

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Fluzone (Influenza Virus Vaccine) or Fluzone High-Dose (Influenza Virus Vaccine) safely and effectively. See full prescribing information for Fluzone and Fluzone High-Dose.

**Fluzone (Influenza Virus Vaccine)**  
**Fluzone High-Dose (Influenza Virus Vaccine)**  
**Suspension for Intramuscular Injection**  
**2010-2011 Formula**

**Initial US Approval (Fluzone): 1980**

### RECENT MAJOR CHANGES

**Indications and Usage (1)** [12/2009]  
**Dosage and Administration (2)** [12/2009]  
**Warnings and Precautions (5)** [07/2010]

### INDICATIONS AND USAGE

**Fluzone** is an inactivated influenza virus vaccine indicated for active immunization of persons 6 months of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. (1)

**Fluzone High-Dose** is an inactivated influenza virus vaccine indicated for active immunization of persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. (1)  
This indication is based on the immune response elicited by Fluzone High-Dose; there have been no controlled clinical studies demonstrating a decrease in influenza disease after vaccination with Fluzone High-Dose.

### DOSAGE AND ADMINISTRATION

#### Fluzone

Vaccination Status and Age	Dose/Route	Schedule
Previously unvaccinated or incompletely vaccinated with an influenza vaccine (ie, no previous dose or vaccinated for the first time in the last influenza season and received only 1 dose)		
6 through 35 months	0.25 mL/Intramuscular	2 doses at least 1 month apart
36 months through 8 years	0.5 mL/Intramuscular	2 doses at least 1 month apart
Previously vaccinated with an influenza vaccine (ie, received two doses last influenza season or one or more doses at any time before last season)		
6 through 35 months	0.25 mL/Intramuscular	1 dose
36 months through 8 years	0.5 mL/Intramuscular	1 dose
<b>Any vaccination status</b>		
9 years and older	0.5 mL/Intramuscular	1 dose

#### Fluzone High-Dose - Adults 65 years of age and older

Any vaccination status	Dose/Route	Schedule
65 years and older	0.5 mL/Intramuscular	1 dose

### DOSAGE FORMS AND STRENGTHS

#### Fluzone

Sterile suspension for intramuscular injection supplied in four presentations:

- Prefilled syringe, 0.25 mL, pediatric dose, distinguished by a pink syringe plunger rod (3)

- Prefilled syringe, 0.5 mL, distinguished by a clear syringe plunger rod (3)
- Single-dose vial, 0.5 mL (3)
- Multi-dose vial, 5 mL, for 6 months of age and older, contains thimerosal as a preservative. (3, 11)

Each 0.25 mL dose is formulated to contain a total of 22.5 mcg (7.5 mcg of each strain) of influenza virus hemagglutinin and each 0.5 mL dose is formulated to contain a total of 45 mcg (15 mcg of each strain) of influenza virus hemagglutinin. (3, 11)

#### Fluzone High-Dose

Sterile suspension for intramuscular injection supplied in prefilled syringes, 0.5 mL, distinguished by a gray syringe plunger rod. (3)  
Each 0.5 mL dose is formulated to contain a total of 180 mcg (60 mcg of each strain) of influenza virus hemagglutinin. (3, 11)

### CONTRAINDICATIONS

Hypersensitivity to egg proteins or life-threatening reactions after previous administration of any influenza vaccine. (4, 11)

### WARNINGS AND PRECAUTIONS

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

The tip caps of the prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals. (5.3)

### ADVERSE REACTIONS

#### Fluzone

- Most common ( $\geq 10\%$ ) injection-site reactions were injection site tenderness, pain, swelling and arm stiffness. (6)
- Most common ( $\geq 10\%$ ) systemic adverse events were headache and myalgia. (6)

#### Fluzone High-Dose

- Most common ( $\geq 10\%$ ) injection-site reactions were injection site pain and erythema. (6)
- Most common ( $\geq 10\%$ ) systemic adverse events were myalgia, malaise, and headache. (6)

**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](http://www.vaers.hhs.gov).**

### USE IN SPECIFIC POPULATIONS

#### Fluzone

Safety and effectiveness of Fluzone have not been established in pregnant women, nursing mothers, or children <6 months of age. (8.1, 8.3, 8.4)

#### Fluzone High-Dose

Safety and effectiveness of Fluzone High-Dose have not been established in pregnant women, nursing mothers, or individuals <65 years of age. (8.1, 8.3, 8.4)

See **17 PATIENT COUNSELING INFORMATION**.

Revised: July 2010

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## FULL PRESCRIBING INFORMATION:

### 1. INDICATIONS AND USAGE

Fluzone® is an inactivated influenza virus vaccine indicated for active immunization of persons 6 months of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. [See *Dosage Forms and Strengths (3)*.]

Fluzone High-Dose is an inactivated influenza virus vaccine indicated for active immunization of persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. [See *Dosage Forms and Strengths (3)*.]

This indication is based on the immune response elicited by Fluzone High-Dose; there have been no controlled clinical studies demonstrating a decrease in influenza disease after vaccination with Fluzone High-Dose.

### 2. DOSAGE AND ADMINISTRATION

#### 2.1. Dosage and Schedule

Basic dosing information for Fluzone and Fluzone High-Dose, and their respective age indications, are presented in [Table 1](#) and [Table 2](#).

**Table 1: Fluzone**

<b>Vaccination Status and Age</b>	<b>Dose/Route</b>	<b>Schedule</b>
Previously unvaccinated or incompletely vaccinated with an influenza vaccine (ie, no previous dose or vaccinated for the first time in the last influenza season and received only 1 dose)		
6 through 35 months	0.25 mL/Intramuscular	2 doses at least 1 month apart
36 months through 8 years	0.5 mL/Intramuscular	2 doses at least 1 month apart
Previously vaccinated with an influenza vaccine (ie, received two doses last influenza season or one or more doses at any time before last season)		
6 through 35 months	0.25 mL/Intramuscular	1 dose
36 months through 8 years	0.5 mL/Intramuscular	1 dose
<b>Any vaccination status</b>		
9 years and older	0.5 mL/Intramuscular	1 dose

**Table 2: Fluzone High-Dose**

<b>Any vaccination status</b>	<b>Dose/Route</b>	<b>Schedule</b>
65 years and older	0.5 mL/Intramuscular	1 dose

## 2.2. Administration

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

Shake the syringe or single-dose vial before administering the vaccine and shake the multi-dose vial each time before withdrawing a dose of vaccine.

The vaccine should not be injected into the gluteal region or into areas where there may be a major nerve trunk. For needle length, refer to the Advisory Committee on Immunization Practices (ACIP) recommendations. (1)

If Fluzone or Fluzone High-Dose are to be given at the same time as another injectable vaccine(s), the vaccine(s) should always be administered at separate injection sites.

### **Pediatrics**

The preferred sites for intramuscular injections are the anterolateral aspect of the thigh in infants (6-12 months of age) or the deltoid muscle of the upper arm in children (12 months through 17 years of age).

### **Adults 18 years of age and older**

Fluzone should be administered as a single intramuscular dose preferably in the deltoid muscle.

### **Adults 65 years of age and older**

Fluzone High-Dose should be administered as a single intramuscular dose preferably in the deltoid muscle.

## **3. DOSAGE FORMS AND STRENGTHS**

Sterile suspension for intramuscular injection is supplied in 5 presentations: 4 presentations of Fluzone (including 2 dosage strengths in pre-filled syringes) and 1 presentation of Fluzone High-

Dose in a pre-filled syringe. Dosage strengths of the 3 different pre-filled syringes are distinguished by different colored plungers.

### **Fluzone**

Sterile suspension for intramuscular injection supplied in 4 presentations:

- 1) Prefilled syringe, 0.25 mL, pediatric dose, for 6 through 35 months of age, distinguished by a pink syringe plunger rod.
- 2) Prefilled syringe, 0.5 mL, for 36 months of age and older, distinguished by a clear syringe plunger rod.
- 3) Single-dose vial, 0.5 mL, for 36 months of age and older.
- 4) Multi-dose vial, 5 mL, for 6 months of age and older, contains thimerosal as a preservative.

[See *Description (11)*.]

Each 0.25 mL dose of Fluzone contains influenza split virus antigens that are formulated to contain a total of 22.5 mcg of influenza virus hemagglutinin, 7.5 mcg each from the 3 influenza virus strains in the vaccine. Each 0.5 mL dose of Fluzone contains influenza split virus antigens formulated to contain a total of 45 mcg of influenza virus hemagglutinin, 15 mcg each from the 3 influenza virus strains in the vaccine. [See *Description (11)*.]

### **Fluzone High-Dose**

Sterile suspension for intramuscular injection supplied in prefilled syringes, 0.5 mL, for adults 65 years of age and older, distinguished by a gray syringe plunger rod.

Each 0.5 mL dose of Fluzone High-Dose contains influenza split virus antigens that are formulated to contain a total of 180 mcg of influenza virus hemagglutinin, 60 mcg each from the 3 influenza virus strains in the vaccine. [See *Description (11)*.]

## 4. CONTRAINDICATIONS

Do not administer Fluzone or Fluzone High-Dose to anyone with a known hypersensitivity to egg proteins or any component of the vaccine listed in [Table 5](#) or life-threatening reactions after previous administration of any influenza vaccine. [See *Warnings and Precautions (5)* and *Description (11)*].

## 5. WARNINGS AND PRECAUTIONS

### 5.1. Guillain-Barré Syndrome

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

### 5.2. Altered Immunocompetence

If either Fluzone or Fluzone High-Dose are administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

### 5.3. Preventing and Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. The tip caps of the Fluzone and Fluzone High-

Dose prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

#### **5.4. Limitations of Vaccine Effectiveness**

Vaccination with either Fluzone or Fluzone High-Dose may not protect all recipients.

## **6. ADVERSE REACTIONS**

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.

### **6.1. Clinical Trial Experience**

#### **Fluzone – Pediatric Studies**

The 2003-2004 formulation of Fluzone was studied in 19 children 6 to 23 months of age and in 12 children 24 to 36 months of age, given in 2 doses one month apart. Local reactions and systemic events were solicited for 3 days after each dose. Most local and systemic reactions were mild. The proportions of local and systemic reactions in children were similar to the proportions in adults.

#### **Fluzone - Adults**

In two observational studies, 120 adults 18-60 years of age received a single dose of either the Year 1999-2000 or the Year 2000-2001 formulations of Fluzone. Solicited injection site and systemic reactogenicity data were collected for three days following vaccination. The most common (occurring in >10% of the study participants in either of the two studies) solicited events were injection site pain, tenderness, swelling, arm stiffness, headache, and myalgia. Most of the

solicited injection site and systemic adverse events were reported as mild and resolved within 3 days.

### **Fluzone High-Dose**

A total of 3,876 individuals 65 years of age and older were randomized to receive either Fluzone High-Dose or Fluzone in a phase 3, multi-center, active-controlled, double-blind trial conducted in the US. The safety analysis set included 2,573 Fluzone High-Dose recipients and 1,260 Fluzone recipients.

[Table 3](#) summarizes solicited injection site reactions and systemic adverse events collected within 7 days post vaccination via diary cards. Onset was usually within the first 3 days after vaccination and majority of the reactions resolved within 3 days.



**Table 3: Frequency of Solicited Injection Site and Systemic Adverse Events within 7 Days**

**Post-Vaccination**

	<b>Fluzone High-Dose (N<sup>a</sup>= 2573) Percent</b>	<b>Fluzone (N<sup>a</sup>= 1260) Percent</b>
<b>Injection site reactions</b>		
Pain	35.6	24.3
Erythema	14.9	10.8
Swelling	8.9	5.8
<b>Systemic adverse events</b>		
Myalgia	21.4	18.3
Malaise	18.0	14.0
Headache	16.8	14.4
Fever	3.6	2.3

<sup>a</sup>N is the number of subjects in the Safety Analysis Set.

Solicited injection site reactions and systemic adverse events were more frequent after vaccination with Fluzone High-Dose compared to standard Fluzone in adults 65 years of age and older.

Table 4 summarizes the severity of solicited adverse events that occurred during the first week after vaccination (2):

**Table 4: Frequency and Severity of Solicited Injection Site and Systemic Adverse Events within 7 Days Post-Vaccination**

	<b>Fluzone High-Dose (N<sup>a</sup>= 2573) Percent</b>	<b>Fluzone (N<sup>a</sup>= 1260) Percent</b>
<b>Injection Site Pain</b>		
Mild	31.5	22.5
Moderate	3.7	1.7
Severe	0.3	0.2
<b>Injection Site Erythema</b>		
Mild	11.3	9.4
Moderate	1.9	0.8
Severe	1.8	0.6
<b>Injection Site Swelling</b>		
Mild	5.8	3.9
Moderate	1.6	1.3
Severe	1.5	0.6
<b>Myalgia</b>		
Mild	15.6	14.8
Moderate	4.2	3.2
Severe	1.6	0.2
<b>Malaise</b>		
Mild	11.7	9.8
Moderate	4.7	3.7
Severe	1.6	0.6
<b>Headache</b>		
Mild	12.6	11.7
Moderate	3.1	2.5
Severe	1.1	0.3
<b>Fever</b>		
Mild	2.5	2.0
Moderate	1.1	0.2
Severe	0.0	0.1

<sup>a</sup>N is the number of subjects in the Safety Analysis Set

The rates of Serious Adverse Events (SAEs) were comparable between the two groups; 156/2573 (6.1%) of Fluzone High-Dose recipients and 93/1260 (7.4%) of Fluzone recipients experienced SAEs.

No deaths were reported within 28 days post-vaccination. A total of 23 deaths were reported during the follow-up period of the study; 16/2573 (0.6%) among Fluzone High-Dose recipients and 7/1260 (0.6%) among Fluzone recipients. The majority of these participants had a medical history of cardiac, hepatic, neoplastic, renal, and/or respiratory diseases.

## 6.2. Post-Marketing Experience

The following events have been 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.

- *Blood and Lymphatic System Disorders:* Thrombocytopenia, lymphadenopathy
- *Immune System Disorders:* Anaphylaxis, other allergic/hypersensitivity reactions (including urticaria, angioedema)
- *Nervous System Disorders:* Guillain-Barré syndrome (GBS), 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 Disorders:* Dyspnea, pharyngitis, rhinitis
- *Skin and Subcutaneous Tissue Disorders:* Stevens-Johnson syndrome
- *General Disorders and Administration Site Conditions:* Pruritus, asthenia/fatigue, pain in extremities, chest pain

### **6.3. Other Adverse Events Associated with Influenza Vaccines**

Anaphylaxis has been reported after administration of Fluzone and other influenza vaccines.

Although Fluzone and Fluzone High-Dose contain only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have egg allergy.

Allergic reactions include anaphylaxis, angioedema, hives, and asthma. [See [Contraindications \(4\)](#).]

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear. If influenza vaccine does pose a risk, it is probably slightly more than 1 additional case/1 million persons vaccinated.

## **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**

#### **Fluzone**

Safety and effectiveness of Fluzone in children below the age of 6 months have not been established. The immune response and safety of Fluzone was evaluated in 31 children between the ages of 6-36 months. [See *Clinical Studies (14)*.]

#### **Fluzone High-Dose**

Safety and effectiveness of Fluzone High-Dose in children have not been established.

### **8.5. Geriatric Use**

#### **Fluzone**

In two observational studies of Fluzone in 118 adults 18-60 years of age and 123 adults greater than 60 years of age, geometric mean antibody titers post vaccination were lower in the older adults [See *Clinical Studies (14)*.]

## Fluzone High-Dose

Fluzone High-Dose is indicated for adults 65 years of age and older. [See *Indications and Usage (1) and Clinical Studies (14)*.]

## 11. DESCRIPTION

Fluzone (Influenza Virus Vaccine) and Fluzone High-Dose (Influenza Virus Vaccine) are inactivated influenza virus vaccines, for intramuscular use, 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 and Fluzone High-Dose are clear and slightly opalescent in color. Antibiotics are not used in the manufacture of Fluzone or Fluzone High-Dose. The tip caps of the Fluzone and Fluzone High-Dose prefilled syringes may contain natural rubber latex. Vial presentations of Fluzone do not contain latex.

Fluzone and Fluzone High-Dose are standardized according to United States Public Health Service (USPHS) requirements and are formulated to contain the amount of HA per 0.5 mL dose

(see Table 5) for each of the three influenza strains recommended for the 2010-2011 Northern Hemisphere influenza season: A/California/07/2009 X-179A (H1N1), A/Victoria/210/2009 X-187 (an A/Perth/16/2009 – like virus) (H3N2), and B/Brisbane/60/2008. (1)

**Table 5: Fluzone and Fluzone High-Dose Presentations**

Component	Quantity (per dose)		
	Fluzone Pediatric (0.25mL Prefilled Syringe)	Fluzone	Fluzone High-Dose (0.5 mL Prefilled Syringe)
<b>Active Substance: Split influenza virus, inactivated strains <sup>a</sup>:</b>	22.5 mcg HA total	45 mcg HA total	180 mcg HA total
A (H1N1)	7.5 mcg HA	15 mcg HA	60 mcg HA
A (H3N2)	7.5 mcg HA	15 mcg HA	60 mcg HA
B	7.5 mcg HA	15 mcg HA	60 mcg HA
<b>Other:</b>			
Sodium phosphate-buffered isotonic sodium chloride solution	QS <sup>b</sup> to appropriate volume	QS <sup>b</sup> to appropriate volume	QS <sup>b</sup> to appropriate volume
Formaldehyde	≤50 mcg	≤100 mcg	≤100 mcg
Octylphenol Ethoxylate	≤50 mcg	≤100 mcg	≤250 mcg
Gelatin	0.05%	0.05%	None
Preservative			
Single Dose Presentations	None	None	None
Multi-Dose Presentation (Thimerosal)	N/A	25 mcg mercury	N/A

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

<sup>b</sup>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  $\geq 1:40$  have been associated with protection from influenza illness in up to 50% of subjects. (3) (4)

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 (ie, typically two type A and one type B), 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. (1)

## **13. NON-CLINICAL TOXICOLOGY**

### **13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility**



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

## **14. CLINICAL STUDIES**

### **14.1. Immunogenicity of Fluzone in Children**

In a study of 2 doses one month apart of Fluzone (2003-2004) in 31 healthy children 6-36 months of age, 77%, 77%, and 48% achieved post vaccination HI titers of 1:40 or greater for the A/H1, A/H3, and B strains, respectively.

### **14.2. Immunogenicity of Fluzone in Adults**

In two observational studies of the immunogenicity of Fluzone, younger adults (median age: 38, range: 19 through 59 years of age) and older adults (median age: 72, range: 61 through 86 years of age) were evaluated. The following results were obtained after vaccination with a single-dose of either the year 1999-2000 (cohort 1999) or 2000-2001 (cohort 2000) formulation of Fluzone. (See [Table 6.](#))

**Table 6: Percentage (%) Achieving an HI Titer  $\geq 1:40$  and 4-Fold Increase in Younger and Older Adults**

Antigen			Titer $\geq 1:40$ Percent	4-Fold Increase Percent
A (H3N2)	Cohort 1999	Younger Adults (N = 60)	72	46
		Older Adults (N = 61)	70	42
	Cohort 2000	Younger Adults (N = 58)	79	45
		Older Adults (N = 62)	68	44
A (H1N1)	Cohort 1999	Younger Adults (N = 60)	49	34
		Older Adults (N = 61)	38	27
	Cohort 2000	Younger Adults (N = 58)	54	52
		Older Adults (N = 62)	23	39
B	Cohort 1999	Younger Adults (N = 60)	38	30
		Older Adults (N = 61)	10	10
	Cohort 2000	Younger Adults (N = 58)	38	29
		Older Adults (N = 62)	11	5

N = Number of participants

### 14.3. Immunogenicity of Fluzone High-Dose in Adults 65 Years of Age and Older

A total of 3,876 individuals 65 years of age and older were randomized to receive either Fluzone High-Dose or Fluzone in a phase 3, multi-center, randomized, active-controlled, double blind trial conducted in the US. Of those, 3,851 (2,576 randomized to Fluzone High-Dose and 1,275

randomized to Fluzone) were included in the immunogenicity analysis according to the vaccine they were randomized to receive. (2)

**Table 7: Demographic Distribution of Participants in the Phase 3 Trial**

	<b>Fluzone High-Dose (N=2576)</b>	<b>Fluzone (N=1275)</b>
<b>Gender (Percent)</b>		
Female	51.3	54.7
Male	48.7	45.3
<b>Age (Years)</b>		
Mean (min, max)	72.9 (65, 97)	72.9 (65, 94)
75 years and older (%)	35%	36%
<b>Race (Percent)</b>		
Asian	0.3	0.5
American Indian or Alaska Native	0.1	0.0
Black	2.7	2.7
Caucasian	91.7	92.9
Hispanic	4.8	3.7
Native Hawaiian or other Pacific Islander	0.1	0.1
Other	0.3	0.2

N = Number of participants in the immunogenicity analysis set

The primary endpoint of the study was HI titer 28 days after vaccination. Pre-specified statistical superiority criteria required that (1) 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 (2) the lower limit of the 2-sided 95% CI of the seroconversion rate difference [Fluzone High-Dose - 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 8](#), statistically superior HI titers after vaccination with Fluzone High-Dose compared to standard dose Fluzone were demonstrated for two of the three influenza strains. There are no data demonstrating clinically relevant prevention of culture-confirmed influenza or its complications after vaccination with Fluzone High-Dose compared to standard dose Fluzone in individuals 65 years of age and older.

**Table 8: GMT Ratios and Seroconversion Rates following Vaccination with Fluzone High-Dose**

Influenza Strain	GMT		GMT Ratio	Seroconversion % <sup>a</sup>		Difference	Met Both Pre-defined Endpoints? <sup>c</sup>
	Fluzone High-Dose N <sup>b</sup> =2576	Fluzone N <sup>b</sup> =1275	Fluzone High-Dose over Fluzone (95% CI)	Fluzone High-Dose N <sup>b</sup> =2576	Fluzone N <sup>b</sup> =1275	Fluzone High-Dose minus Fluzone (95% CI)	
<b>A (H1N1)</b>	115.8	67.3	1.7 (1.6; 1.8)	48.6	23.1	25.4 (22.4; 28.5)	Yes
<b>A (H3N2)</b>	608.9	332.5	1.8 (1.7; 2.0)	69.1	50.7	18.4 (15.1; 21.7)	Yes
<b>B</b>	69.1	52.3	1.3 (1.2; 1.4)	41.8	29.9	11.8 (8.6; 15.0)	No

Note: As defined in the study protocol:

<sup>a</sup>Seroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination (day 28) titer ≥1:40 or a 4-fold increase for those with pre-vaccination titer ≥1:10.

<sup>b</sup>N is the number of subjects in the Immunogenicity Analysis Set.

<sup>c</sup>Predefined superiority endpoint 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 endpoint for GMT ratio: the lower limit of the 95% CI for GMT ratio (Fluzone High-Dose divided by Fluzone) is >1.5.

## 15. REFERENCES

- 1 Centers for Disease Control and Prevention. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2009;58(RR-8):1-52.
- 2 NCT00391053: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
- 3 Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza vaccination. Virus Res 2004;103:133-138.
- 4 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**

The tip caps of the Fluzone and Fluzone High-Dose prefilled syringes may contain natural rubber latex. Vial presentations of Fluzone do not contain latex.

#### **Fluzone**

Prefilled syringe, without needle, 0.25 mL, package of 10 prefilled syringes per carton (may contain latex) – NDC 49281-010-25.

Prefilled syringe, without needle, 0.5 mL, package of 10 prefilled syringes per carton (may contain latex) – NDC 49281-010-50.

Single-dose vial, 0.5 mL, package of 10 vials per carton (contains no latex) – NDC 49281-010-10.

Multi-dose vial, 5 mL, one vial per carton (contains no latex). The vial contains ten 0.5 mL doses – NDC 49281-386-15.

#### **Fluzone High-Dose**

Prefilled syringe, without needle, 0.5 mL, package of 10 prefilled syringes per carton (may contain latex) – NDC 49281-387-65.

### **16.2. Storage and Handling**

Store all Fluzone and Fluzone High-Dose 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

Inform the patient or guardian that Fluzone and Fluzone High-Dose contain killed viruses and cannot cause influenza. Fluzone and Fluzone High-Dose do not prevent other respiratory infections.

- Vaccine recipients and guardians should be instructed to report any severe or unusual adverse reactions to their health care provider and/or to VAERS (see Highlights, Adverse Reactions).

Fluzone is a registered trademark of Sanofi Pasteur Inc.

Product information

as of July 2010.

Manufactured by:

**Sanofi Pasteur Inc.**

Swiftwater PA 18370 USA

5959-5961