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
2016-2017 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	-

[a]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 (≥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 (≥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 (≥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 (≥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 XXXX

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION:

1 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.

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

2 DOSAGE AND ADMINISTRATION

- **For intramuscular use only**

2.1 Dose and Schedule

The dose and schedule for Fluzone Quadrivalent are presented in Table 1.

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	-

[a]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

2.2 Administration

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

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 Use a separate sterile needle and syringe for each dose withdrawn from the multi-dose vial.

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

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

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

3 DOSAGE FORMS AND STRENGTHS

Fluzone Quadrivalent is a suspension for injection.

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

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

5.3 Altered Immunocompetence

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

5.4 Limitations of Vaccine Effectiveness

Vaccination with Fluzone Quadrivalent may not protect all recipients.

6 ADVERSE REACTIONS

In children 6 months through 35 months of age, the most common (≥10%) injection-site reactions were pain (57%)[a] or tenderness (54%)[b], erythema (37%), and swelling (22%); the most common solicited systemic adverse reactions were irritability (54%)[b], abnormal crying (41%)[b], malaise (38%)[a], drowsiness (38%)[b], appetite loss (32%)[b], myalgia (27%)[a], vomiting (15%)[b], and fever (14%). In children 3 years through 8 years of age, the most common (≥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%). In adults 18 years and older, the most common (≥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

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

6.1 Clinical Trials Experience

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

Children 6 Months Through 8 Years of Age

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

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

Table 2: Study 1[a]: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 7 Days After Vaccination in Children 6 Months Through 35 Months of Age (Safety 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									
- Pain[i]	57.0	10.2	1.0	52.3	11.5	0.8	50.3	5.4	2.7
- Tenderness[j]	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
- Malaise[i]	38.1	14.5	4.6	35.2	14.8	4.7	32.4	12.8	6.8
- Myalgia[i]	26.7	6.6	1.9	26.6	9.4	1.6	25.0	6.8	2.7
- Headache[i]	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

- 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

[a]NCT01240746

[b]The safety analysis set includes all persons who received at least one dose of study vaccine

[c] Fluzone 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)

[d]2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

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

[f]N is the number of participants in the safety analysis set

[g]Grade 2 - Injection-site pain: sufficiently discomforting to interfere with normal behavior or activities; Injection-site tenderness: cries and protests when injection-site is touched; Injection-site erythema, Injection-site swelling: ≥2.5 cm 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 months); Malaise, Myalgia, and Headache: some interference with activity; Irritability: requiring increased attention; Crying abnormal: 1 to 3 hours; Drowsiness: not interested in surroundings or did not wake up for a feed/meal; Appetite loss: missed 1 or 2 feeds/meals completely; Vomiting: 2 to 5 episodes per 24 hours

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

[i]Assessed in children 24 months through 35 months of age

[j]Assessed in children 6 months through 23 months of age

[k]Fever measured by any route

Table 3: Study 1[a]: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 7 Days After Vaccination in Children 3 Years Through 8 Years of Age (Safety 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									
- 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

[a]NCT01240746

[b]The safety analysis set includes all persons who received at least one dose of study vaccine

[c] Fluzone 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)

[d]2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

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

[f]N is the number of participants in the safety analysis set

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

[h]Grade 3 - Injection-site pain: incapacitating, unable to perform usual activities; Injection-site erythema, Injection-site swelling: ≥5 cm; Fever: ≥102.1°F; Headache, Malaise, and Myalgia: Significant; prevents daily activity

[i]Fever measured by any route

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

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

Adults

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

Table 4: Study 2[a]: Percentage of Solicited Injection-site and Systemic Adverse Reactions 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

[a]NCT00988143

[b]The safety analysis set includes all persons who received study vaccine

[c]Fluzone 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)

[d]2009-2010 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

[e]2008-2009 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Florida/04/2006 (Yamagata lineage), licensed

[f]N is the number of participants in the safety analysis set

[g]Grade 2 - Injection-site pain: Some interference with activity; Injection-site erythema, Injection-site swelling, Injection-site induration, and Injection-site ecchymosis: ≥5.1 to ≤10 cm; Fever: ≥101.2°F to ≤102.0°F; Myalgia, Headache, Malaise, and Shivering: some interference with activity

[h]Grade 3 - Injection-site pain: Significant; prevents daily activity; Injection-site erythema, Injection-site swelling, Injection-site induration, and Injection-site ecchymosis: >10 cm; Fever: ≥102.1°F; Myalgia, Headache, Malaise, and Shivering: Significant; prevents daily activity

[i]Fever measured by any route

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

Geriatric Adults

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

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

Table 5: Study 3[a]: Percentage of Solicited Injection-site and Systemic Adverse Reactions 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

[a]NCT01218646

[b]The safety analysis set includes all persons who received study vaccine

[c] Fluzone 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)

[d]2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

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

[f]N is the number of participants in the safety analysis set

[g]Grade 2 - Injection-site pain: some interference with activity; Injection-site erythema and Injection-site swelling: ≥5.1 to ≤10 cm; Fever: ≥101.2°F to ≤102.0°F; Myalgia, Headache, and Malaise: some interference with activity

[h]Grade 3 - Injection-site pain: Significant; prevents daily activity; Injection-site erythema and Injection-site swelling: >10 cm; Fever: ≥102.1°F; Myalgia, Headache, and Malaise: Significant; prevents daily activity

[i]Fever measured by any route

Unsolicited non-serious adverse events were reported in 28 (12.4%) recipients in the Fluzone Quadrivalent group, 22 (9.8%) recipients in the TIV-1 group, and 22 (9.8%) recipients in the TIV-

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

6.2 Post-Marketing Experience

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

11 DESCRIPTION

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

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

Antibiotics are not used in the manufacture of Fluzone Quadrivalent.

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

Fluzone Quadrivalent is standardized according to United States Public Health Service requirements and is formulated to contain HA of each of the following four influenza strains recommended for the 2016-2017influenza season: A/California/07/2009 X-179A (H1N1),

A/Hong Kong/4801/2014 X-263B(H3N2), B/Phuket/3073/2013 (B Yamagata lineage), and B/Brisbane/60/2008 (B Victoria lineage). The amounts of HA and other ingredients per dose of vaccine are listed in Table 6. The single-dose, pre-filled syringe (0.25 mL and 0.5 mL) and the single-dose vial (0.5 mL) are manufactured and formulated without thimerosal or any other preservative. The 5 mL multi-dose vial presentation contains thimerosal, a mercury derivative, added as a preservative. Each 0.5 mL dose from the multi-dose vial contains 25 mcg mercury. Each 0.25 mL dose from the multi-dose vial contains 12.5 mcg mercury.

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

[a]per United States Public Health Service (USPHS) requirement
[b]Quantity Sufficient
"-" Indicates information is not applicable

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

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

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

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

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

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

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

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

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

	Fluzone[b]				Placebo[c]				Fluzone vs. Placebo	
Year	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)

[a]The intent-to-treat analysis set includes all enrolled participants who were randomly assigned to receive Fluzone or placebo and vaccinated
[b]Fluzone: 1999-2000 formulation containing A/Beijing/262/95 (H1N1), A/Sydney/15/97 (H3N2), and B/Yamanashi/166/98 (Yamagata lineage) and 2000-2001 formulation containing A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), and B/Yamanashi/166/98 (Yamagata lineage)
[c]Placebo: 0.4% NaCl
[d]n is the number of participants with culture-confirmed influenza for the given year of study as listed in the first column
[e]N is the number of participants randomly assigned to receive Fluzone or placebo for the given year of study as listed in the column headers (intent-to-treat analysis set)
[f]Rate (%) = (n/N) * 100
[g]Relative reduction in vaccine efficacy was defined as (1-relative risk) x 100
[h]Includes all culture confirmed influenza cases throughout the study duration for Year 1 (12 months of follow-up)
[i]Includes all culture-confirmed influenza cases throughout the study duration for Year 2 (6 months of follow-up)

14.2 Efficacy of Fluzone (Trivalent Influenza Vaccine) in Adults

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

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

Table 8: Estimated Efficacy of Fluzone (Trivalent Influenza Vaccine) Against Influenza in Adults Aged 18 through 49 Years during the 2007-2008 Influenza Season – Intent-to-Treat 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)

[a]NCT00538512
[b]The intent-to-treat analysis set includes all enrolled participants who were randomly assigned to receive Fluzone or placebo and vaccinated
[c]Fluzone: 2007-2008 formulation containing A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004 (Victoria lineage)
[d]Placebo: 0.9% NaCl
[e]N is the number of participants randomly assigned to receive Fluzone or placebo
[f]n is the number of participants satisfying the criteria listed in the first column
[g]Rate (%) = (n/N) * 100
[h]Relative reduction in vaccine efficacy was defined as (1 - relative risk) x 100

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

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

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

Table 9: Study 1[a]: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by HI Antibody GMTs at 28 Days Post-Vaccination, Persons 6 Months Through 8 Years of 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)

[a]NCT01240746

[b]Per-protocol analysis set included all persons who had no study protocol deviations

[c]Fluzone 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)

[d]N is the number of participants in the per-protocol analysis set

[e]Pooled TIV group includes participants vaccinated with either TIV-1 or TIV-2

[f]Non-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

[g]2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

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

[i]TIV-2 did not contain B/Brisbane/60/2008

[j]TIV-1 did not contain B/Florida/04/2006

Table 10: Study 1[a]: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by Seroconversion Rates at 28 Days Post-Vaccination, Persons 6 Months Through 8 Years 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)

[a]NCT01240746

[b]Per-protocol analysis set included all persons who had no study protocol deviations

[c]Fluzone 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)

[d]N is the number of participants in the per-protocol analysis set

[e]Pooled TIV group includes participants vaccinated with either TIV-1 or TIV-2

[f]Seroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination titer ≥1:40 or a minimum 4-fold increase for participants with pre-vaccination titer ≥1:10

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

[h]2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

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

[j]TIV-2 did not contain B/Brisbane/60/2008

[k]TIV-1 did not contain B/Florida/04/2006

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

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

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

HI antibody GMTs 21 days following vaccination with Fluzone Quadrivalent were non-inferior to those following each TIV for all four strains, based on pre-specified criteria (see Table11).

Table 11: Study 2[a]: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by HI Antibody GMTs at 21 Days Post-Vaccination, Adults 18 Years of Age and Older (Per-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)

[a]NCT00988143

[b]Per-protocol analysis set included all persons who had no study protocol deviations

[c]Fluzone Quadrivalent containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)

[d]N is the number of participants in the per-protocol analysis set

[e]Pooled TIV group includes participants vaccinated with either TIV-1 or TIV-2

[f]Non-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 >2/3

[g]2009-2010 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

[h]2008-2009 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Florida/04/2006 (Yamagata lineage), licensed

[i]TIV-2 did not contain B/Brisbane/60/2008

[j]TIV-1 did not contain B/Florida/04/2006

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

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

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

Table 12: Study 3[a]: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by HI Antibody GMTs 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		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)

[a]NCT01218646
[b]Per-protocol analysis set included all persons who had no study protocol deviations
[c]Fluzone 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)
[d]N is the number of participants in the per-protocol analysis set
[e]Pooled TIV group includes participants vaccinated with either TIV-1 or TIV-2
[f]Non-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
[g]2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed
[h]Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed
[i]TIV-2 did not contain B/Brisbane/60/2008
[j]TIV-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)

[a]NCT01218646
[b]Per-protocol analysis set included all persons who had no study protocol deviations

[c]Fluzone 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)

[d]N is the number of participants in the per-protocol analysis set

[e]Pooled TIV group includes participants vaccinated with either TIV-1 or TIV-2

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

[g]Seroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination titer ≥1:40 or a minimum 4-fold increase for participants with pre-vaccination titer ≥1:10

[h]2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

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

[j]TIV-2 did not contain B/Brisbane/60/2008

[k]TIV-1 did not contain B/Florida/04/2006

15 REFERENCES

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Single-dose, prefilled syringe (yellow plunger rod), without needle, 0.25 mL (NDC 49281-516-00) (not made with natural rubber latex). Supplied as package of 10 (NDC 49281- 516-25).

Single-dose, prefilled syringe (purple plunger rod), without needle, 0.5 mL (NDC 49281-416-88) (not made with natural rubber latex). Supplied as package of 10 (NDC 49281-416-50

Single-dose vial, 0.5 mL (NDC 49281-416-58) (not made with natural rubber latex). Supplied as package of 10 (NDC 49281-416-10).

Multi-dose vial, 5 mL (NDC 49281-625-78) (not made with natural rubber latex). Supplied as package of 1 (NDC 49281- 625-15). A maximum of ten doses can be withdrawn from the multi-dose vial.

16.2 Storage and Handling

Store all Fluzone Quadrivalent presentations refrigerated at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Discard if vaccine has been frozen.

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

17 PATIENT COUNSELING INFORMATION

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

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

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

Fluzone is a registered trademark of Sanofi Pasteur Inc.

Manufactured by:

Sanofi Pasteur Inc.

Swiftwater PA 18370 USA 6872, 6879, 6883

Patient Information Sheet
Fluzone® Quadrivalent
Influenza Vaccine

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

What is Fluzone Quadrivalent vaccine?

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

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

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

Who should not get Fluzone Quadrivalent vaccine?

You should not get Fluzone Quadrivalent vaccine if you:

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

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

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

How is the Fluzone Quadrivalent vaccine given?

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

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

What are the possible side effects of Fluzone Quadrivalent vaccine?

The most common side effects of Fluzone Quadrivalent vaccine are:

- pain, redness, and swelling where you got the shot
- muscle aches
- tiredness
- headache
- fever

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

Call your healthcare provider for advice about any side effects that concern you. You may report side effects to the Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967 or *http://vaers.hhs.gov*. Sanofi Pasteur Inc. is collecting information on pregnancy outcomes and the health of newborns following vaccination with Fluzone Quadrivalent during pregnancy. Women who receive Fluzone Quadrivalent during pregnancy are encouraged to contact Sanofi Pasteur Inc. directly or have their healthcare provider contact Sanofi Pasteur Inc. at 1-800-822-2463.

What are the ingredients in Fluzone Quadrivalent vaccine?

Fluzone Quadrivalent vaccine contains 4 killed flu virus strains.

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

Manufactured by:

Sanofi Pasteur Inc.

Swiftwater, PA 18370 USA