HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Fluzone High-Dose (Influenza Virus Vaccine)
Suspension for Intramuscular Injection
2013-2014 Formula
Initial US Approval: 2009

----------**INDICATIONS AND USAGE**----------
Fluzone High-Dose is indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. (1)
Fluzone High-Dose is approved for use in persons 65 years of age and older. (1)

Approval of Fluzone High-Dose is based on superior immune response relative to Fluzone. Data demonstrating a decrease in influenza disease after vaccination with Fluzone High-Dose are not available.

----------**DOSAGE AND ADMINISTRATION**----------
- **For intramuscular use only**

A single 0.5 mL dose for intramuscular injection in adults 65 years and older. (2.1)

----------**DOSAGE FORMS AND STRENGTHS**----------
Suspension for injection in prefilled syringe (gray plunger rod), 0.5 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 High-Dose should be based on careful consideration of the potential benefits and risks. (5.1)

----------**ADVERSE REACTIONS**----------
- In adults ≥65 years of age, the most common injection-site reaction was pain (>30%); the most common solicited systemic adverse events were headache, myalgia, erythema 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 High-Dose has not been established in pregnant women. (8.1)

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

Revised: April 2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

Fluzone® High-Dose is an inactivated influenza virus vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

Fluzone High-Dose is approved for use in persons 65 years of age and older.

Approval of Fluzone High-Dose is based on superior immune response relative to Fluzone. Data demonstrating a decrease in influenza disease after vaccination with Fluzone High-Dose relative to Fluzone are not available.

2 DOSAGE AND ADMINISTRATION

- **For intramuscular use only**

2.1 Dose and Schedule

Fluzone High-Dose should be administered as a single 0.5 mL injection by the intramuscular route in adults 65 years and older.

2.2 Administration

Inspect Fluzone High-Dose syringes 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.

The preferred site for intramuscular injection is the deltoid muscle. 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 High-Dose vaccine should not be combined through reconstitution or mixed with any other vaccine.

3 DOSAGE FORMS AND STRENGTHS

Fluzone High-Dose is a suspension for injection.

Fluzone High-Dose is supplied in prefilled syringes (gray syringe plunger rod), 0.5 mL, for adults 65 years 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 High-Dose.

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 of previous influenza vaccination, the decision to give Fluzone High-Dose 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 High-Dose 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 High-Dose 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 trials of a vaccine cannot be directly compared to rates in the clinical trial of another vaccine, and may not reflect the rates observed in practice.

Adults 65 years of age and older were randomized to receive either Fluzone High-Dose or Fluzone (year 2006-2007 formulation) in a multi-center, double-blind trial conducted in the US. The safety analysis set included 2573 Fluzone High-Dose recipients and 1260 Fluzone recipients.

Table 1 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. Solicited injection-site reactions and systemic adverse events were more frequent after vaccination with Fluzone High-Dose compared to Fluzone.

Table 1: Frequency of Solicited Injection-Site Reactions and Systemic Adverse Events Within 7 Days After Vaccination with Fluzone High-Dose or Fluzone, Adults 65 Years of Age and Older

	Fluzone High-Dose (N[a]=2569-2572) Percentage			Fluzone (N[a]=1258-1260) Percentage		
	Any	**Moderate[b]**	**Severe[c]**	**Any**	**Moderate[b]**	**Severe[c]**
Injection-Site Pain	35.6	3.7	0.3	24.3	1.7	0.2
Injection-Site Erythema	14.9	1.9	1.8	10.8	0.8	0.6
Injection-Site Swelling	8.9	1.6	1.5	5.8	1.3	0.6
Myalgia	21.4	4.2	1.6	18.3	3.2	0.2
Malaise	18.0	4.7	1.6	14.0	3.7	0.6
Headache	16.8	3.1	1.1	14.4	2.5	0.3
Fever[d]	3.6	1.1	0.0	2.3	0.2	0.1

[a]N is the number of vaccinated subjects 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 - Any Fever indicates ≥99.5°F. The percentage of temperature measurements that were taken by oral route or not recorded were 97.9% and 2.1%, respectively for Fluzone High-Dose; and 98.6% and 1.4%, respectively for Fluzone

Within 6 months post-vaccination, 156 (6.1%) Fluzone High-Dose recipients and 93 (7.4%) Fluzone recipients experienced a serious adverse event. No deaths were reported within 28 days post-vaccination. A total of 23 deaths were reported during the period Day 29–180 post-

vaccination: 16 (0.6%) among Fluzone High-Dose recipients and 7 (0.6%) among Fluzone recipients. 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 or Fluzone High-Dose. 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 or Fluzone High-Dose.

Events Reported During Post-Approval Use of 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

Other Events Reported During Post-Approval Use of Fluzone High-Dose.

- *Gastrointestinal Disorders:* Nausea, diarrhea
- *General Disorders and Administration Site Conditions:* Chills

7 DRUG INTERACTIONS

Data evaluating the concomitant administration of Fluzone High-Dose 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 High-Dose. It is also not known whether Fluzone High-Dose can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Fluzone High-Dose should be given to a pregnant woman only if clearly needed.

8.4 Pediatric Use

Safety and effectiveness of Fluzone High-Dose in persons <65 years of age have not been established.

8.5 Geriatric Use

Safety and immunogenicity of Fluzone High-Dose have been evaluated in adults 65 years of age and older. [See *Adverse Reactions* (6.1) and *Clinical Studies* (14)]

11 DESCRIPTION

Fluzone High-Dose (Influenza Virus Vaccine) for intramuscular injection is an inactivated influenza virus 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 High-Dose process uses an additional concentration factor after the ultrafiltration step in order to obtain a higher hemagglutinin (HA) antigen concentration.

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

Neither antibiotics nor preservative are used in the manufacture of Fluzone High-Dose.

The Fluzone High-Dose prefilled syringe presentation is not made with natural rubber latex.

Fluzone High-Dose 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 2013-2014 influenza season: A/California/07/2009 NYMC X-179A (H1N1), A/Texas/50/2012 X-223A (H3N2) and B/Massachusetts/02/2012. The amounts of HA and other ingredients per dose of vaccine are listed in Table 2.

Table 2: Fluzone High-Dose Ingredients

	Quantity (per dose)
Ingredient	**Fluzone High-Dose 0.5 mL Dose**
Active Substance: Split influenza virus, inactivated strains[a]:	180 mcg HA total
A (H1N1)	60 mcg HA
A (H3N2)	60 mcg HA
B	60 mcg HA
Other:	
Sodium phosphate-buffered isotonic sodium chloride solution	QS[b] to appropriate volume
Formaldehyde	≤100 mcg
Octylphenol Ethoxylate	≤250 mcg
Gelatin	None
Preservative	None

[a]per United States Public Health Service (USPHS) requirement

[b]Quantity Sufficient

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 subjects. (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 in the upcoming winter.

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 High-Dose has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

14 CLINICAL STUDIES

14.1 Immunogenicity of Fluzone High-Dose in Geriatric Adults

Adults 65 years of age and older were randomized to receive either Fluzone High-Dose or Fluzone (year 2006-2007 formulation) in a multi-center, double-blind trial conducted in the US. For immunogenicity analyses, 2576 participants were randomized to Fluzone High-Dose and 1275 participants were randomized to Fluzone. Females accounted for 51.3% of participants in the Fluzone High-Dose group and 54.7% of participants in the Fluzone group. In both groups, the mean age was 72.9 years (ranged from 65 through 97 years in the Fluzone High-Dose group and 65 through 94 years in the Fluzone group); 35% of participants in the Fluzone High-Dose group and 36% of participants in the Fluzone group were 75 years of age or older. Most participants in the Fluzone High-Dose and Fluzone groups, respectively, were Caucasian (91.7% and 92.9%), followed by Hispanic (4.8% and 3.7%), and Black (2.7% and 2.7%).

The primary endpoints of the study were HI GMTs and seroconversion rates 28 days after vaccination. Pre-specified statistical superiority criteria required that the lower limit (LL) of the 2-sided 95% CI of the GMT ratio (Fluzone High-Dose/Fluzone) be greater than 1.50 for at least two of the strains, and if one strain failed, non-inferiority of that strain must be demonstrated (LL>0.67), and that the lower limit of the 2-sided 95% CI of the seroconversion rate difference

(Fluzone High-Dose minus Fluzone) be greater than 10% for at least two of the strains, and if one strain failed, non-inferiority of that strain must be demonstrated (LL>-10%). As shown in Table 3, statistically superior HI GMTs and seroconversion rates after vaccination with Fluzone High-Dose compared to Fluzone were demonstrated for influenza A subtypes, A (H1N1) and A (H3N2), but not for influenza type B. For strain B, non-inferiority of Fluzone High-Dose compared to Fluzone was demonstrated for both the HI GMTs and seroconversion rates. There are no data demonstrating clinically relevant prevention of culture-confirmed influenza or its complications after vaccination with Fluzone High-Dose compared to Fluzone in individuals 65 years of age and older.

Table 3: Post-Vaccination HI Antibody GMTs and Seroconversion Rates and Analyses of Superiority of Fluzone High-Dose Relative to Fluzone, Adults 65 Years of Age and Older

Influenza Strain	GMT		GMT Ratio	Seroconversion %[a]		Difference	Met Both Pre-defined Superiority Criteria[c]
	Fluzone High-Dose N[b]=2542-2544	Fluzone N[b]=1252	Fluzone High-Dose over Fluzone (95% CI)	Fluzone High-Dose N[b]=2529-2531	Fluzone N[b]=1248-1249	Fluzone High-Dose minus Fluzone (95% CI)	
A (H1N1)	115.8	67.3	1.7 (1.6; 1.8)	48.6	23.1	25.4 (22.4; 28.5)	Yes
A (H3N2)	608.9	332.5	1.8 (1.7; 2.0)	69.1	50.7	18.4 (15.1; 21.7)	Yes
B	69.1	52.3	1.3 (1.2; 1.4)	41.8	29.9	11.8 (8.6; 15.0)	No

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

[b]N is the number of vaccinated subjects with available data for the immunologic endpoint listed

[c]Predefined superiority criterion for seroconversion: the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (Fluzone High-Dose minus Fluzone) is >10%. Predefined superiority criterion for the GMT ratio: the lower limit of the 95% CI for the GMT ratio (Fluzone High-Dose divided by Fluzone) is >1.5

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 49281-393-88) (not made with natural rubber latex). Supplied as package of 10 (NDC 49281-393-65).

16.2 Storage and Handling

Store Fluzone High-Dose 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 patient or caregiver that Fluzone High-Dose contains killed viruses and cannot cause influenza.
- Fluzone High-Dose 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 caregivers to report adverse reactions to their healthcare provider and/or to Vaccine Adverse Event Reporting System (VAERS).

Manufactured by:

Sanofi Pasteur Inc.

Swiftwater PA 18370 USA 6393

Patient Information Sheet
Fluzone® High-Dose
Influenza Virus Vaccine

Please read this information sheet before getting Fluzone® High-Dose 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 High-Dose vaccine?

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

Fluzone High-Dose vaccine is for people 65 years of age and older.

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

Who should not get Fluzone High-Dose vaccine?

You should not get Fluzone High-Dose 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 65 years of age.

Tell your healthcare provider if you 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 Fluzone High-Dose vaccine given?

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

What are the possible side effects of Fluzone High-Dose vaccine?

The most common side effects of Fluzone High-Dose vaccine are:

- soreness, pain and swelling, redness where you got the shot
- muscle ache
- tiredness
- headache

These are not all of the possible side effects of Fluzone High-Dose 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 High-Dose vaccine?

Fluzone High-Dose vaccine contains 3 killed flu virus strains.

Inactive ingredients include formaldehyde and octylphenol ethoxylate.

Manufactured by: Sanofi Pasteur Inc.

Swiftwater, PA 18370 USA

SANOFI PASTEUR