal, a mercury  
 230 derivative, added as a preservative. Each 0.5 mL dose from the multi-dose vial contains 25 mcg  
 231 mercury. Each 0.25 mL dose from the multi-dose vial contains 12.5 mcg mercury.

232 **Table 6: Fluzone Ingredients**

Ingredient	Quantity (per dose)	
	Fluzone 0.25 mL Dose	Fluzone 0.5 mL Dose
<b>Active Substance: Split influenza virus, inactivated strains<sup>a</sup>:</b>	22.5 mcg HA total	45 mcg HA total
A (H1N1)	7.5 mcg HA	15 mcg HA
A (H3N2)	7.5 mcg HA	15 mcg HA
B	7.5 mcg HA	15 mcg HA
<b>Other:</b>		
Sodium phosphate-buffered isotonic sodium chloride solution	QS <sup>b</sup> to appropriate volume	QS <sup>b</sup> to appropriate volume
Formaldehyde	≤50 mcg	≤100 mcg
Octylphenol ethoxylate	≤75 mcg	≤150 mcg
Gelatin	0.05%	0.05%
<b>Preservative</b>		
Single-dose presentations	-	-
Multi-dose presentation (thimerosal)	12.5 mcg mercury	25 mcg mercury

233 <sup>a</sup> per United States Public Health Service (USPHS) requirement

234 <sup>b</sup> Quantity Sufficient

235 "-" Indicates information is not applicable

236

## 237 12 CLINICAL PHARMACOLOGY

### 238 12.1 Mechanism of Action

239 Influenza illness and its complications follow infection with influenza viruses. Global surveillance  
240 of influenza identifies yearly antigenic variants. For example, since 1977, antigenic variants of  
241 influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation.  
242 Specific levels of hemagglutination inhibition (HI) antibody titer post-vaccination with  
243 inactivated influenza virus vaccines have not been correlated with protection from influenza virus  
244 infection. In some human studies, antibody titers  $\geq 1:40$  have been associated with protection from  
245 influenza illness in up to 50% of participants. (2) (3)

246

247 Antibodies against one influenza virus type or subtype confer limited or no protection against  
248 another. Furthermore, antibodies to one antigenic variant of influenza virus might not protect  
249 against a new antigenic variant of the same type or subtype. Frequent development of antigenic  
250 variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the  
251 usual change of one or more new strains in each year's influenza vaccine. Therefore, influenza  
252 vaccines are standardized to contain the hemagglutinins of influenza virus strains representing the  
253 influenza viruses likely to be circulating in the US during the influenza season.

254

255 Annual vaccination with the current vaccine is recommended because immunity during the year  
256 after vaccination declines and because circulating strains of influenza virus change from year to  
257 year.

258

## 259 **13 NON-CLINICAL TOXICOLOGY**

### 260 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

261 Fluzone has not been evaluated for carcinogenic or mutagenic potential or for impairment of  
262 fertility.

263

## 264 **14 CLINICAL STUDIES**

### 265 **14.1 Efficacy of Fluzone in Children 6 through 24 Months of Age**

266 A randomized, double-blind, placebo-controlled study was conducted at a single US center during  
267 the 1999-2000 (Year 1) and 2000-2001 (Year 2) influenza seasons. The intent-to-treat analysis set  
268 included a total of 786 children 6 through 24 months of age. Participants received two doses of  
269 either Fluzone (N = 525) or a placebo (N = 261). Among all randomized participants in both  
270 years, the mean age was 13.8 months; 52.5% were male, 50.8% were Caucasian, 42.0% were  
271 Black, and 7.2% were of other racial groups. Cases of influenza were identified through active  
272 and passive surveillance for influenza-like illness or acute otitis media and confirmed by culture.  
273 Influenza-like illness was defined as fever with signs or symptoms of an upper respiratory  
274 infection. Vaccine efficacy against all influenza viral types and subtypes was a secondary  
275 endpoint and is presented in [Table 7](#).

276 **Table 7: Estimated Efficacy of Fluzone Against Culture-Confirmed Influenza in Children**  
277 **Aged 6 through 24 Months during the 1999-2000 and 2000-2001 Influenza Seasons – Intent-**  
278 **to-Treat Analysis Set<sup>a</sup>**

Year	Fluzone <sup>b</sup>				Placebo <sup>c</sup>				Fluzone vs. Placebo	
	n <sup>d</sup>	N <sup>e</sup>	Rate (n/N) <sup>f</sup>	(95% CI)	n <sup>d</sup>	N <sup>e</sup>	Rate (n/N) <sup>f</sup>	(95% CI)	Relative Risk (95% CI)	Percent Relative Reduction <sup>g</sup> (95% CI)
Year 1 <sup>h</sup> (1999-2000)	15	273	5.5	(3.1; 8.9)	22	138	15.9	(10.3; 23.1)	0.34 (0.18; 0.64)	66 (36; 82)
Year 2 <sup>i</sup> (2000-2001)	9	252	3.6	(1.6; 6.7)	4	123	3.3	(0.9; 8.1)	1.10 (0.34; 3.50)	-10 (-250; 66)

279 <sup>a</sup>The intent-to-treat analysis set includes all enrolled participants who were randomly assigned to receive Fluzone or  
280 placebo and vaccinated

281 <sup>b</sup>Fluzone: 1999-2000 formulation containing A/Beijing/262/95 (H1N1), A/Sydney/15/97 (H3N2), and  
282 B/Yamanashi/166/98 (Yamagata lineage) and 2000-2001 formulation containing A/New Caledonia/20/99 (H1N1),  
283 A/Panama/2007/99 (H3N2), and B/Yamanashi/166/98 (Yamagata lineage)

284 <sup>c</sup>Placebo: 0.4% NaCl

285 <sup>d</sup>n is the number of participants with culture-confirmed influenza for the given year of study as listed in the first  
286 column

287 <sup>e</sup>N is the number of participants randomly assigned to receive Fluzone or placebo for the given year of study as listed  
288 in the column headers (intent-to-treat analysis set)

289 <sup>f</sup>Rate (%) = (n/N) \* 100

290 <sup>g</sup>Relative reduction in vaccine efficacy was defined as (1-relative risk) x 100

291 <sup>h</sup>Includes all culture confirmed influenza cases throughout the study duration for Year 1 (12 months of follow-up)

292 <sup>i</sup>Includes all culture-confirmed influenza cases throughout the study duration for Year 2 (6 months of follow-up)

## 293 14.2 Efficacy of Fluzone in Adults

294 A randomized, double-blind, placebo-controlled study was conducted in a single US center during  
295 the 2007-2008 influenza season. Participants received one dose of either Fluzone vaccine (N =  
296 813), an active comparator (N = 814), or placebo (N = 325). The intent-to-treat analysis set  
297 included 1138 healthy adults who received Fluzone or placebo. Participants were 18 through 49  
298 years of age (mean age was 23.3 years); 63.3% were female, 83.1% were Caucasian, and 16.9%



299 were of other racial/ethnic groups. Cases of influenza were identified through active and passive  
300 surveillance and confirmed by cell culture and/or real-time polymerase chain reaction (PCR).  
301 Influenza-like illness was defined as an illness with at least 1 respiratory symptom (cough or nasal  
302 congestion) and at least 1 constitutional symptom (fever or feverishness, chills, or body aches).  
303 Vaccine efficacy of Fluzone against all influenza viral types and subtypes is presented in [Table 8](#).

304 **Table 8: Estimated Efficacy of Fluzone Vaccine Against Influenza in Adults Aged 18**  
305 **through 49 Years during the 2007-2008 Influenza Season – Intent-to-Treat Analysis Set<sup>a</sup>**

Laboratory-Confirmed Symptomatic Influenza	Fluzone <sup>b</sup> (N=813) <sup>d</sup>			Placebo <sup>c</sup> (N=325) <sup>d</sup>			Fluzone vs. Placebo	
	n <sup>e</sup>	Rate (%) <sup>f</sup>	(95% CI)	n <sup>e</sup>	Rate (%) <sup>f</sup>	(95% CI)	Relative Risk (95% CI)	Percent Relative Reduction <sup>g</sup> (95% CI)
<b>Positive culture</b>	21	2.6	(1.6; 3.9)	31	9.5	(6.6; 13.3)	0.27 (0.16; 0.46)	73 (54; 84)
<b>Positive PCR</b>	28	3.4	(2.3; 4.9)	35	10.8	(7.6; 14.7)	0.32 (0.20; 0.52)	68 (48; 80)
<b>Positive culture, positive PCR, or both</b>	28	3.4	(2.3; 4.9)	35	10.8	(7.6; 14.7)	0.32 (0.20; 0.52)	68 (48; 80)

306 <sup>a</sup>The intent-to-treat analysis set includes all enrolled participants who were randomly assigned to receive Fluzone or  
307 placebo and vaccinated

308 <sup>b</sup>Fluzone: 2007-2008 formulation containing A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and  
309 B/Malaysia/2506/2004 (Victoria lineage)

310 <sup>c</sup>Placebo: 0.9% NaCl

311 <sup>d</sup>N is the number of participants randomly assigned to receive Fluzone or placebo

312 <sup>e</sup>n is the number of participants satisfying the criteria listed in the first column

313 <sup>f</sup>Rate (%) = (n/N) \* 100

314 <sup>g</sup>Relative reduction in vaccine efficacy was defined as (1 - relative risk) x 100

315

316

317 **14.3 Immunogenicity of Fluzone in Children 6 Months through 8 Years of Age**

318 In a multi-center study conducted in the US, 68 children 6 months through 35 months of age  
 319 given two 0.25 mL doses of Fluzone and 120 children 3 years through 8 years of age given two  
 320 0.5 mL doses of Fluzone were included in the per-protocol analysis set. The two doses (2006-  
 321 2007 formulation) were administered 26 to 30 days apart. Females accounted for 42.6% of the  
 322 participants in the 6 months through 35 months age group and 53.3% of the participants in the 3  
 323 years through 8 years age group. Most participants in the 6 months through 35 months and 3 years  
 324 through 8 years age groups, respectively, were Caucasian (70.6% and 79.2%), followed by  
 325 Hispanic (19.1% and 13.3%), and Black (7.4% and 4.2%).

326

327 The percentage of participants who received influenza vaccination during the previous influenza  
 328 season was 54.4% for the 6 months through 35 months age group and 27.5% for the 3 years  
 329 through 8 years age group. [Table 9](#) shows seroconversion rates and the percentage of participants  
 330 with an HI titer  $\geq 1:40$  pre-vaccination and one month following the second dose of Fluzone.

331 **Table 9: Percentage (%) with Pre and Post-Vaccination HI Titers  $\geq 1:40$  and Seroconversion**  
 332 **Following the Second Vaccine Injection with Fluzone<sup>a</sup> in Children 6 Months Through 35**  
 333 **Months and 3 Years Through 8 Years of Age**

Antigen	Age Group	Pre-Vaccination Titer $\geq 1:40$ % (95% CI)	Post-Vaccination <sup>b</sup> Titer $\geq 1:40$ % (95% CI)	Seroconversion <sup>c</sup> % (95% CI)
		N=68 (6 to 35 months); N=120 (3 through 8 years)		
A (H1N1)	6 through 35 months	11.8 (5.2; 21.9)	92.6 (83.7; 97.6)	88.2 (78.1; 94.8)
	3 through 8 years	40.0 (31.2; 49.3)	99.2 (95.4; 100.0)	78.3 (69.9; 85.3)
A (H3N2)	6 through 35 months	29.4 (19.0; 41.7)	100.0 (94.7; 100.0)	91.2 (81.8; 96.7)
	3 through 8 years	80.0 (71.7; 86.7)	100.0 (97.0; 100.0)	61.7 (52.4; 70.4)
B	6 through 35 months	1.5 (0.0; 7.9)	20.6 (11.7; 32.1)	20.6 (11.7; 32.1)

Antigen	Age Group	Pre-Vaccination Titer $\geq$ 1:40 % (95% CI)	Post-Vaccination <sup>b</sup> Titer $\geq$ 1:40 % (95% CI)	Seroconversion <sup>c</sup> % (95% CI)
	3 through 8 years	3.3 (0.9; 8.3)	58.3 (49.0; 67.3)	53.3 (44.0; 62.5)

334 <sup>a</sup> Children received two doses of Fluzone administered 26 to 30 days apart, irrespective of previous influenza  
335 vaccination history

336 <sup>b</sup> Post-vaccination HI titers drawn at 28 days post-dose

337 <sup>c</sup> Seroconversion: Paired samples with pre-vaccination HI titer  $<$ 1:10 and post-vaccination (28 days post-dose 2) titer  
338  $\geq$ 1:40 or a minimum 4-fold increase for participants with pre-vaccination titer  $\geq$ 1:10  
339

#### 340 14.4 Immunogenicity of Fluzone in Adults

341 Adults 18 through 64 years of age received Fluzone (2008-2009 formulation) in a multi-center  
342 trial conducted in the US. For immunogenicity analyses, there were 1287 participants who  
343 received Fluzone in the per-protocol analysis set. There were fewer males (35.8%) than females.  
344 The mean age was 42.6 years (ranged from 18.2 through 65.0 years). Most participants were  
345 Caucasian (80.0%), followed by Hispanic (11.0%), and Black (6.3%). [Table 10](#) shows  
346 seroconversion rates at 28 days following vaccination and the percentage of participants with an  
347 HI titer  $\geq$ 1:40 prior to vaccination and 28 days following vaccination.

348 **Table 10: Percentage (%) with Pre and Post-Vaccination HI Titers  $\geq$ 1:40 and**  
349 **Seroconversion in Adult Fluzone Recipients 18 Through 64 Years of Age**

Antigen	Pre-Vaccination Titer $\geq$ 1:40 % (95% CI) N <sup>c</sup> =1285-1286	Post-Vaccination <sup>a</sup> Titer $\geq$ 1:40 % (95% CI) N <sup>c</sup> =1283-1285	Seroconversion <sup>b</sup> % (95% CI) N <sup>c</sup> =1283-1285
<b>A (H1N1)</b>	39.1 (36.4; 41.8)	91.7 (90.0; 93.1)	60.5 (57.7; 63.2)
<b>A (H3N2)</b>	33.6 (31.0; 36.2)	91.4 (89.8; 92.9)	74.8 (72.3; 77.1)
<b>B</b>	41.2 (38.5; 44.0)	89.3 (87.4; 90.9)	54.2 (51.4; 56.9)

350 <sup>a</sup> Post-vaccination HI titers drawn at 28 days post-dose

351 <sup>b</sup> Seroconversion: Paired samples with pre-vaccination HI titer  $<$ 1:10 and post-vaccination (28 days post-dose) titer  
352  $\geq$ 1:40 or a minimum 4-fold increase for participants with pre-vaccination titer  $\geq$ 1:10  
353

<sup>c</sup> N is the number of vaccinated participants with available data for the immunologic endpoint listed

354 **14.5 Immunogenicity of Fluzone in Geriatric Adults**

355 Adults 65 years of age and older received Fluzone (2006-2007 formulation) in a multi-center trial  
 356 conducted in the US. For immunogenicity analyses, there were 1275 participants who received  
 357 Fluzone in the immunogenicity analysis set. Females accounted for 54.7% of participants. The  
 358 mean age was 72.9 years (ranged from 65 through 94 years of age); 36% of participants were 75  
 359 years of age or older. Most participants were Caucasian (92.9%), followed by Hispanic (3.7%),  
 360 and Black (2.7%). Table 11 shows seroconversion rates at 28 days following vaccination and the  
 361 percentage of participants with an HI titer  $\geq 1:40$  prior to vaccination and 28 days following  
 362 vaccination.

363 **Table 11: Percentage (%) with Pre and Post-Vaccination HI Titers  $\geq 1:40$  and**  
 364 **Seroconversion in Adult Fluzone Recipients 65 Years of Age and Older**

Antigen	Pre-Vaccination HI Titer $\geq 1:40$ % (95% CI) N <sup>c</sup> =1267-1268	Post-Vaccination <sup>a</sup> Titer $\geq 1:40$ % (95% CI) N <sup>c</sup> =1252	Seroconversion <sup>b</sup> % (95% CI) N <sup>c</sup> =1248-1249
A (H1N1)	45.9 (43.2; 48.7)	76.8 (74.3; 79.1)	23.1 (20.8; 25.6)
A (H3N2)	68.6 (66.0; 71.2)	96.5 (95.3; 97.4)	50.7 (47.9; 53.5)
B	27.3 (24.9; 29.9)	67.6 (64.9; 70.2)	29.9 (27.4; 32.6)

365 <sup>a</sup> Post-vaccination HI titers drawn at 28 days post-dose

366 <sup>b</sup> Seroconversion: Paired samples with pre-vaccination HI titer  $< 1:10$  and post-vaccination (28 days post-dose) titer  
 367  $\geq 1:40$  or a minimum 4-fold increase for participants with pre-vaccination titer  $\geq 1:10$

368 <sup>c</sup> N is the number of vaccinated participants with available data for the immunologic endpoint listed

1 **15 REFERENCES**

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10

11

## 1 **16 HOW SUPPLIED/STORAGE AND HANDLING**

### 2 **16.1 How Supplied**

3

4 Multi-dose vial, 5 mL (NDC 49281-396-78) (not made with natural rubber latex). Supplied as  
5 package of one (NDC 49281-396-15). A maximum of ten doses can be withdrawn from the multi-  
6 dose vial.

7

### 8 **16.2 Storage and Handling**

9 Store all Fluzone presentations refrigerated at 2° to 8°C (35° to 46°F). DO NOT FREEZE.

10 Discard if vaccine has been frozen.

11

12 Between uses, return the multi-dose vial to the recommended storage conditions at 2° to 8°C (35°  
13 to 46°F).

14

15 Do not use after the expiration date shown on the label.

16

## 17 **17 PATIENT COUNSELING INFORMATION**

18 See FDA-approved patient labeling (Patient Information).

- 19
- Inform the patient or guardian that Fluzone contains killed viruses and cannot cause influenza.
  - Fluzone stimulates the immune system to produce antibodies that help protect against  
21 influenza, but does not prevent other respiratory infections.
  - Annual influenza vaccination is recommended.
- 22

- 1 • Instruct vaccine recipients and guardians to report adverse reactions to their healthcare  
2 provider and/or to the Vaccine Adverse Event Reporting System (VAERS).

3

4 Fluzone is a registered trademark of Sanofi Pasteur Inc.

5

6 Manufactured by:

7 **Sanofi Pasteur Inc.**

8 Swiftwater PA 18370 USA

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9

SANOFI PASTEUR 

10

1 **Patient Information Sheet**  
2 **Fluzone®**  
3 **Influenza Vaccine**  
4

5 Please read this information sheet before getting Fluzone vaccine. This summary is not intended  
6 to take the place of talking with your healthcare provider. If you have questions or would like  
7 more information, please talk with your healthcare provider.

8

9 **What is Fluzone vaccine?**

10 Fluzone is a vaccine that helps protect against influenza illness (flu).

11 Fluzone vaccine is for people who are 6 months of age and older.

12 Vaccination with Fluzone vaccine may not protect all people who receive the vaccine.

13

14 **Who should not get Fluzone vaccine?**

15 You should not get Fluzone vaccine if you:

- 16 • ever had a severe allergic reaction to eggs or egg products.  
17 • ever had a severe allergic reaction after getting any flu vaccine.  
18 • are younger than 6 months of age.

19

20 Tell your healthcare provider if you or your child have or have had:

- 21 • Guillain-Barré syndrome (severe muscle weakness) after getting a flu vaccine.  
22 • problems with your immune system as the immune response may be diminished.

23



1 **How is the Fluzone vaccine given?**

2 Fluzone vaccine is a shot given into the muscle of the arm.

3 For infants, Fluzone vaccine is a shot given into the muscle of the thigh.

4  
5 **What are the possible side effects of Fluzone vaccine?**

6 The most common side effects of Fluzone vaccine are:

- 7 • pain, redness, swelling, bruising and hardness where you got the shot
- 8 • muscle aches
- 9 • tiredness
- 10 • headache
- 11 • fever

12 These are not all of the possible side effects of Fluzone vaccine. You can ask your healthcare  
13 provider for a list of other side effects that is available to healthcare professionals.

14  
15 Call your healthcare provider for advice about any side effects that concern you. You may report  
16 side effects to the Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967 or  
17 <http://vaers.hhs.gov>.

18  
19 **What are the ingredients in Fluzone vaccine?**

20 Fluzone vaccine contains 3 killed flu virus strains.

21 Inactive ingredients include formaldehyde, octylphenol ethoxylate, and gelatin. The preservative  
22 thimerosal is only in the multi-dose vial of Fluzone vaccine.

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2 Swiftwater, PA 18370 USA

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4