HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Fluzone (Influenza Vaccine)
Suspension for Intramuscular Injection
2014-2015 Formula
Initial US Approval 1980

----------**INDICATIONS AND USAGE**----------

Fluzone is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B virus contained in the vaccine. (1)
Fluzone is approved for use in persons 6 months of age and older. (1)

----------**DOSAGE AND ADMINISTRATION**----------

- **For intramuscular use only**

Age	Dose	Schedule
6 months through 35 months	One or two doses [a], 0.25 mL each	If 2 doses, administer at least 1 month apart
36 months through 8 years	One or two doses [a], 0.5 mL each	If 2 doses, administer at least 1 month 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 2 presentations:; prefilled syringe (clear plunger rod), 0.5 mL; multi-dose vial, 5 mL. (3)

----------**CONTRAINDICATIONS**----------

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

----------**WARNINGS AND PRECAUTIONS**----------

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

----------**ADVERSE REACTIONS**----------

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

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

----------**USE IN SPECIFIC POPULATIONS**----------

- Safety and effectiveness of Fluzone has not been established in pregnant women. (8.1)
- Antibody responses to Fluzone are lower in persons ≥65 years of age than in younger adults. (8.5)

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

Revised: XXXX 2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

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

Fluzone 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 are presented in Table 1.

Table 1: Dose and Schedule for Fluzone

Age	Dose	Schedule
6 months through 35 months	One or two doses[a] , 0.25 mL each	If 2 doses, administer at least 1 month apart
36 months through 8 years	One or two doses[a] , 0.5 mL each	If 2 doses, administer at least 1 month 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

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

Before administering a dose of vaccine, shake the prefilled syringe or multi-dose vial. Withdraw a single dose of vaccine 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 or subcutaneously.

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

3 DOSAGE FORMS AND STRENGTHS

Fluzone is a suspension for injection.

Fluzone is supplied in 2 presentations:

1) Prefilled syringe (clear syringe plunger rod), 0.5 mL, for persons 36 months of age and older.

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

4 CONTRAINDICATIONS

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 is a contraindication to administration of Fluzone.

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. (1) If GBS has occurred within 6 weeks following previous influenza vaccination, the decision to give Fluzone 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 the vaccine.

5.3 Altered Immunocompetence

If Fluzone 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 may not protect all recipients.

6 ADVERSE REACTIONS

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

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

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

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

[a] N is the number of vaccinated participants with available data for the events listed

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

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

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

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

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

[a] N is the number of vaccinated participants with available data for the events listed

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

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

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

"-" Indicates information was not collected

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

Adults

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

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

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

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

[a] N is the number of vaccinated participants with available data for the events listed

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

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

[d] Fever - The percentage of temperature measurements that were taken by oral or axillary routes, or not recorded were 99.6%, 0.0%, and 0.4%, respectively

Within 28 days and 6 months post-vaccination, a serious adverse event was reported by 5 (0.4%) and 20 (1.4%) Fluzone recipients, respectively. No serious adverse event was considered to be caused by vaccination. No deaths were reported during the 6 months post-vaccination.

Geriatric Adults

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

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

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

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

[a] N is the number of vaccinated participants with available data for the events listed

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

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

[d] Fever - The percentage of temperature measurements that were taken by oral route or not recorded were 98.6% and 1.4%, respectively

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

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

6.2 Post-Marketing Experience

The following events have been spontaneously reported during the post-approval use 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

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

11 DESCRIPTION

Fluzone (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.

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

Antibiotics are not used in the manufacture of Fluzone.

No presentation of Fluzone is made with natural rubber latex.

Fluzone is standardized according to United States Public Health Service requirements and is formulated to contain HA of each of the following three influenza strains recommended for the 2014-2015 influenza season: A/California/07/2009 X-179A (H1N1), A/Texas/50/2012 X-223A

(H3N2), and B/Massachusetts/02/2012 (B Yamagata lineage). The amounts of HA and other ingredients per dose of vaccine are listed in Table 6. The 0.5 mL single-dose, pre-filled syringe presentation is 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 Ingredients

Ingredient	Quantity (per dose)	
	Fluzone 0.25 mL Dose	**Fluzone 0.5 mL Dose**
Active Substance: Split influenza virus, inactivated strains[a]:	22.5 mcg HA total	45 mcg HA total
A (H1N1)	7.5 mcg HA	15 mcg HA
A (H3N2)	7.5 mcg HA	15 mcg HA
B	7.5 mcg HA	15 mcg HA
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	≤75 mcg	≤150 mcg
Gelatin	0.05%	0.05%
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. For example, since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. Specific levels of hemagglutination inhibition (HI) antibody titer post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza virus infection. In some human studies, antibody titers ≥1:40 have been associated with protection from influenza illness in up to 50% of participants. (2) (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 current 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 has not been evaluated for carcinogenic or mutagenic potential or for impairment of fertility.

14 CLINICAL STUDIES

14.1 Efficacy of Fluzone 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 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 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 Vaccine Against Influenza in Adults Aged 18 through 49 Years during the 2007-2008 Influenza Season – Intent-to-Treat Analysis Set[a]

Laboratory-Confirmed Symptomatic Influenza	Fluzone[b] (N=813)[d]			Placebo[c] (N=325)[d]			Fluzone vs. Placebo	
	n[e]	Rate (%)[f]	(95% CI)	n[e]	Rate (%)[f]	(95% CI)	Relative Risk (95% CI)	Percent Relative Reduction[g] (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]The intent-to-treat analysis set includes all enrolled participants who were randomly assigned to receive Fluzone or placebo and vaccinated[b]Fluzone: 2007-2008 formulation containing A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004 (Victoria lineage)
[c]Placebo: 0.9% NaCl
[d]N is the number of participants randomly assigned to receive Fluzone or placebo
[e]n is the number of participants satisfying the criteria listed in the first column
[f]Rate (%) = (n/N) * 100
[g]Relative reduction in vaccine efficacy was defined as (1 - relative risk) x 100

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

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

The percentage of participants who received influenza vaccination during the previous influenza season was 54.4% for the 6 months through 35 months age group and 27.5% for the 3 years through 8 years age group. Table 9 shows seroconversion rates and the percentage of participants with an HI titer ≥1:40 pre-vaccination and one month following the second dose of Fluzone.

Table 9: Percentage (%) with Pre and Post-Vaccination HI Titers ≥1:40 and Seroconversion Following the Second Vaccine Injection with Fluzone[a] in Children 6 Months Through 35 Months and 3 Years Through 8 Years of Age

Antigen	Age Group	Pre-Vaccination Titer ≥1:40 % (95% CI)	Post-Vaccination[b] Titer ≥1:40 % (95% CI)	Seroconversion[c] % (95% CI)
		N=68 (6 to 35 months); N=120 (3 through 8 years)		
A (H1N1)	6 through 35 months	11.8 (5.2; 21.9)	92.6 (83.7; 97.6)	88.2 (78.1; 94.8)
	3 through 8 years	40.0 (31.2; 49.3)	99.2 (95.4; 100.0)	78.3 (69.9; 85.3)
A (H3N2)	6 through 35 months	29.4 (19.0; 41.7)	100.0 (94.7; 100.0)	91.2 (81.8; 96.7)
	3 through 8 years	80.0 (71.7; 86.7)	100.0 (97.0; 100.0)	61.7 (52.4; 70.4)
B	6 through 35 months	1.5 (0.0; 7.9)	20.6 (11.7; 32.1)	20.6 (11.7; 32.1)
	3 through 8 years	3.3 (0.9; 8.3)	58.3 (49.0; 67.3)	53.3 (44.0; 62.5)

[a] Children received two doses of Fluzone administered 26 to 30 days apart, irrespective of previous influenza vaccination history

[b] Post-vaccination HI titers drawn at 28 days post-dose

[c] Seroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination (28 days post-dose 2) titer ≥1:40 or a minimum 4-fold increase for participants with pre-vaccination titer ≥1:10

14.4 Immunogenicity of Fluzone in Adults

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

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

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

[a] Post-vaccination HI titers drawn at 28 days post-dose

[b] Seroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination (28 days post-dose) titer ≥1:40 or a minimum 4-fold increase for participants with pre-vaccination titer ≥1:10

[c] N is the number of vaccinated participants with available data for the immunologic endpoint listed

14.5 Immunogenicity of Fluzone in Geriatric Adults

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

Table 11: Percentage (%) with Pre and Post-Vaccination HI Titers ≥1:40 and Seroconversion in Adult Fluzone Recipients 65 Years of Age and Older

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

[a] Post-vaccination HI titers drawn at 28 days post-dose

[b] Seroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination (28 days post-dose) titer ≥1:40 or a minimum 4-fold increase for participants with pre-vaccination titer ≥1:10

[c] N is the number of vaccinated participants with available data for the immunologic endpoint listed

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, without needle, 0.5 mL (NDC 49281-014-88) (not made with natural rubber latex). Supplied as package of 10 (NDC 49281-014-50).

Multi-dose vial, 5 mL (NDC 49281-394-78) (not made with natural rubber latex). Supplied as package of one (NDC 49281-394-15). A maximum of ten doses can be withdrawn from the multi-dose vial.

16.2 Storage and Handling

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

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

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

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

- Annual influenza vaccination is recommended.
- Instruct vaccine recipients and guardians to report adverse reactions to their healthcare provider and/or to the Vaccine Adverse Event Reporting System (VAERS).

Fluzone is a registered trademark of Sanofi Pasteur Inc.

Manufactured by:

Sanofi Pasteur Inc.

Swiftwater PA 18370 USA 6551, 6552, 6553

SANOFI PASTEUR

Patient Information Sheet

Fluzone®

Influenza Vaccine

Please read this information sheet before getting Fluzone 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 vaccine?

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

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

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

Who should not get Fluzone vaccine?

You should not get Fluzone 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 vaccine given?

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

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

What are the possible side effects of Fluzone vaccine?

The most common side effects of Fluzone vaccine are:

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

These are not all of the possible side effects of Fluzone 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*.

What are the ingredients in Fluzone vaccine?

Fluzone vaccine contains 3 killed flu virus strains.

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

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Swiftwater, PA 18370 USA