

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**Fluzone Quadrivalent (Influenza Vaccine)  
Suspension for Intramuscular Injection  
2015-2016 Formula  
Initial US Approval (Fluzone Quadrivalent): 2013**

### INDICATIONS AND USAGE

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

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

### DOSAGE AND ADMINISTRATION

- For intramuscular use only (2)

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 4 weeks apart
36 months through 8 years	One or two doses <sup>a</sup> , 0.5 mL each	If 2 doses, administer at least 4 weeks 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 4 presentations: prefilled single-dose syringe (yellow plunger rod), 0.25 mL; prefilled single-dose syringe (purple plunger rod), 0.5 mL; single-dose vial, 0.5 mL; multi-dose vial, 5 mL. (3)

### CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) 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 following previous influenza vaccination, the decision to give Fluzone Quadrivalent should be based on careful consideration of the potential benefits and risks. (5.1)

### ADVERSE REACTIONS

- In children 6 months through 35 months of age, the most common ( $\geq 10\%$ ) injection-site reactions were pain (57%) or tenderness (54%), erythema (37%), and swelling (22%); the most common solicited systemic adverse reactions were irritability (54%), abnormal crying (41%), malaise (38%), drowsiness (38%), appetite loss (32%), myalgia (27%), vomiting (15%), and fever (14%). (6.1)
- In children 3 years through 8 years of age, the most common ( $\geq 10\%$ ) injection-site reactions were pain (67%), erythema (34%), and swelling (25%); the most common solicited systemic adverse reactions were myalgia (39%), malaise (32%), and headache (23%). (6.1)
- In adults 18 years and older, the most common ( $\geq 10\%$ ) injection-site reaction was pain (47%); the most common solicited systemic adverse reactions were myalgia (24%), headache (16%), and malaise (11%). (6.1)
- In adults 65 years of age and older, the most common ( $\geq 10\%$ ) injection-site reaction was pain (33%); the most common solicited systemic adverse reactions were myalgia (18%), headache (13%), and malaise (11%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Pasteur Inc., 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 Quadrivalent have not been established in pregnant women or children less than 6 months of age. (8.1) (8.4)
- Pregnancy: Pregnancy registry available. Call Sanofi Pasteur Inc. at 1-800-822-2463. (8.1)
- Antibody responses to Fluzone Quadrivalent are lower in persons  $\geq 65$  years of age than in younger adults. (8.5)

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

Revised: XXXX XXXX

## FULL PRESCRIBING INFORMATION: CONTENTS\*

- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
  - Dose and Schedule
  - Administration
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
- WARNINGS AND PRECAUTIONS
  - Guillain-Barré Syndrome
  - Preventing and Managing Allergic Reactions
  - Altered Immunocompetence
  - Limitations of Vaccine Effectiveness
- ADVERSE REACTIONS
  - Clinical Trials Experience
  - Post-Marketing Experience
- USE IN SPECIFIC POPULATIONS
  - Pregnancy
  - Nursing Mothers
  - Pediatric Use
  - Geriatric Use

- DESCRIPTION
- CLINICAL PHARMACOLOGY
  - Mechanism of Action
- CLINICAL STUDIES
  - Immunogenicity of Fluzone Quadrivalent in Children 6 Months through 8 Years of Age
  - Immunogenicity of Fluzone Quadrivalent in Adults  $\geq 18$  years of age
  - Immunogenicity of Fluzone Quadrivalent in Geriatric Adults  $\geq 65$  years of age
- REFERENCES
- HOW SUPPLIED/STORAGE AND HANDLING
  - How Supplied
  - Storage and Handling
- 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 Fluzone® Quadrivalent is a vaccine indicated for active immunization for the prevention of  
4 influenza disease caused by influenza A subtype viruses and type B viruses contained in the  
5 vaccine.

6

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

8

9 **2 DOSAGE AND ADMINISTRATION**

- 10 • **For intramuscular use only**

11 **2.1 Dose and Schedule**

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

13 **Table 1: Dose and Schedule for Fluzone Quadrivalent**

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 4 weeks apart
36 months through 8 years	One or two doses <sup>a</sup> , 0.5 mL each	If 2 doses, administer at least 4 weeks apart
9 years and older	One dose, 0.5 mL	-

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

16 "-" Indicates information is not applicable

17

18 **2.2 Administration**

1 Inspect Fluzone Quadrivalent visually for particulate matter and/or discoloration prior to  
2 administration. If any of these defects or conditions exist, the vaccine should not be administered.

3

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

7

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

13

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

15

16 Fluzone Quadrivalent should not be combined through reconstitution or mixed with any other  
17 vaccine.

18

### 19 **3 DOSAGE FORMS AND STRENGTHS**

20 Fluzone Quadrivalent is a suspension for injection.

21

22 Fluzone Quadrivalent is supplied in 4 presentations:

- 1) Prefilled single-dose syringe (yellow syringe plunger rod), 0.25 mL, for persons 6 months through 35 months of age.
- 2) Prefilled single-dose syringe (purple syringe plunger rod), 0.5 mL, for persons 36 months of age and older.
- 3) Single-dose vial, 0.5 mL, for persons 36 months of age and older.
- 4) Multi-dose vial, 5 mL, for persons 6 months of age and older.

## 4 CONTRAINDICATIONS

Do not administer Fluzone Quadrivalent to anyone with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine [see [Description \(11\)](#)], including egg protein, or to a previous dose of any influenza vaccine.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Guillain-Barré Syndrome

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

### 5.2 Preventing and Managing Allergic Reactions

1 Appropriate medical treatment and supervision must be available to manage possible anaphylactic  
2 reactions following administration of Fluzone Quadrivalent.

3

### 4 **5.3 Altered Immunocompetence**

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

7

### 8 **5.4 Limitations of Vaccine Effectiveness**

9 Vaccination with Fluzone Quadrivalent may not protect all recipients.

10

## 11 **6 ADVERSE REACTIONS**

12 In children 6 months through 35 months of age, the most common ( $\geq 10\%$ ) injection-site reactions  
13 were pain (57%)<sup>a</sup> or tenderness (54%)<sup>b</sup>, erythema (37%), and swelling (22%); the most common  
14 solicited systemic adverse reactions were irritability (54%)<sup>b</sup>, abnormal crying (41%)<sup>b</sup>, malaise  
15 (38%)<sup>a</sup>, drowsiness (38%)<sup>b</sup>, appetite loss (32%)<sup>b</sup>, myalgia (27%)<sup>a</sup>, vomiting (15%)<sup>b</sup>, and fever  
16 (14%). In children 3 years through 8 years of age, the most common ( $\geq 10\%$ ) injection-site  
17 reactions were pain (67%), erythema (34%), and swelling (25%); the most common solicited  
18 systemic adverse reactions were myalgia (39%), malaise (32%), and headache (23%). In adults 18  
19 years and older, the most common ( $\geq 10\%$ ) injection-site reaction was pain (47%); the most  
20 common solicited systemic adverse reactions were myalgia (24%), headache (16%), and malaise

---

<sup>a</sup> Assessed in children 24 months through 35 months of age

<sup>b</sup> Assessed in children 6 months through 23 months of age

1 (11%). In adults 65 years of age and older, the most common ( $\geq 10\%$ ) injection-site reaction was  
2 pain (33%); the most common solicited systemic adverse reactions were myalgia (18%), headache  
3 (13%), and malaise (11%).

4

## 5 **6.1 Clinical Trials Experience**

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

9

### 10 **Children 6 Months Through 8 Years of Age**

11 Study 1 (NCT01240746, see <http://clinicaltrials.gov>) was a single-blind, randomized, active-  
12 controlled multi-center safety and immunogenicity study conducted in the US. In this study,  
13 children 6 months through 35 months of age received one or two 0.25 mL doses of either Fluzone  
14 Quadrivalent or one of two formulations of a comparator trivalent influenza vaccine (TIV-1 or  
15 TIV-2), and children 3 years through 8 years of age received one or two 0.5 mL doses of either  
16 Fluzone Quadrivalent, TIV-1, or TIV-2. Each of the trivalent formulations contained an influenza  
17 type B virus that corresponded to one of the two type B viruses in Fluzone Quadrivalent (a type B  
18 virus of the Victoria lineage or a type B virus of the Yamagata lineage). For participants who  
19 received two doses, the doses were administered approximately 4 weeks apart. The safety analysis  
20 set included 1841 children 6 months through 35 months of age and 2506 children 3 years through  
21 8 years of age. Among participants 6 months through 8 years of age in the three vaccine groups  
22 combined, 49.3% were female (Fluzone Quadrivalent, 49.2%; TIV-1, 49.8%; TIV-2, 49.4%),  
23 58.4% Caucasian (Fluzone Quadrivalent, 58.4%; TIV-1, 58.9%; TIV-2, 57.8%), 20.2% Black

1 (Fluzone Quadrivalent, 20.5%; TIV-1, 19.9%; TIV-2, 19.1%), 14.1% Hispanic (Fluzone  
2 Quadrivalent, 14.3%; TIV-1, 13.2%; TIV-2, 14.7%), and 7.3% were of other racial/ethnic groups  
3 (Fluzone Quadrivalent, 6.8%; TIV-1, 8.0%; TIV-2, 8.5%). [Table 2](#) and [Table 3](#) summarize  
4 solicited injection-site and systemic adverse reactions reported within 7 days post-vaccination via  
5 diary cards. Participants were monitored for unsolicited adverse events for 28 days after each dose  
6 and serious adverse events (SAEs) during the 6 months following the last dose.

7 **Table 2: Study 1<sup>a</sup>: Percentage of Solicited Injection-site and Systemic Adverse Reactions**  
8 **Within 7 Days After Vaccination in Children 6 Months Through 35 Months of Age (Safety**  
9 **Analysis Set)<sup>b</sup>**

	Fluzone Quadrivalent (N <sup>c</sup> =1223)			TIV-1 <sup>c</sup> (B Victoria) (N <sup>c</sup> =310)			TIV-2 <sup>d</sup> (B Yamagata) (N <sup>c</sup> =308)		
	Any (%)	Grade 2 <sup>i</sup> (%)	Grade 3 <sup>g</sup> (%)	Any (%)	Grade 2 <sup>i</sup> (%)	Grade 3 <sup>g</sup> (%)	Any (%)	Grade 2 <sup>i</sup> (%)	Grade 3 <sup>g</sup> (%)
<b>Injection-site adverse reactions</b>									
- Pain <sup>h</sup>	57.0	10.2	1.0	52.3	11.5	0.8	50.3	5.4	2.7
- Tenderness <sup>i</sup>	54.1	11.3	1.9	48.4	8.2	1.9	49.7	10.3	0.0
- Erythema	37.3	1.5	0.2	32.9	1.0	0.0	33.3	1.0	0.0
- Swelling	21.6	0.8	0.2	19.7	1.0	0.0	17.3	0.0	0.0
<b>Systemic adverse reactions</b>									
- Fever (≥100.4°F) <sup>j</sup>	14.3	5.5	2.1	16.0	6.6	1.7	13.0	4.1	2.0
- Malaise <sup>h</sup>	38.1	14.5	4.6	35.2	14.8	4.7	32.4	12.8	6.8
- Myalgia <sup>h</sup>	26.7	6.6	1.9	26.6	9.4	1.6	25.0	6.8	2.7
- Headache <sup>h</sup>	8.9	2.5	0.6	9.4	3.9	0.0	12.2	4.7	0.0
- Irritability <sup>i</sup>	54.0	26.4	3.2	52.8	20.1	3.1	53.5	22.9	2.8
- Crying abnormal <sup>i</sup>	41.2	12.3	3.3	36.5	8.2	1.9	29.9	10.4	2.1
- Drowsiness <sup>i</sup>	37.7	8.4	1.3	32.1	3.8	0.6	31.9	5.6	0.7
- Appetite loss <sup>i</sup>	32.3	9.1	1.8	33.3	5.7	1.9	25.0	8.3	0.7
- Vomiting <sup>i</sup>	14.8	6.2	1.0	11.3	4.4	0.6	13.9	6.3	0.0

- 1 <sup>a</sup>NCT01240746  
2 <sup>b</sup>The safety analysis set includes all persons who received at least one dose of study vaccine  
3 <sup>c</sup>2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and  
4 B/Brisbane/60/2008 (Victoria lineage), licensed  
5 <sup>d</sup>Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006  
6 (Yamagata lineage), non-licensed  
7 <sup>e</sup>N is the number of participants in the safety analysis set  
8 <sup>f</sup>Grade 2 - Injection-site pain: sufficiently discomforting to interfere with normal behavior or activities; Injection-site  
9 tenderness: cries and protests when injection-site is touched; Injection-site erythema, Injection-site swelling:  $\geq 2.5$  cm  
10 to  $< 5$  cm; Fever:  $> 101.3^{\circ}\text{F}$  to  $\leq 103.1^{\circ}\text{F}$  (6 months through 23 months);  $\geq 101.2^{\circ}\text{F}$  to  $\leq 102.0^{\circ}\text{F}$  (24 months through 35  
11 months); Malaise, Myalgia, and Headache: some interference with activity; Irritability: requiring increased attention;  
12 Crying abnormal: 1 to 3 hours; Drowsiness: not interested in surroundings or did not wake up for a feed/meal;  
13 Appetite loss: missed 1 or 2 feeds/meals completely; Vomiting: 2 to 5 episodes per 24 hours  
14 <sup>g</sup>Grade 3 - Injection-site pain: incapacitating, unable to perform usual activities; Injection-site tenderness: cries when  
15 injected limb is moved, or the movement of the injected limb is reduced; Injection-site erythema, Injection-site  
16 swelling:  $\geq 5$  cm; Fever:  $> 103.1^{\circ}\text{F}$  (6 months through 23 months);  $\geq 102.1^{\circ}\text{F}$  (24 months through 35 months); Malaise,  
17 Myalgia, and Headache: Significant; prevents daily activity; Irritability: inconsolable; Crying abnormal:  $> 3$  hours;  
18 Drowsiness: sleeping most of the time or difficult to wake up; Appetite loss: refuses  $\geq 3$  feeds/meals or refuses most  
19 feeds/meals; Vomiting:  $\geq 6$  episodes per 24 hours or requiring parenteral hydration  
20 <sup>h</sup>Assessed in children 24 months through 35 months of age  
21 <sup>i</sup>Assessed in children 6 months through 23 months of age  
22 <sup>j</sup>Fever measured by any route  
23

24 **Table 3: Study 1<sup>a</sup>: Percentage of Solicited Injection-site and Systemic Adverse Reactions**  
25 **Within 7 Days After Vaccination in Children 3 Years Through 8 Years of Age (Safety**  
26 **Analysis Set)<sup>b</sup>**

	Fluzone Quadrivalent (N <sup>c</sup> =1669)			TIV-1 <sup>c</sup> (B Victoria) (N <sup>c</sup> =424)			TIV-2 <sup>d</sup> (B Yamagata) (N <sup>c</sup> =413)		
	Any (%)	Grade 2 <sup>f</sup> (%)	Grade 3 <sup>g</sup> (%)	Any (%)	Grade 2 <sup>f</sup> (%)	Grade 3 <sup>g</sup> (%)	Any (%)	Grade 2 <sup>f</sup> (%)	Grade 3 <sup>g</sup> (%)
<b>Injection-site adverse reactions</b>									
<b>- Pain</b>	66.6	15.8	2.1	64.6	9.5	2.0	63.8	11.6	2.8
<b>- Erythema</b>	34.1	2.9	1.8	36.8	3.4	1.2	35.2	2.5	1.8
<b>- Swelling</b>	24.8	2.8	1.4	25.4	1.5	1.2	25.9	2.5	1.8
<b>Systemic adverse reactions</b>									
<b>- Fever (<math>\geq 100.4^{\circ}\text{F}</math>)<sup>h</sup></b>	7.0	2.1	2.1	7.1	2.2	1.2	7.6	2.8	0.8
<b>- Headache</b>	23.1	6.8	2.2	21.2	5.1	2.7	24.4	7.5	2.0



	Fluzone Quadrivalent (N <sup>c</sup> =1669)			TIV-1 <sup>c</sup> (B Victoria) (N <sup>c</sup> =424)			TIV-2 <sup>d</sup> (B Yamagata) (N <sup>c</sup> =413)		
	Any (%)	Grade 2 <sup>f</sup> (%)	Grade 3 <sup>g</sup> (%)	Any (%)	Grade 2 <sup>f</sup> (%)	Grade 3 <sup>g</sup> (%)	Any (%)	Grade 2 <sup>f</sup> (%)	Grade 3 <sup>g</sup> (%)
- Malaise	31.9	11.2	5.5	32.8	11.4	5.6	33.4	10.8	5.0
- Myalgia	38.6	12.2	3.3	34.1	9.0	2.7	38.4	11.1	2.8

1 <sup>a</sup>NCT01240746

2 <sup>b</sup>The safety analysis set includes all persons who received at least one dose of study vaccine

3 <sup>c</sup>2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and  
4 B/Brisbane/60/2008 (Victoria lineage), licensed

5 <sup>d</sup>Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006  
6 (Yamagata lineage), non-licensed

7 <sup>e</sup>N is the number of participants in the safety analysis set

8 <sup>f</sup>Grade 2 - Injection-site pain: sufficiently discomforting to interfere with normal behavior or activities; Injection-site  
9 erythema, Injection-site swelling: ≥2.5 cm to <5 cm; Fever: ≥101.2°F to ≤102.0°F; Headache, Malaise, and Myalgia:  
10 some interference with activity

11 <sup>g</sup>Grade 3 - Injection-site pain: incapacitating, unable to perform usual activities; Injection-site erythema, Injection-site  
12 swelling: ≥5 cm; Fever: ≥102.1°F; Headache, Malaise, and Myalgia: Significant; prevents daily activity

13 <sup>h</sup>Fever measured by any route

14

15 Among children 6 months through 8 years of age, unsolicited non-serious adverse events were  
16 reported in 1360 (47.0%) recipients in the Fluzone Quadrivalent group, 352 (48.0%) recipients in  
17 the TIV-1 group, and 346 (48.0%) recipients in the TIV-2 group. The most commonly reported  
18 unsolicited non-serious adverse events were cough, vomiting, and pyrexia. During the 28 days  
19 following vaccination, a total of 16 (0.6%) recipients in the Fluzone Quadrivalent group, 4 (0.5%)  
20 recipients in the TIV-1 group, and 4 (0.6%) recipients in the TIV-2 group, experienced at least  
21 one SAE; no deaths occurred. Throughout the study period, a total of 41 (1.4%) recipients in the  
22 Fluzone Quadrivalent group, 7 (1.0%) recipients in the TIV-1 group, and 14 (1.9%) recipients in  
23 the TIV-2 group, experienced at least one SAE. Three SAEs were considered to be possibly  
24 related to vaccination: croup in a Fluzone Quadrivalent recipient and 2 episodes of febrile seizure,

1 1 each in a TIV-1 recipient and a TIV-2 recipient. One death occurred in the TIV-1 group (a  
2 drowning 43 days post-vaccination).

3

#### 4 **Adults**

5 In study 2 (NCT00988143, see <http://clinicaltrials.gov>), a multi-centered randomized, open-label  
6 trial conducted in the US, adults 18 years of age and older received one dose of either Fluzone  
7 Quadrivalent or one of two formulations of comparator trivalent influenza vaccine (TIV-1 or TIV-  
8 2). Each of the trivalent formulations contained an influenza type B virus that corresponded to one  
9 of the two type B viruses in Fluzone Quadrivalent (a type B virus of the Victoria lineage or a type  
10 B virus of the Yamagata lineage). The safety analysis set included 570 recipients, half aged 18-60  
11 years and half aged 61 years or older. Among participants in the three vaccine groups combined,  
12 67.2% were female (Fluzone Quadrivalent, 68.4%; TIV-1, 67.9%; TIV-2, 65.3%), 88.4%  
13 Caucasian (Fluzone Quadrivalent, 91.1%; TIV-1, 86.8%; TIV-2, 87.4%), 9.6% Black (Fluzone  
14 Quadrivalent, 6.8%; TIV-1, 12.1%; TIV-2, 10.0%), 0.4% Hispanic (Fluzone Quadrivalent, 0.0%;  
15 TIV-1, 0.5%; TIV-2, 0.5%), and 1.7% were of other racial/ethnic groups (Fluzone Quadrivalent,  
16 2.1%; TIV-1, 0.5%; TIV-2, 2.2%). **Table 4** summarizes solicited injection-site and systemic  
17 adverse reactions reported within 3 days post-vaccination via diary cards. Participants were  
18 monitored for unsolicited adverse events and SAEs during the 21 days following vaccination.

1 **Table 4: Study 2<sup>a</sup>: Percentage of Solicited Injection-site and Systemic Adverse Reactions**  
2 **Within 3 Days After Vaccination in Adults 18 Years of Age and Older (Safety Analysis Set)<sup>b</sup>**

	Fluzone Quadrivalent (N <sup>c</sup> =190)			TIV-1 <sup>c</sup> (B Victoria) (N <sup>c</sup> =190)			TIV-2 <sup>d</sup> (B Yamagata) (N <sup>c</sup> =190)		
	Any (%)	Grade 2 <sup>f</sup> (%)	Grade 3 <sup>g</sup> (%)	Any (%)	Grade 2 <sup>f</sup> (%)	Grade 3 <sup>g</sup> (%)	Any (%)	Grade 2 <sup>f</sup> (%)	Grade 3 <sup>g</sup> (%)
<b>Injection-site adverse reactions</b>									
- Pain	47.4	6.8	0.5	52.1	7.9	0.5	43.2	6.3	0.0
- Erythema	1.1	0.0	0.0	1.6	0.5	0.0	1.6	0.5	0.0
- Swelling	0.5	0.0	0.0	3.2	0.5	0.0	1.1	0.0	0.0
- Induration	0.5	0.0	0.0	1.6	0.5	0.0	0.5	0.0	0.0
- Ecchymosis	0.5	0.0	0.0	0.5	0.0	0.0	0.5	0.0	0.0
<b>Systemic adverse reactions</b>									
- Myalgia	23.7	5.8	0.0	25.3	5.8	0.0	16.8	5.8	0.0
- Headache	15.8	3.2	0.5	18.4	6.3	0.5	18.0	4.2	0.0
- Malaise	10.5	1.6	1.1	14.7	3.2	1.1	12.1	4.7	0.5
- Shivering	2.6	0.5	0.0	5.3	1.1	0.0	3.2	0.5	0.0
- Fever (≥100.4°F) <sup>h</sup>	0.0	0.0	0.0	0.5	0.5	0.0	0.5	0.5	0.0

3 <sup>a</sup>NCT00988143

4 <sup>b</sup>The safety analysis set includes all persons who received study vaccine

5 <sup>c</sup>2009-2010 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and  
6 B/Brisbane/60/2008 (Victoria lineage), licensed

7 <sup>d</sup>2008-2009 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and  
8 B/Florida/04/2006 (Yamagata lineage), licensed

9 <sup>e</sup>N is the number of participants in the safety analysis set

10 <sup>f</sup>Grade 2 - Injection-site pain: Some interference with activity; Injection-site erythema, Injection-site swelling,  
11 Injection-site induration, and Injection-site ecchymosis: ≥5.1 to ≤10 cm; Fever: ≥101.2°F to ≤102.0°F; Myalgia,  
12 Headache, Malaise, and Shivering: some interference with activity

13 <sup>g</sup>Grade 3 - Injection-site pain: Significant; prevents daily activity; Injection-site erythema, Injection-site swelling,  
14 Injection-site induration, and Injection-site ecchymosis: >10 cm; Fever: ≥102.1°F; Myalgia, Headache, Malaise, and  
15 Shivering: Significant; prevents daily activity

16 <sup>h</sup>Fever measured by any route

17

18 Unsolicited non-serious adverse events were reported in 33 (17.4%) recipients in the Fluzone

19 Quadrivalent group, 45 (23.7%) recipients in the TIV-1 group, and 45 (23.7%) recipients in the

1 TIV-2 group. The most commonly reported unsolicited non-serious adverse events were  
2 headache, cough, and oropharyngeal pain. In the follow-up period, there were two SAEs, 1 (0.5%)  
3 in the Fluzone Quadrivalent group and 1 (0.5%) in the TIV-2 group. No deaths were reported  
4 during the trial period.

5

## 6 **Geriatric Adults**

7 In Study 3 (NCT01218646, see <http://clinicaltrials.gov>), a multi-center, randomized, double-blind  
8 trial conducted in the US, adults 65 years of age and older received one dose of either Fluzone  
9 Quadrivalent, or one of two formulations of comparator trivalent influenza vaccine (TIV-1 or  
10 TIV-2). Each of the trivalent formulations contained an influenza type B virus that corresponded  
11 to one of the two type B viruses in Fluzone Quadrivalent (a type B virus of the Victoria lineage or  
12 a type B virus of the Yamagata lineage). The safety analysis set included 675 recipients. Among  
13 participants in the three vaccine groups combined, 55.7% were female (Fluzone Quadrivalent,  
14 57.3%; TIV-1, 56.0%; TIV-2, 53.8%), 89.5% Caucasian (Fluzone Quadrivalent, 87.6%; TIV-1,  
15 89.8%; TIV-2, 91.1%), 2.2% Black (Fluzone Quadrivalent, 4.0%; TIV-1, 1.8%; TIV-2, 0.9%),  
16 7.4% Hispanic (Fluzone Quadrivalent, 8.4%; TIV-1, 7.6%; TIV-2, 6.2%) and 0.9% were of other  
17 racial/ethnic groups (Fluzone Quadrivalent, 0.0%; TIV-1, 0.9%; TIV-2, 1.8%).

18

19 [Table 5](#) summarizes solicited injection-site and systemic adverse reactions reported within 7 days  
20 post-vaccination via diary cards. Participants were monitored for unsolicited adverse events and  
21 SAEs during the 21 days following vaccination.

22

1 **Table 5: Study 3<sup>a</sup>: Percentage of Solicited Injection-site and Systemic Adverse Reactions**  
2 **Within 7 Days After Vaccination in Adults 65 Years of Age and Older (Safety Analysis Set)<sup>b</sup>**

	Fluzone Quadrivalent (N <sup>c</sup> =225)			TIV-1 <sup>c</sup> (B Victoria) (N <sup>c</sup> =225)			TIV-2 <sup>d</sup> (B Yamagata) (N <sup>c</sup> =225)		
	Any (%)	Grade 2 <sup>f</sup> (%)	Grade 3 <sup>g</sup> (%)	Any (%)	Grade 2 <sup>f</sup> (%)	Grade 3 <sup>g</sup> (%)	Any (%)	Grade 2 <sup>f</sup> (%)	Grade 3 <sup>g</sup> (%)
<b>Injection-site adverse reactions</b>									
- Pain	32.6	1.3	0.9	28.6	2.7	0.0	23.1	0.9	0.0
- Erythema	2.7	0.9	0.0	1.3	0.0	0.0	1.3	0.4	0.0
- Swelling	1.8	0.4	0.0	1.3	0.0	0.0	0.0	0.0	0.0
<b>Systemic adverse reactions</b>									
- Myalgia	18.3	4.0	0.4	18.3	4.0	0.0	14.2	2.7	0.4
- Headache	13.4	1.3	0.4	11.6	1.3	0.0	11.6	1.8	0.4
- Malaise	10.7	4.5	0.4	6.3	0.4	0.0	11.6	2.7	0.9
- Fever (≥100.4°F) <sup>h</sup>	1.3	0.0	0.4	0.0	0.0	0.0	0.9	0.4	0.4

3 <sup>a</sup>NCT01218646

4 <sup>b</sup>The safety analysis set includes all persons who received study vaccine

5 <sup>c</sup>2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and  
6 B/Brisbane/60/2008 (Victoria lineage), licensed

7 <sup>d</sup>Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006  
8 (Yamagata lineage), non-licensed

9 <sup>e</sup>N is the number of participants in the safety analysis set

10 <sup>f</sup>Grade 2 - Injection-site pain: some interference with activity; Injection-site erythema and Injection-site swelling:  
11 ≥5.1 to ≤10 cm; Fever: ≥101.2°F to ≤102.0°F; Myalgia, Headache, and Malaise: some interference with activity

12 <sup>g</sup>Grade 3 - Injection-site pain: Significant; prevents daily activity; Injection-site erythema and Injection-site swelling:  
13 >10 cm; Fever: ≥102.1°F; Myalgia, Headache, and Malaise: Significant; prevents daily activity

14 <sup>h</sup>Fever measured by any route

15

16 Unsolicited non-serious adverse events were reported in 28 (12.4%) recipients in the Fluzone

17 Quadrivalent group, 22 (9.8%) recipients in the TIV-1 group, and 22 (9.8%) recipients in the TIV-

18 2 group. The most commonly reported adverse events were oropharyngeal pain, rhinorrhea,

19 injection-site induration, and headache. Three SAEs were reported during the follow-up period, 2

1 (0.9%) in the TIV-1 group and 1 (0.4%) in the TIV-2 group. No deaths were reported during the  
2 trial period.

3

## 4 **6.2 Post-Marketing Experience**

5 Currently, there are no post-marketing data available for Fluzone Quadrivalent vaccine.

6

7 The following events have been spontaneously reported during the post-approval use of the  
8 trivalent formulation of Fluzone. Because these events are reported voluntarily from a population  
9 of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal  
10 relationship to vaccine exposure. Adverse events were included based on one or more of the  
11 following factors: severity, frequency of reporting, or strength of evidence for a causal  
12 relationship to Fluzone.

13

- 14 • *Blood and Lymphatic System Disorders:* Thrombocytopenia, lymphadenopathy
- 15 • *Immune System Disorders:* Anaphylaxis, other allergic/hypersensitivity reactions (including  
16 urticaria, angioedema)
- 17 • *Eye disorders:* Ocular hyperemia
- 18 • *Nervous System Disorders:* Guillain-Barré syndrome (GBS), convulsions, febrile  
19 convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy  
20 (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination),  
21 dizziness, paresthesia
- 22 • *Vascular Disorders:* Vasculitis, vasodilatation/flushing

- 1 • *Respiratory, Thoracic and Mediastinal Disorders*: Dyspnea, pharyngitis, rhinitis, cough,  
2 wheezing, throat tightness
- 3 • *Skin and Subcutaneous Tissue Disorders*: Stevens-Johnson syndrome
- 4 • *General Disorders and Administration Site Conditions*: Pruritus, asthenia/fatigue, pain in  
5 extremities, chest pain
- 6 • *Gastrointestinal Disorders*: Vomiting

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

### 9 **8.1 Pregnancy**

10 Pregnancy Category B: A developmental and reproductive toxicity study has been performed in  
11 female rabbits at a dose approximately 20 times the human dose (on a mg/kg basis) and has  
12 revealed no evidence of impaired female fertility or harm to the fetus due to Fluzone  
13 Quadrivalent. There are, however, no adequate and well-controlled studies in pregnant women.  
14 Because animal reproduction studies are not always predictive of human response, Fluzone  
15 Quadrivalent should be given to a pregnant woman only if clearly needed.

16

17 In the developmental and reproductive toxicity study, female rabbits were administered Fluzone  
18 Quadrivalent or control saline (each 0.5 mL/dose) by intramuscular injection 24 and 10 days  
19 before insemination, and on Days 6, 12, and 27 of gestation. The administration of Fluzone  
20 Quadrivalent did not result in systemic maternal toxicity (no adverse clinical signs and no change  
21 in body weight or food consumption). In addition, no adverse effects on pregnancy, parturition,  
22 lactation, or embryo-fetal or pre-weaning development were observed. There were no vaccine-  
23 related fetal malformations or other evidence of teratogenesis noted in this study.

1 Sanofi Pasteur Inc. is maintaining a prospective pregnancy exposure registry to collect data on  
2 pregnancy outcomes and newborn health status following vaccination with Fluzone Quadrivalent  
3 during pregnancy. Healthcare providers are encouraged to enroll women who receive Fluzone  
4 Quadrivalent during pregnancy in Sanofi Pasteur Inc.'s vaccination pregnancy registry by calling  
5 1-800-822-2463.

6

### 7 **8.3 Nursing Mothers**

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

11

### 12 **8.4 Pediatric Use**

13 Safety and effectiveness of Fluzone Quadrivalent in children below the age of 6 months have not  
14 been established. Safety and immunogenicity of Fluzone Quadrivalent were evaluated in children  
15 6 months through 8 years of age. [See [Adverse Reactions \(6.1\)](#) and [Clinical Studies \(14.1\)](#).]

16

### 17 **8.5 Geriatric Use**

18 Safety and immunogenicity of Fluzone Quadrivalent were evaluated in adults 65 years of age and  
19 older. [See [Clinical Studies \(14.3\)](#).] Antibody responses to Fluzone Quadrivalent are lower in  
20 persons  $\geq 65$  years of age than in younger adults.

21

## 22 **11 DESCRIPTION**



1 Fluzone Quadrivalent (Influenza Vaccine) for intramuscular injection is an inactivated influenza  
2 vaccine, prepared from influenza viruses propagated in embryonated chicken eggs. The virus-  
3 containing allantoic fluid is harvested and inactivated with formaldehyde. Influenza virus is  
4 concentrated and purified in a linear sucrose density gradient solution using a continuous flow  
5 centrifuge. The virus is then chemically disrupted using a non-ionic surfactant, octylphenol  
6 ethoxylate (Triton® X-100), producing a “split virus”. The split virus is further purified and then  
7 suspended in sodium phosphate-buffered isotonic sodium chloride solution. The Fluzone  
8 Quadrivalent process uses an additional concentration factor after the ultrafiltration step in order  
9 to obtain a higher hemagglutinin (HA) antigen concentration. Antigens from the four strains  
10 included in the vaccine are produced separately and then combined to make the quadrivalent  
11 formulation.

12

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

14

15 Antibiotics are not used in the manufacture of Fluzone Quadrivalent.

16

17 The Fluzone Quadrivalent prefilled syringe and vial presentations are not made with natural  
18 rubber latex.

19

20 Fluzone Quadrivalent is standardized according to United States Public Health Service  
21 requirements and is formulated to contain HA of each of the following four influenza strains  
22 recommended for the 2015-2016 influenza season: A/California/07/2009 X-179A (H1N1),  
23 A/Switzerland/9715293/2013 NIB-88 (H3N2), B/Phuket/3073/2013 (B Yamagata lineage), and

1 B/Brisbane/60/2008 (B Victoria lineage). The amounts of HA and other ingredients per dose of  
2 vaccine are listed in [Table 6](#). The single-dose, pre-filled syringe (0.25 mL and 0.5 mL) and the  
3 single-dose vial (0.5 mL) are manufactured and formulated without thimerosal or any other  
4 preservative. The 5 mL multi-dose vial presentation contains thimerosal, a mercury derivative,  
5 added as a preservative. Each 0.5 mL dose from the multi-dose vial contains 25 mcg mercury.  
6 Each 0.25 mL dose from the multi-dose vial contains 12.5 mcg mercury.

1 **Table 6: Fluzone Quadrivalent Ingredients**

Ingredient	Quantity (per dose)	
	Fluzone Quadrivalent 0.25 mL Dose	Fluzone Quadrivalent 0.5 mL Dose
<b>Active Substance: Split influenza virus, inactivated strains<sup>a</sup>:</b>	30 mcg HA total	60 mcg HA total
A (H1N1)	7.5 mcg HA	15 mcg HA
A (H3N2)	7.5 mcg HA	15 mcg HA
B/(Victoria lineage)	7.5 mcg HA	15 mcg HA
B/(Yamagata lineage)	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	≤125 mcg	≤250 mcg
<b>Preservative</b>		
Single-dose presentations	-	-
Multi-dose presentation (thimerosal)	12.5 mcg mercury	25 mcg mercury

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

3 <sup>b</sup>Quantity Sufficient

4 "-" Indicates information is not applicable

5

## 6 **12 CLINICAL PHARMACOLOGY**

### 7 **12.1 Mechanism of Action**

8 Influenza illness and its complications follow infection with influenza viruses. Global surveillance  
9 of influenza identifies yearly antigenic variants. Since 1977, antigenic variants of influenza A  
10 (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. Since 2001,  
11 two distinct lineages of influenza B (Victoria and Yamagata lineages) have co-circulated  
12 worldwide. Protection from influenza virus infection has not been correlated with a specific level  
13 of hemagglutination inhibition (HI) antibody titer post-vaccination. However, in some human

1 studies, antibody titers  $\geq 1:40$  have been associated with protection from influenza illness in up to  
2 50% of subjects. (See ref. 2) (See ref. 3)

3

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

11

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

15

## 16 **14 CLINICAL STUDIES**

### 17 **14.1 Immunogenicity of Fluzone Quadrivalent in Children 6 Months through 8** 18 **Years of Age**

19 In Study 1 (NCT01240746) [see [Adverse Reactions \(6.1\)](#)], 1419 children 6 months through 35  
20 months of age and 2101 children 3 years through 8 years of age were included in the per-protocol  
21 immunogenicity analysis. Participants received one or two 0.25 mL doses or one or two 0.5 mL  
22 doses, respectively of Fluzone Quadrivalent, TIV-1, or TIV-2. For participants who received two

1 doses, the doses were administered approximately 4 weeks apart. The distribution of demographic  
2 characteristics was similar to that of the safety analysis [see *Adverse Reactions (6.1)*].  
3  
4 HI antibody geometric mean titers (GMTs) and seroconversion rates 28 days following  
5 vaccination with Fluzone Quadrivalent were non-inferior to those following each TIV for all four  
6 strains, based on pre-specified criteria (see [Table 7](#) and [Table 8](#)).

7 **Table 7: Study 1<sup>a</sup>: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain**  
8 **by HI Antibody GMTs at 28 Days Post-Vaccination, Persons 6 Months Through 8 Years of**  
9 **Age (Per-protocol Analysis Set)<sup>b</sup>**

Antigen Strain	Fluzone Quadrivalent N <sup>c</sup> =2339	Pooled TIV <sup>d</sup> N <sup>c</sup> =1181		GMT Ratio (95% CI) <sup>e</sup>
	GMT	GMT		
A (H1N1)	1124	1096		1.03 (0.93; 1.14)
A (H3N2)	822	828		0.99 (0.91; 1.08)
	Fluzone Quadrivalent N <sup>c</sup> =2339	TIV-1 <sup>f</sup> (B Victoria) N <sup>c</sup> =582	TIV-2 <sup>g</sup> (B Yamagata) N <sup>c</sup> =599	GMT Ratio (95% CI) <sup>e</sup>
	GMT	GMT	GMT	
<b>B/Brisbane/60/2008 (B Victoria)</b>	86.1	64.3	(19.5) <sup>h</sup>	1.34 (1.20; 1.50)
<b>B/Florida/04/2006 (B Yamagata)</b>	61.5	(16.3) <sup>i</sup>	58.3	1.06 (0.94; 1.18)

10 <sup>a</sup>NCT01240746

11 <sup>b</sup>Per-protocol analysis set included all persons who had no study protocol deviations

12 <sup>c</sup>N is the number of participants in the per-protocol analysis set

13 <sup>d</sup>Pooled TIV group includes participants vaccinated with either TIV-1 or TIV-2

14 <sup>e</sup>Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio of GMTs (Fluzone  
15 Quadrivalent divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >0.66

16 <sup>f</sup>2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and  
17 B/Brisbane/60/2008 (Victoria lineage), licensed

18 <sup>g</sup>Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006  
19 (Yamagata lineage), non-licensed

20 <sup>h</sup>TIV-2 did not contain B/Brisbane/60/2008

21 <sup>i</sup>TIV-1 did not contain B/Florida/04/2006

22

1 **Table 8: Study 1<sup>a</sup>: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain**  
 2 **by Seroconversion Rates at 28 Days Post-Vaccination, Persons 6 Months Through 8 Years**  
 3 **of Age (Per-protocol Analysis Set)<sup>b</sup>**

Antigen Strain	Fluzone Quadrivalent N <sup>c</sup> =2339	Pooled TIV <sup>d</sup> N <sup>c</sup> =1181		Difference of Seroconversion Rates (95% CI) <sup>f</sup>
	Seroconversion <sup>e</sup> (%)			
A (H1N1)	92.4	91.4		0.9 (-0.9; 3.0)
A (H3N2)	88.0	84.2		3.8 (1.4; 6.3)
	Fluzone Quadrivalent N <sup>c</sup> =2339	TIV-1 <sup>g</sup> (B Victoria) N <sup>c</sup> =582	TIV-2 <sup>h</sup> (B Yamagata) N <sup>c</sup> =599	Difference of Seroconversion Rates (95% CI) <sup>f</sup>
	Seroconversion <sup>e</sup> (%)			
B/Brisbane/60/2008 (B Victoria)	71.8	61.1	(20.0) <sup>i</sup>	10.7 (6.4; 15.1)
B/Florida/04/2006 (B Yamagata)	66.1	(17.9) <sup>j</sup>	64.0	2.0 (-2.2; 6.4)

4 <sup>a</sup>NCT01240746

5 <sup>b</sup>Per-protocol analysis set included all persons who had no study protocol deviations

6 <sup>c</sup>N is the number of participants in the per-protocol analysis set

7 <sup>d</sup>Pooled TIV group includes participants vaccinated with either TIV-1 or TIV-2

8 <sup>e</sup>Seroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination titer ≥1:40 or a minimum  
 9 4-fold increase for participants with pre-vaccination titer ≥1:10

10 <sup>f</sup>Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference in seroconversion rates  
 11 (Fluzone Quadrivalent minus pooled TIV for the A strains, or the TIV containing the corresponding B strain) was  
 12 >-10%

13 <sup>g</sup>2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and  
 14 B/Brisbane/60/2008 (Victoria lineage), licensed

15 <sup>h</sup>Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006  
 16 (Yamagata lineage), non-licensed

17 <sup>i</sup>TIV-2 did not contain B/Brisbane/60/2008

18 <sup>j</sup>TIV-1 did not contain B/Florida/04/2006

19

20 Non-inferiority immunogenicity criteria based on HI antibody GMTs and seroconversion rates

21 were also met when age subgroups (6 months to <36 months and 3 years to <9 years) were

22 examined. In addition, HI antibody GMTs and seroconversion rates following Fluzone

23 Quadrivalent were higher than those following TIV for the B strain not contained in each

24 respective TIV based on pre-specified criteria (the lower limit of the 2-sided 95% CI of the ratio

1 of the GMTs [Fluzone Quadrivalent divided by TIV] >1.5 for each B strain in Fluzone  
2 Quadrivalent compared with the corresponding B strain not contained in each TIV and the lower  
3 limit of the two 2-sided 95% CI of the difference of the seroconversion rates [Fluzone  
4 Quadrivalent minus TIV] >10% for each B strain in Fluzone Quadrivalent compared with the  
5 corresponding B strain not contained in each TIV).

6

## 7 14.2 Immunogenicity of Fluzone Quadrivalent in Adults ≥18 Years of Age

8 In Study 2 (NCT00988143) [see [Adverse Reactions \(6.1\)](#)], 565 adults 18 years of age and older  
9 who had received one dose of Fluzone Quadrivalent, TIV-1, or TIV-2 were included in the per-  
10 protocol immunogenicity analysis. The distribution of demographic characteristics was similar to  
11 that of the safety analysis [see [Adverse Reactions \(6.1\)](#)].

12

13 HI antibody GMTs 21 days following vaccination with Fluzone Quadrivalent were non-inferior to  
14 those following each TIV for all four strains, based on pre-specified criteria (see [Table 9](#)).

15 **Table 9: Study 2<sup>a</sup>: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain**  
16 **by HI Antibody GMTs at 21 Days Post-Vaccination, Adults 18 Years of Age and Older (Per-**  
17 **protocol Analysis Set)<sup>b</sup>**

Antigen Strain	Fluzone Quadrivalent N <sup>c</sup> =190	Pooled TIV <sup>d</sup> N <sup>c</sup> =375		GMT Ratio (95% CI) <sup>e</sup>
	GMT	GMT		
A (H1N1)	161	151		1.06 (0.87; 1.31)
A (H3N2)	304	339		0.90 (0.70; 1.15)
	Fluzone Quadrivalent N <sup>c</sup> =190	TIV-1 <sup>f</sup> (B Victoria) N <sup>c</sup> =187	TIV-2 <sup>g</sup> (B Yamagata) N <sup>c</sup> =188	GMT Ratio (95% CI) <sup>e</sup>
	GMT	GMT	GMT	

<b>B/Brisbane/60/2008 (B Victoria)</b>	101	114	(44.0) <sup>h</sup>	0.89 (0.70; 1.12)
<b>B/Florida/04/2006 (B Yamagata)</b>	155	(78.1) <sup>i</sup>	135	1.15 (0.93; 1.42)

1 <sup>a</sup>NCT00988143

2 <sup>b</sup>Per-protocol analysis set included all persons who had no study protocol deviations

3 <sup>c</sup>N is the number of participants in the per-protocol analysis set

4 <sup>d</sup>Pooled TIV group includes participants vaccinated with either TIV-1 or TIV-2

5 <sup>e</sup>Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio of GMTs (Fluzone  
6 Quadrivalent divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >2/3

7 <sup>f</sup>2009-2010 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and  
8 B/Brisbane/60/2008 (Victoria lineage), licensed

9 <sup>g</sup>2008-2009 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and  
10 B/Florida/04/2006 (Yamagata lineage), licensed

11 <sup>h</sup>TIV-2 did not contain B/Brisbane/60/2008

12 <sup>i</sup>TIV-1 did not contain B/Florida/04/2006

13

### 14 **14.3 Immunogenicity of Fluzone Quadrivalent in Geriatric Adults ≥65 Years of** 15 **Age**

16 In Study 3 (NCT01218646) [see [Adverse Reactions \(6.1\)](#)], 660 adults 65 years of age and older  
17 were included in the per-protocol immunogenicity analysis. The distribution of demographic  
18 characteristics was similar to that of the safety analysis [see [Adverse Reactions \(6.1\)](#)].

19

20 HI antibody GMTs 21 days following vaccination with Fluzone Quadrivalent were non-inferior to  
21 those following TIV for all four strains, based on pre-specified criteria (see [Table 10](#)).

22 Seroconversion rates 21 days following Fluzone Quadrivalent were non-inferior to those

23 following TIV for H3N2, B/Brisbane, and B/Florida, but not for H1N1 (see [Table 11](#)). The HI

24 antibody GMT following Fluzone Quadrivalent was higher than that following TIV-1 for

25 B/Florida but not higher than that following TIV-2 for B/Brisbane, based on pre-specified criteria

26 (the lower limit of the 2-sided 95% CI of the ratio of the GMTs [Fluzone Quadrivalent divided by

27 TIV] >1.5 for each B strain in Fluzone Quadrivalent compared with the corresponding B strain



1 not contained in each TIV). Seroconversion rates following Fluzone Quadrivalent were higher  
2 than those following TIV for the B strain not contained in each respective TIV, based on pre-  
3 specified criteria (the lower limit of the two 2-sided 95% CI of the difference of the  
4 seroconversion rates [Fluzone Quadrivalent minus TIV] >10% for each B strain in Fluzone  
5 Quadrivalent compared with the corresponding B strain not contained in each TIV).

6 **Table 10: Study 3<sup>a</sup>: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain**  
7 **by HI Antibody GMTs at 21 Days Post-Vaccination, Adults 65 Years of Age and Older (Per-**  
8 **protocol Analysis Set)<sup>b</sup>**

Antigen Strain	Fluzone Quadrivalent N <sup>c</sup> =220	Pooled TIV <sup>d</sup> N <sup>c</sup> =440		GMT Ratio (95% CI) <sup>e</sup>
	GMT	GMT		
A (H1N1)	231	270		0.85 (0.67; 1.09)
A (H3N2)	501	324		1.55 (1.25; 1.92)
	Fluzone Quadrivalent N <sup>c</sup> =220	TIV-1 <sup>f</sup> (B Victoria) N <sup>c</sup> =219	TIV-2 <sup>g</sup> (B Yamagata) N <sup>c</sup> =221	GMT Ratio (95% CI) <sup>e</sup>
	GMT	GMT	GMT	
B/Brisbane/60/2008 (B Victoria)	73.8	57.9	(42.2) <sup>h</sup>	1.27 (1.05; 1.55)
B/Florida/04/2006 (B Yamagata)	61.1	(28.5) <sup>i</sup>	54.8	1.11 (0.90; 1.37)

9 <sup>a</sup>NCT01218646

10 <sup>b</sup>Per-protocol analysis set included all persons who had no study protocol deviations

11 <sup>c</sup>N is the number of participants in the per-protocol analysis set

12 <sup>d</sup>Pooled TIV group includes participants vaccinated with either TIV-1 or TIV-2

13 <sup>e</sup>Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio of GMTs (Fluzone  
14 Quadrivalent divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >0.66

15 <sup>f</sup>2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and  
16 B/Brisbane/60/2008 (Victoria lineage), licensed

17 <sup>g</sup>Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006  
18 (Yamagata lineage), non-licensed

19 <sup>h</sup>TIV-2 did not contain B/Brisbane/60/2008

20 <sup>i</sup>TIV-1 did not contain B/Florida/04/2006

21

1 **Table 11: Study 3<sup>a</sup>: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain**  
 2 **by Seroconversion Rates at 21 Days Post-Vaccination, Adults 65 Years of Age and Older**  
 3 **(Per-protocol Analysis Set)<sup>b</sup>**

Antigen Strain	Fluzone Quadrivalent N <sup>c</sup> =220	Pooled TIV <sup>d</sup> N <sup>c</sup> =440		Difference of Seroconversion Rate (95% CI) <sup>e</sup>
	Seroconversion <sup>f</sup> (%)			
A (H1N1)	65.91	69.77		-3.86 (-11.50; 3.56)
A (H3N2)	69.09	59.32		9.77 (1.96; 17.20)
	Fluzone Quadrivalent N <sup>c</sup> =220	TIV-1 <sup>g</sup> (B Victoria) N <sup>c</sup> =219	TIV-2 <sup>h</sup> (B Yamagata) N <sup>c</sup> =221	Difference of Seroconversion Rate (95% CI) <sup>e</sup>
	Seroconversion <sup>f</sup> (%)			
B/Brisbane/60/2008 (B Victoria)	28.64	18.72	(8.60) <sup>i</sup>	9.91 (1.96; 17.70)
B/Florida/04/2006 (B Yamagata)	33.18	(9.13) <sup>j</sup>	31.22	1.96 (-6.73; 10.60)

4 <sup>a</sup>NCT01218646

5 <sup>b</sup>Per-protocol analysis set included all persons who had no study protocol deviations

6 <sup>c</sup>N is the number of participants in the per-protocol analysis set

7 <sup>d</sup>Pooled TIV group includes participants vaccinated with either TIV-1 or TIV-2

8 <sup>e</sup>Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference in seroconversion rates  
 9 (Fluzone Quadrivalent minus pooled TIV for the A strains, or the TIV containing the corresponding B strain) was  
 10 >-10%

11 <sup>f</sup>Seroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination titer ≥1:40 or a minimum  
 12 4-fold increase for participants with pre-vaccination titer ≥1:10

13 <sup>g</sup>2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and  
 14 B/Brisbane/60/2008 (Victoria lineage), licensed

15 <sup>h</sup>Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006  
 16 (Yamagata lineage), non-licensed

17 <sup>i</sup>TIV-2 did not contain B/Brisbane/60/2008

18 <sup>j</sup>TIV-1 did not contain B/Florida/04/2006

19

20

21

1 **15 REFERENCES**

- 2 1 Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barré syndrome and the 1992-1993  
3 and 1993-1994 influenza vaccines. *N Engl J Med* 1998;339:1797-802.
- 4 2 Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza  
5 vaccination. *Virus Res* 2004;103:133-138.
- 6 3 Hobson D, Curry RL, Beare AS, Ward-Gardner A. The role of serum haemagglutination-  
7 inhibiting antibody in protection against challenge infection with influenza A2 and B  
8 viruses. *J Hyg Camb* 1972;70:767-777.

9

10

11

12

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

2 **16.1 How Supplied**

3 Single-dose, prefilled syringe (yellow plunger rod), without needle, 0.25 mL

4 (NDC 49281-515-00) (not made with natural rubber latex). Supplied as package of 10

5 (NDC 49281-515-25).

6

7 Single-dose, prefilled syringe (purple plunger rod), without needle, 0.5 mL (NDC 49281-415-88)

8 (not made with natural rubber latex). Supplied as package of 10 (NDC 49281-415-50).

9

10 Single-dose vial, 0.5 mL (NDC 49281-415-58) (not made with natural rubber latex). Supplied as  
11 package of 10 (NDC 49281-415-10).

12

13 Multi-dose vial, 5 mL (NDC 49281-623-78) (not made with natural rubber latex). Supplied as  
14 package of 1 (NDC 49281-623-15). A maximum of ten doses can be withdrawn from the multi-  
15 dose vial.

16

17 **16.2 Storage and Handling**

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

19 FREEZE. Discard if vaccine has been frozen.

20

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

22

23 **17 PATIENT COUNSELING INFORMATION**

---

1 See FDA-approved patient labeling (Patient Information). Inform the vaccine recipient or  
2 guardian:

- 3 • Fluzone Quadrivalent contains killed viruses and cannot cause influenza.
- 4 • Fluzone Quadrivalent stimulates the immune system to protect against influenza, but does not  
5 prevent other respiratory infections.
- 6 • Annual influenza vaccination is recommended.
- 7 • Report adverse reactions to their healthcare provider and/or to the Vaccine Adverse Event  
8 Reporting System (VAERS) at 1-800-822-7967.
- 9 • Sanofi Pasteur Inc. is maintaining a prospective pregnancy exposure registry to collect data on  
10 pregnancy outcomes and newborn health status following vaccination with Fluzone  
11 Quadrivalent during pregnancy. Women who receive Fluzone Quadrivalent during pregnancy  
12 are encouraged to contact Sanofi Pasteur Inc. directly or have their healthcare provider contact  
13 Sanofi Pasteur Inc. at 1-800-822-2463.

14

15 Vaccine Information Statements must be provided to vaccine recipients or their guardians, as  
16 required by the National Childhood Vaccine Injury Act of 1986 prior to immunization. These  
17 materials are available free of charge at the Centers for Disease Control and Prevention (CDC)  
18 website ([www.cdc.gov/vaccines](http://www.cdc.gov/vaccines)).

19

20 Fluzone is a registered trademark of Sanofi Pasteur Inc.

21

22 Manufactured by:

1 **Sanofi Pasteur Inc.**

2 Swiftwater PA 18370 USA

6754, 6761, 6765

3

4

SANOFI PASTEUR 

5

1 **Patient Information Sheet**

2 **Fluzone® Quadrivalent**

3 **Influenza Vaccine**

4  
5 Please read this information sheet before getting Fluzone Quadrivalent vaccine. This summary is  
6 not intended to take the place of talking with your healthcare provider. If you have questions or  
7 would like more information, please talk with your healthcare provider.

8  
9 **What is Fluzone Quadrivalent vaccine?**

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

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

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

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

16 You should not get Fluzone Quadrivalent vaccine if you:

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

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

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

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

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

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

4

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

6 The most common side effects of Fluzone Quadrivalent vaccine are:

7 • pain, redness, and swelling 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 Quadrivalent vaccine. You can ask your

13 healthcare 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>. Sanofi Pasteur Inc. is collecting information on pregnancy outcomes and the

18 health of newborns following vaccination with Fluzone Quadrivalent during pregnancy. Women

19 who receive Fluzone Quadrivalent during pregnancy are encouraged to contact Sanofi Pasteur Inc.

20 directly or have their healthcare provider contact Sanofi Pasteur Inc. at 1-800-822-2463.

21

22 **What are the ingredients in Fluzone Quadrivalent vaccine?**

23 Fluzone Quadrivalent vaccine contains 4 killed flu virus strains.



1

2 Inactive ingredients include formaldehyde and octylphenol ethoxylate. The preservative  
3 thimerosal is only in the multi-dose vial of Fluzone Quadrivalent vaccine.

4

5 Manufactured by:

6 **Sanofi Pasteur Inc.**

7 Swiftwater, PA 18370 USA

8

9 SANOFI PASTEUR 