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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
2018-2019 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 ^a , 0.25 mL each	If 2 doses, administer at least 4 weeks apart
36 months through 8 years	One or two doses ^a , 0.5 mL each	If 2 doses, administer at least 4 weeks apart
9 years and older	One dose, 0.5 mL	-

^a1 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 (pink plunger rod), 0.25 mL; prefilled single-dose syringe (clear 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.

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. (8.4)
- Pregnancy: Pregnancy registry available. Call Sanofi Pasteur Inc. at 1-800-822-2463.
- Antibody responses to Fluzone Quadrivalent are lower in persons ≥ 65 years of age than in younger adults. (8.5)

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

Revised: XXXX

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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 ^a , 0.25 mL each	If 2 doses, administer at least 4 weeks apart
36 months through 8 years	One or two doses ^a , 0.5 mL each	If 2 doses, administer at least 4 weeks apart
9 years and older	One dose, 0.5 mL	-

14 ^a1 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 Parenteral drug products should be inspected visually for particulate matter and/or discoloration
2 prior to administration, whenever solution and container permit. If any of these defects or
3 conditions exist, Fluzone Quadrivalent should not be administered.

4

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7 and syringe for each dose withdrawn from the multi-dose vial.

8

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

14

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

16

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

19

20 **3 DOSAGE FORMS AND STRENGTHS**

21 Fluzone Quadrivalent is a suspension for injection.

22

23 Fluzone Quadrivalent is supplied in 4 presentations:

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

7

8 **4 CONTRAINDICATIONS**

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

12

13 **5 WARNINGS AND PRECAUTIONS**

14 **5.1 Guillain-Barré Syndrome**

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

21

22 **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%)^a or tenderness (54%)^b, erythema (37%), and swelling (22%); the most common
14 solicited systemic adverse reactions were irritability (54%)^b, abnormal crying (41%)^b, malaise
15 (38%)^a, drowsiness (38%)^b, appetite loss (32%)^b, myalgia (27%)^a, vomiting (15%)^b, 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

^a Assessed in children 24 months through 35 months of age

^b Assessed in children 6 months through 23 months of age

1 common solicited systemic adverse reactions were myalgia (24%), headache (16%), and malaise
2 (11%). In adults 65 years of age and older, the most common ($\geq 10\%$) injection-site reaction was
3 pain (33%); the most common solicited systemic adverse reactions were myalgia (18%), headache
4 (13%), and malaise (11%).

5

6 **6.1 Clinical Trials Experience**

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

10

11 **Children 6 Months Through 8 Years of Age**

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

1 58.4% Caucasian (Fluzone Quadrivalent, 58.4%; TIV-1, 58.9%; TIV-2, 57.8%), 20.2% Black
 2 (Fluzone Quadrivalent, 20.5%; TIV-1, 19.9%; TIV-2, 19.1%), 14.1% Hispanic (Fluzone
 3 Quadrivalent, 14.3%; TIV-1, 13.2%; TIV-2, 14.7%), and 7.3% were of other racial/ethnic groups
 4 (Fluzone Quadrivalent, 6.8%; TIV-1, 8.0%; TIV-2, 8.5%). [Table 2](#) and [Table 3](#) summarize
 5 solicited injection-site and systemic adverse reactions reported within 7 days post-vaccination via
 6 diary cards. Participants were monitored for unsolicited adverse events for 28 days after each dose
 7 and serious adverse events (SAEs) during the 6 months following the last dose.

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

	Fluzone Quadrivalent ^c (N ^f =1223)			TIV-1 ^d (B Victoria) (N ^f =310)			TIV-2 ^e (B Yamagata) (N ^f =308)		
	Any (%)	Grade 2 ^g (%)	Grade 3 ^h (%)	Any (%)	Grade 2 ^g (%)	Grade 3 ^h (%)	Any (%)	Grade 2 ^g (%)	Grade 3 ^h (%)
Injection-site adverse reactions									
Painⁱ	57.0	10.2	1.0	52.3	11.5	0.8	50.3	5.4	2.7
Tendernessⁱ	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
Systemic adverse reactions									
Fever (≥100.4°F)^k	14.3	5.5	2.1	16.0	6.6	1.7	13.0	4.1	2.0
Malaiseⁱ	38.1	14.5	4.6	35.2	14.8	4.7	32.4	12.8	6.8
Myalgiaⁱ	26.7	6.6	1.9	26.6	9.4	1.6	25.0	6.8	2.7
Headacheⁱ	8.9	2.5	0.6	9.4	3.9	0.0	12.2	4.7	0.0
Irritability^j	54.0	26.4	3.2	52.8	20.1	3.1	53.5	22.9	2.8
Crying abnormal^j	41.2	12.3	3.3	36.5	8.2	1.9	29.9	10.4	2.1
Drowsiness^j	37.7	8.4	1.3	32.1	3.8	0.6	31.9	5.6	0.7

	Fluzone Quadrivalent ^c (N ^f =1223)			TIV-1 ^d (B Victoria) (N ^f =310)			TIV-2 ^e (B Yamagata) (N ^f =308)		
	Any (%)	Grade 2 ^g (%)	Grade 3 ^h (%)	Any (%)	Grade 2 ^g (%)	Grade 3 ^h (%)	Any (%)	Grade 2 ^g (%)	Grade 3 ^h (%)
Appetite loss^j	32.3	9.1	1.8	33.3	5.7	1.9	25.0	8.3	0.7
Vomiting^j	14.8	6.2	1.0	11.3	4.4	0.6	13.9	6.3	0.0

1 ^aNCT01240746

2 ^bThe safety analysis set includes all persons who received at least one dose of study vaccine

3 ^cFluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008
4 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)

5 ^d2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and
6 B/Brisbane/60/2008 (Victoria lineage), licensed

7 ^eInvestigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006
8 (Yamagata lineage), non-licensed

9 ^fN is the number of participants in the safety analysis set

10 ^gGrade 2 - Injection-site pain: sufficiently discomforting to interfere with normal behavior or activities; Injection-site
11 tenderness: cries and protests when injection-site is touched; Injection-site erythema, Injection-site swelling: ≥2.5 cm
12 to <5 cm; Fever: >101.3°F to ≤103.1°F (6 months through 23 months); ≥101.2°F to ≤102.0°F (24 months through 35
13 months); Malaise, Myalgia, and Headache: some interference with activity; Irritability: requiring increased attention;
14 Crying abnormal: 1 to 3 hours; Drowsiness: not interested in surroundings or did not wake up for a feed/meal;
15 Appetite loss: missed 1 or 2 feeds/meals completely; Vomiting: 2 to 5 episodes per 24 hours

16 ^hGrade 3 - Injection-site pain: incapacitating, unable to perform usual activities; Injection-site tenderness: cries when
17 injected limb is moved, or the movement of the injected limb is reduced; Injection-site erythema, Injection-site
18 swelling: ≥5 cm; Fever: >103.1°F (6 months through 23 months); ≥102.1°F (24 months through 35 months); Malaise,
19 Myalgia, and Headache: Significant; prevents daily activity; Irritability: inconsolable; Crying abnormal: >3 hours;
20 Drowsiness: sleeping most of the time or difficult to wake up; Appetite loss: refuses ≥3 feeds/meals or refuses most
21 feeds/meals; Vomiting: ≥6 episodes per 24 hours or requiring parenteral hydration

22 ⁱAssessed in children 24 months through 35 months of age

23 ^jAssessed in children 6 months through 23 months of age

24 ^kFever measured by any route

25

26 **Table 3: Study 1^a: Percentage of Solicited Injection-site and Systemic Adverse Reactions**
27 **Within 7 Days After Vaccination in Children 3 Years Through 8 Years of Age (Safety**
28 **Analysis Set)^b**

	Fluzone Quadrivalent ^c (N ^f =1669)			TIV-1 ^d (B Victoria) (N ^f =424)			TIV-2 ^e (B Yamagata) (N ^f =413)		
	Any (%)	Grade 2 ^g (%)	Grade 3 ^h (%)	Any (%)	Grade 2 ^g (%)	Grade 3 ^h (%)	Any (%)	Grade 2 ^g (%)	Grade 3 ^h (%)
Injection-site adverse reactions									

	Fluzone Quadrivalent ^c (N ^f =1669)			TIV-1 ^d (B Victoria) (N ^f =424)			TIV-2 ^e (B Yamagata) (N ^f =413)		
	Any (%)	Grade 2 ^g (%)	Grade 3 ^h (%)	Any (%)	Grade 2 ^g (%)	Grade 3 ^h (%)	Any (%)	Grade 2 ^g (%)	Grade 3 ^h (%)
Pain	66.6	15.8	2.1	64.6	9.5	2.0	63.8	11.6	2.8
Erythema	34.1	2.9	1.8	36.8	3.4	1.2	35.2	2.5	1.8
Swelling	24.8	2.8	1.4	25.4	1.5	1.2	25.9	2.5	1.8
Systemic adverse reactions									
Fever (≥100.4°F)ⁱ	7.0	2.1	2.1	7.1	2.2	1.2	7.6	2.8	0.8
Headache	23.1	6.8	2.2	21.2	5.1	2.7	24.4	7.5	2.0
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 ^aNCT01240746

2 ^bThe safety analysis set includes all persons who received at least one dose of study vaccine

3 ^cFluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008
4 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)

5 ^d2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and
6 B/Brisbane/60/2008 (Victoria lineage), licensed

7 ^eInvestigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006
8 (Yamagata lineage), non-licensed

9 ^fN is the number of participants in the safety analysis set

10 ^gGrade 2 - Injection-site pain: sufficiently discomforting to interfere with normal behavior or activities; Injection-site
11 erythema, Injection-site swelling: ≥2.5 cm to <5 cm; Fever: ≥101.2°F to ≤102.0°F; Headache, Malaise, and Myalgia:
12 some interference with activity

13 ^hGrade 3 - Injection-site pain: incapacitating, unable to perform usual activities; Injection-site erythema, Injection-site
14 swelling: ≥5 cm; Fever: ≥102.1°F; Headache, Malaise, and Myalgia: Significant; prevents daily activity

15 ⁱFever measured by any route

16

17 Among children 6 months through 8 years of age, unsolicited non-serious adverse events were
18 reported in 1360 (47.0%) recipients in the Fluzone Quadrivalent group, 352 (48.0%) recipients in
19 the TIV-1 group, and 346 (48.0%) recipients in the TIV-2 group. The most commonly reported
20 unsolicited non-serious adverse events were cough, vomiting, and pyrexia. During the 28 days
21 following vaccination, a total of 16 (0.6%) recipients in the Fluzone Quadrivalent group, 4 (0.5%)

1 recipients in the TIV-1 group, and 4 (0.6%) recipients in the TIV-2 group, experienced at least
2 one SAE; no deaths occurred. Throughout the study period, a total of 41 (1.4%) recipients in the
3 Fluzone Quadrivalent group, 7 (1.0%) recipients in the TIV-1 group, and 14 (1.9%) recipients in
4 the TIV-2 group, experienced at least one SAE. Three SAEs were considered to be possibly
5 related to vaccination: croup in a Fluzone Quadrivalent recipient and 2 episodes of febrile seizure,
6 1 each in a TIV-1 recipient and a TIV-2 recipient. One death occurred in the TIV-1 group (a
7 drowning 43 days post-vaccination).

8

9 **Adults**

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

1 **Table 4: Study 2^a: 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)^b**

	Fluzone Quadrivalent ^c (N ^f =190)			TIV-1 ^d (B Victoria) (N ^f =190)			TIV-2 ^e (B Yamagata) (N ^f =190)		
	Any (%)	Grade 2 ^g (%)	Grade 3 ^h (%)	Any (%)	Grade 2 ^g (%)	Grade 3 ^h (%)	Any (%)	Grade 2 ^g (%)	Grade 3 ^h (%)
Injection-site adverse reactions									
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
Systemic adverse reactions									
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)ⁱ	0.0	0.0	0.0	0.5	0.5	0.0	0.5	0.5	0.0

3 ^aNCT00988143

4 ^bThe safety analysis set includes all persons who received study vaccine

5 ^cFluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008
6 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)

7 ^d2009-2010 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and
8 B/Brisbane/60/2008 (Victoria lineage), licensed

9 ^e2008-2009 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and
10 B/Florida/04/2006 (Yamagata lineage), licensed

11 ^fN is the number of participants in the safety analysis set

12 ^gGrade 2 - Injection-site pain: Some interference with activity; Injection-site erythema, Injection-site swelling,
13 Injection-site induration, and Injection-site ecchymosis: ≥5.1 to ≤10 cm; Fever: ≥101.2°F to ≤102.0°F; Myalgia,
14 Headache, Malaise, and Shivering: some interference with activity

15 ^hGrade 3 - Injection-site pain: Significant; prevents daily activity; Injection-site erythema, Injection-site swelling,
16 Injection-site induration, and Injection-site ecchymosis: >10 cm; Fever: ≥102.1°F; Myalgia, Headache, Malaise, and
17 Shivering: Significant; prevents daily activity

18 ⁱFever measured by any route

19

1 Unsolicited non-serious adverse events were reported in 33 (17.4%) recipients in the Fluzone
2 Quadrivalent group, 45 (23.7%) recipients in the TIV-1 group, and 45 (23.7%) recipients in the
3 TIV-2 group. The most commonly reported unsolicited non-serious adverse events were
4 headache, cough, and oropharyngeal pain. In the follow-up period, there were two SAEs, 1 (0.5%)
5 in the Fluzone Quadrivalent group and 1 (0.5%) in the TIV-2 group. No deaths were reported
6 during the trial period.

7

8 **Geriatric Adults**

9 In Study 3 (NCT01218646, see <http://clinicaltrials.gov>), a multi-center, randomized, double-blind
10 trial conducted in the US, adults 65 years of age and older received one dose of either Fluzone
11 Quadrivalent, or one of two formulations of comparator trivalent influenza vaccine (TIV-1 or
12 TIV-2). Each of the trivalent formulations contained an influenza type B virus that corresponded
13 to one of the two type B viruses in Fluzone Quadrivalent (a type B virus of the Victoria lineage or
14 a type B virus of the Yamagata lineage). The safety analysis set included 675 recipients. Among
15 participants in the three vaccine groups combined, 55.7% were female (Fluzone Quadrivalent,
16 57.3%; TIV-1, 56.0%; TIV-2, 53.8%), 89.5% Caucasian (Fluzone Quadrivalent, 87.6%; TIV-1,
17 89.8%; TIV-2, 91.1%), 2.2% Black (Fluzone Quadrivalent, 4.0%; TIV-1, 1.8%; TIV-2, 0.9%),
18 7.4% Hispanic (Fluzone Quadrivalent, 8.4%; TIV-1, 7.6%; TIV-2, 6.2%) and 0.9% were of other
19 racial/ethnic groups (Fluzone Quadrivalent, 0.0%; TIV-1, 0.9%; TIV-2, 1.8%).

20

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

1

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

	Fluzone Quadrivalent ^c (N ^f =225)			TIV-1 ^d (B Victoria) (N ^f =225)			TIV-2 ^e (B Yamagata) (N ^f =225)		
	Any (%)	Grade 2 ^g (%)	Grade 3 ^h (%)	Any (%)	Grade 2 ^g (%)	Grade 3 ^h (%)	Any (%)	Grade 2 ^g (%)	Grade 3 ^h (%)
Injection-site adverse reactions									
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
Systemic adverse reactions									
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)ⁱ	1.3	0.0	0.4	0.0	0.0	0.0	0.9	0.4	0.4

4 ^aNCT01218646

5 ^bThe safety analysis set includes all persons who received study vaccine

6 ^cFluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008
7 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)

8 ^d2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and
9 B/Brisbane/60/2008 (Victoria lineage), licensed

10 ^eInvestigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006
11 (Yamagata lineage), non-licensed

12 ^fN is the number of participants in the safety analysis set

13 ^gGrade 2 - Injection-site pain: some interference with activity; Injection-site erythema and Injection-site swelling:
14 ≥5.1 to ≤10 cm; Fever: ≥101.2°F to ≤102.0°F; Myalgia, Headache, and Malaise: some interference with activity

15 ^hGrade 3 - Injection-site pain: Significant; prevents daily activity; Injection-site erythema and Injection-site swelling:
16 >10 cm; Fever: ≥102.1°F; Myalgia, Headache, and Malaise: Significant; prevents daily activity

17 ⁱFever measured by any route

18

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

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

1 2 group. The most commonly reported adverse events were oropharyngeal pain, rhinorrhea,
2 injection-site induration, and headache. Three SAEs were reported during the follow-up period, 2
3 (0.9%) in the TIV-1 group and 1 (0.4%) in the TIV-2 group. No deaths were reported during the
4 trial period.

5

6 **6.2 Post-Marketing Experience**

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

8

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

15

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

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

8

9 **8 USE IN SPECIFIC POPULATIONS**

10 **8.1 Pregnancy**

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

17

18 In the developmental and reproductive toxicity study, female rabbits were administered Fluzone
19 Quadrivalent or control saline (each 0.5 mL/dose) by intramuscular injection 24 and 10 days
20 before insemination, and on Days 6, 12, and 27 of gestation. The administration of Fluzone
21 Quadrivalent did not result in systemic maternal toxicity (no adverse clinical signs and no change
22 in body weight or food consumption). In addition, no adverse effects on pregnancy, parturition,

1 lactation, or embryo-fetal or pre-weaning development were observed. There were no vaccine-
2 related fetal malformations or other evidence of teratogenesis noted in this study.

3

4 Sanofi Pasteur Inc. is maintaining a prospective pregnancy exposure registry to collect data on
5 pregnancy outcomes and newborn health status following vaccination with Fluzone Quadrivalent
6 during pregnancy. Healthcare providers are encouraged to enroll women who receive Fluzone
7 Quadrivalent during pregnancy in Sanofi Pasteur Inc.'s vaccination pregnancy registry by calling
8 1-800-822-2463.

9

10 **8.3 Nursing Mothers**

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

14

15 **8.4 Pediatric Use**

16 Safety and effectiveness of Fluzone Quadrivalent in children below the age of 6 months have not
17 been established.

18

19 **8.5 Geriatric Use**

20 Safety and immunogenicity of Fluzone Quadrivalent were evaluated in adults 65 years of age and
21 older. [See *Clinical Studies* (14.5).] Antibody responses to Fluzone Quadrivalent are lower in
22 persons ≥ 65 years of age than in younger adults.

1

2 **11 DESCRIPTION**

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

14

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

16

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

18

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

21

22 Fluzone Quadrivalent is standardized according to United States Public Health Service

23 requirements and is formulated to contain HA of each of the following four influenza strains

1 recommended for the 2018-2019 influenza season: A/Michigan/45/2015 X-275 (H1N1),
2 A/Singapore/INFIMH-16-0019/2016 IVR-186 (H3N2), B/Phuket/3073/2013 (B Yamagata
3 lineage), and B/Maryland/15/2016 BX-69A (a B/Colorado/6/2017-like virus, B Victoria lineage).
4 The amounts of HA and other ingredients per dose of vaccine are listed in [Table 6](#). The single-
5 dose, pre-filled syringe (0.25 mL and 0.5 mL) and the single-dose vial (0.5 mL) are manufactured
6 and formulated without thimerosal or any other preservative. The 5 mL multi-dose vial
7 presentation contains thimerosal, a mercury derivative, added as a preservative. Each 0.5 mL dose
8 from the multi-dose vial contains 25 mcg mercury. Each 0.25 mL dose from the multi-dose vial
9 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
Active Substance: Split influenza virus, inactivated strains^a:	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
Other:		
Sodium phosphate-buffered isotonic sodium chloride solution	QS ^b to appropriate volume	QS ^b to appropriate volume
Formaldehyde	≤50 mcg	≤100 mcg
Octylphenol ethoxylate	≤125 mcg	≤250 mcg
Preservative		
Single-dose presentations	-	-
Multi-dose presentation (thimerosal)	12.5 mcg mercury	25 mcg mercury

2 ^aper United States Public Health Service (USPHS) requirement

3 ^bQuantity 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 influenza 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 **13 NON-CLINICAL TOXICOLOGY**

16 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

17 Fluzone Quadrivalent has not been evaluated for carcinogenic or mutagenic potential. A
18 reproductive study of female rabbits vaccinated with Fluzone Quadrivalent was performed and
19 revealed no evidence of impaired female fertility [see *Pregnancy* (8.1)].

20

21 **14 CLINICAL STUDIES**

22 The effectiveness of Fluzone Quadrivalent was demonstrated based on clinical endpoint efficacy
23 data for Fluzone (trivalent influenza vaccine) and on an evaluation of serum HI antibody

1 responses to Fluzone Quadrivalent. Fluzone Quadrivalent, an inactivated influenza vaccine that
2 contains the hemagglutinins of two influenza A subtype viruses and two influenza type B viruses,
3 is manufactured according to the same process as Fluzone.

4

5 **14.1 Efficacy of Fluzone (Trivalent Influenza Vaccine) in Children 6 through 24 Months** 6 **of Age**

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

1 **Table 7: Estimated Efficacy of Fluzone (Trivalent Influenza Vaccine) Against Culture-**
 2 **Confirmed Influenza in Children Aged 6 through 24 Months during the 1999-2000 and**
 3 **2000-2001 Influenza Seasons – Intent-to-Treat Analysis Set^a**

Year	Fluzone ^b				Placebo ^c				Fluzone vs. Placebo	
	n ^d	N ^e	Rate (n/N) ^f	(95% CI)	n ^d	N ^e	Rate (n/N) ^f	(95% CI)	Relative Risk (95% CI)	Percent Relative Reduction ^g (95% CI)
Year 1 ^h (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 ⁱ (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)

4 ^aThe intent-to-treat analysis set includes all enrolled participants who were randomly assigned to receive Fluzone or
 5 placebo and vaccinated

6 ^bFluzone: 1999-2000 formulation containing A/Beijing/262/95 (H1N1), A/Sydney/15/97 (H3N2), and
 7 B/Yamanashi/166/98 (Yamagata lineage) and 2000-2001 formulation containing A/New Caledonia/20/99 (H1N1),
 8 A/Panama/2007/99 (H3N2), and B/Yamanashi/166/98 (Yamagata lineage)

9 ^cPlacebo: 0.4% NaCl

10 ^dn is the number of participants with culture-confirmed influenza for the given year of study as listed in the first
 11 column

12 ^eN is the number of participants randomly assigned to receive Fluzone or placebo for the given year of study as listed
 13 in the column headers (intent-to-treat analysis set)

14 ^fRate (%) = (n/N) * 100

15 ^gRelative reduction in vaccine efficacy was defined as (1-relative risk) x 100

16 ^hIncludes all culture confirmed influenza cases throughout the study duration for Year 1 (12 months of follow-up)

17 ⁱIncludes all culture-confirmed influenza cases throughout the study duration for Year 2 (6 months of follow-up)

18 14.2 Efficacy of Fluzone (Trivalent Influenza Vaccine) in Adults

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

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

6 **Table 8: Estimated Efficacy of Fluzone (Trivalent Influenza Vaccine) Against Influenza in**
7 **Adults Aged 18 through 49 Years during the 2007-2008 Influenza Season – Intent-to-Treat**
8 **Analysis Set^{ab}**

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

9 ^aNCT00538512

10 ^bThe intent-to-treat analysis set includes all enrolled participants who were randomly assigned to receive Fluzone or
11 placebo and vaccinated

12 ^cFluzone: 2007-2008 formulation containing A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and
13 B/Malaysia/2506/2004 (Victoria lineage)

14 ^dPlacebo: 0.9% NaCl

15 ^eN is the number of participants randomly assigned to receive Fluzone or placebo

16 ^fn is the number of participants satisfying the criteria listed in the first column

17 ^gRate (%) = (n/N) * 100

18 ^hRelative reduction in vaccine efficacy was defined as (1 - relative risk) x 100

19

1 **14.3 Immunogenicity of Fluzone Quadrivalent in Children 6 Months through 8 Years of**
2 **Age**

3 In Study 1 (NCT01240746) [see [Adverse Reactions \(6.1\)](#)], 1419 children 6 months through 35
4 months of age and 2101 children 3 years through 8 years of age were included in the per-protocol
5 immunogenicity analysis. Participants received one or two 0.25 mL doses or one or two 0.5 mL
6 doses, respectively of Fluzone Quadrivalent, TIV-1, or TIV-2. For participants who received two
7 doses, the doses were administered approximately 4 weeks apart. The distribution of demographic
8 characteristics was similar to that of the safety analysis [see [Adverse Reactions \(6.1\)](#)].

9
10 HI antibody geometric mean titers (GMTs) and seroconversion rates 28 days following
11 vaccination with Fluzone Quadrivalent were non-inferior to those following each TIV for all four
12 strains, based on pre-specified criteria (see [Table 9](#) and [Table 10](#)).

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

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

- 1 ^aNCT01240746
 2 ^bPer-protocol analysis set included all persons who had no study protocol deviations
 3 ^cFluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008
 4 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)
 5 ^dN is the number of participants in the per-protocol analysis set
 6 ^ePooled TIV group includes participants vaccinated with either TIV-1 or TIV-2
 7 ^fNon-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio of GMTs (Fluzone
 8 Quadrivalent divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >0.66
 9 ^g2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and
 10 B/Brisbane/60/2008 (Victoria lineage), licensed
 11 ^hInvestigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006
 12 (Yamagata lineage), non-licensed
 13 ⁱTIV-2 did not contain B/Brisbane/60/2008
 14 ^jTIV-1 did not contain B/Florida/04/2006

15 **Table 10: Study 1^a: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain**
 16 **by Seroconversion Rates at 28 Days Post-Vaccination, Persons 6 Months Through 8 Years**
 17 **of Age (Per-protocol Analysis Set)^b**

Antigen Strain	Fluzone Quadrivalent ^c N ^d =2339	Pooled TIV ^e N ^d =1181		Difference of Seroconversion Rates (95% CI) ^g
	Seroconversion ^f (%)			
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 ^c N ^d =2339	TIV-1 ^h (B Victoria) N ^d =582	TIV-2 ⁱ (B Yamagata) N ^d =599	Difference of Seroconversion Rates (95% CI) ^g
	Seroconversion ^f (%)			
B/Brisbane/60/2008 (B Victoria)	71.8	61.1	(20.0) ^j	10.7 (6.4; 15.1)
B/Florida/04/2006 (B Yamagata)	66.1	(17.9) ^k	64.0	2.0 (-2.2; 6.4)

- 18 ^aNCT01240746
 19 ^bPer-protocol analysis set included all persons who had no study protocol deviations
 20 ^cFluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008
 21 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)
 22 ^dN is the number of participants in the per-protocol analysis set
 23 ^ePooled TIV group includes participants vaccinated with either TIV-1 or TIV-2
 24 ^fSeroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination titer ≥1:40 or a minimum 4-
 25 fold increase for participants with pre-vaccination titer ≥1:10
 26 ^gNon-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference in seroconversion rates
 27 (Fluzone Quadrivalent minus pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >-
 28 10%

1 ^h2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and
2 B/Brisbane/60/2008 (Victoria lineage), licensed
3 ⁱInvestigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006
4 (Yamagata lineage), non-licensed
5 ^jTIV-2 did not contain B/Brisbane/60/2008
6 ^kTIV-1 did not contain B/Florida/04/2006
7

8 Non-inferiority immunogenicity criteria based on HI antibody GMTs and seroconversion rates
9 were also met when age subgroups (6 months to <36 months and 3 years to <9 years) were
10 examined. In addition, HI antibody GMTs and seroconversion rates following Fluzone
11 Quadrivalent were higher than those following TIV for the B strain not contained in each
12 respective TIV based on pre-specified criteria (the lower limit of the 2-sided 95% CI of the ratio
13 of the GMTs [Fluzone Quadrivalent divided by TIV] >1.5 for each B strain in Fluzone
14 Quadrivalent compared with the corresponding B strain not contained in each TIV and the lower
15 limit of the two 2-sided 95% CI of the difference of the seroconversion rates [Fluzone
16 Quadrivalent minus TIV] >10% for each B strain in Fluzone Quadrivalent compared with the
17 corresponding B strain not contained in each TIV).

18

19 **14.4 Immunogenicity of Fluzone Quadrivalent in Adults ≥18 Years of Age**

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

24

25 HI antibody GMTs 21 days following vaccination with Fluzone Quadrivalent were non-inferior to
26 those following each TIV for all four strains, based on pre-specified criteria (see [Table 11](#)).

1 **Table 11: Study 2^a: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain**
 2 **by HI Antibody GMTs at 21 Days Post-Vaccination, Adults 18 Years of Age and Older (Per-**
 3 **protocol Analysis Set)^b**

Antigen Strain	Fluzone Quadrivalent ^c N ^d =190	Pooled TIV ^e N ^d =375		GMT Ratio (95% CI) ^f
	GMT	GMT		
A (H1N1)	161	151		1.06 (0.87; 1.31)
A (H3N2)	304	339		0.90 (0.70; 1.15)
	Fluzone Quadrivalent ^c N ^d =190	TIV-1 ^g (B Victoria) N ^d =187	TIV-2 ^h (B Yamagata) N ^d =188	GMT Ratio (95% CI) ^f
	GMT	GMT	GMT	
B/Brisbane/60/2008 (B Victoria)	101	114	(44.0) ⁱ	0.89 (0.70; 1.12)
B/Florida/04/2006 (B Yamagata)	155	(78.1) ^j	135	1.15 (0.93; 1.42)

4 ^aNCT00988143

5 ^bPer-protocol analysis set included all persons who had no study protocol deviations

6 ^cFluzone Quadrivalent containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), B/Brisbane/60/2008
 7 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)

8 ^dN is the number of participants in the per-protocol analysis set

9 ^ePooled TIV group includes participants vaccinated with either TIV-1 or TIV-2

10 ^fNon-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio of GMTs (Fluzone
 11 Quadrivalent divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >2/3

12 ^g2009-2010 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and
 13 B/Brisbane/60/2008 (Victoria lineage), licensed

14 ^h2008-2009 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and
 15 B/Florida/04/2006 (Yamagata lineage), licensed

16 ⁱTIV-2 did not contain B/Brisbane/60/2008

17 ^jTIV-1 did not contain B/Florida/04/2006

18

19 **14.5 Immunogenicity of Fluzone Quadrivalent in Geriatric Adults ≥65 Years of Age**

20 In Study 3 (NCT01218646) [see [Adverse Reactions \(6.1\)](#)], 660 adults 65 years of age and older

21 were included in the per-protocol immunogenicity analysis. The distribution of demographic

22 characteristics was similar to that of the safety analysis [see [Adverse Reactions \(6.1\)](#)].

23

1 HI antibody GMTs 21 days following vaccination with Fluzone Quadrivalent were non-inferior to
 2 those following TIV for all four strains, based on pre-specified criteria (see [Table 12](#)).

3 Seroconversion rates 21 days following Fluzone Quadrivalent were non-inferior to those
 4 following TIV for H3N2, B/Brisbane, and B/Florida, but not for H1N1 (see [Table 13](#)). The HI
 5 antibody GMT following Fluzone Quadrivalent was higher than that following TIV-1 for
 6 B/Florida but not higher than that following TIV-2 for B/Brisbane, based on pre-specified criteria
 7 (the lower limit of the 2-sided 95% CI of the ratio of the GMTs [Fluzone Quadrivalent divided by
 8 TIV] >1.5 for each B strain in Fluzone Quadrivalent compared with the corresponding B strain
 9 not contained in each TIV). Seroconversion rates following Fluzone Quadrivalent were higher
 10 than those following TIV for the B strain not contained in each respective TIV, based on pre-
 11 specified criteria (the lower limit of the two 2-sided 95% CI of the difference of the
 12 seroconversion rates [Fluzone Quadrivalent minus TIV] >10% for each B strain in Fluzone
 13 Quadrivalent compared with the corresponding B strain not contained in each TIV).

14 **Table 12: Study 3^a: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain**
 15 **by HI Antibody GMTs at 21 Days Post-Vaccination, Adults 65 Years of Age and Older (Per-**
 16 **protocol Analysis Set)^b**

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

B/Florida/04/2006 (B Yamagata)	61.1	(28.5) ^j	54.8	1.11 (0.90; 1.37)
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^aNCT01218646

^bPer-protocol analysis set included all persons who had no study protocol deviations

^cFluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)

^dN is the number of participants in the per-protocol analysis set

^ePooled TIV group includes participants vaccinated with either TIV-1 or TIV-2

^fNon-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio of GMTs (Fluzone Quadrivalent divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >0.66

^g2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

^hInvestigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed

ⁱTIV-2 did not contain B/Brisbane/60/2008

^jTIV-1 did not contain B/Florida/04/2006

Table 13: Study 3^a: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by Seroconversion Rates at 21 Days Post-Vaccination, Adults 65 Years of Age and Older (Per-protocol Analysis Set)^b

Antigen Strain	Fluzone Quadrivalent ^c N ^d =220	Pooled TIV ^e N ^d =440		Difference of Seroconversion Rate (95% CI) ^f
	Seroconversion ^g (%)			
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 ^c N ^d =220	TIV-1 ^h (B Victoria) N ^d =219	TIV-2 ⁱ (B Yamagata) N ^d =221	Difference of Seroconversion Rate (95% CI) ^f
	Seroconversion ^g (%)			
B/Brisbane/60/2008 (B Victoria)	28.64	18.72	(8.60) ^j	9.91 (1.96; 17.70)
B/Florida/04/2006 (B Yamagata)	33.18	(9.13) ^k	31.22	1.96 (-6.73; 10.60)

^aNCT01218646

^bPer-protocol analysis set included all persons who had no study protocol deviations

^cFluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)

^dN is the number of participants in the per-protocol analysis set

^ePooled TIV group includes participants vaccinated with either TIV-1 or TIV-2

- 1 ^fNon-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference in seroconversion rates
2 (Fluzone Quadrivalent minus pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >-
3 10%
- 4 ^gSeroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination titer ≥1:40 or a minimum
5 4-fold increase for participants with pre-vaccination titer ≥1:10
- 6 ^h2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and
7 B/Brisbane/60/2008 (Victoria lineage), licensed
- 8 ⁱInvestigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006
9 (Yamagata lineage), non-licensed
- 10 ^jTIV-2 did not contain B/Brisbane/60/2008
- 11 ^kTIV-1 did not contain B/Florida/04/2006
- 12
- 13

1 **15 REFERENCES**

2

3 1 Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barré syndrome and the 1992-1993
4 and 1993-1994 influenza vaccines. *N Engl J Med* 1998;339:1797-802.

5 2 Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza
6 vaccination. *Virus Res* 2004;103:133-138.

7 3 Hobson D, Curry RL, Beare AS, Ward-Gardner A. The role of serum haemagglutination-
8 inhibiting antibody in protection against challenge infection with influenza A2 and B
9 viruses. *J Hyg Camb* 1972;70:767-777.

10 .

11

12

13

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

2 **16.1 How Supplied**

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

4 (NDC 49281-518-00) (not made with natural rubber latex). Supplied as package of 10

5 (NDC 49281-518-25).

6

7 Single-dose, prefilled syringe (clear plunger rod), without needle, 0.5 mL (NDC 49281-418-88)

8 (not made with natural rubber latex). Supplied as package of 10 (NDC 49281-418-50).

9

10 Single-dose vial, 0.5 mL (NDC 49281-418-58) (not made with natural rubber latex). Supplied as
11 package of 10 (NDC 49281-418-10).

12

13 Multi-dose vial, 5 mL (NDC 49281-629-78) (not made with natural rubber latex). Supplied as
14 package of 1 (NDC 49281-629-15). 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).

19

20

1 Fluzone is a registered trademark of Sanofi Pasteur Inc.

2

3 Manufactured by:

4 **Sanofi Pasteur Inc.**

5 Swiftwater PA 18370 USA

7214,7221,7225

6

7

SANOFI PASTEUR 

8

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.
24

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

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6 **Sanofi Pasteur Inc.**

7 Swiftwater, PA 18370 USA

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