Fluzone High-Dose 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 High-Dose is approved for use in persons 65 years of age and older. (1)

**INDICATIONS AND USAGE**

Fluzone High-Dose 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 High-Dose is approved for use in persons 65 years of age and older. (1)

- For intramuscular use only
  A single 0.5 mL dose for intramuscular injection in adults 65 years of age and older. (2.1)

**Dosage Forms and Strengths**

Suspension for injection in prefilled syringe (gray plunger rod), 0.5 mL. (3)

**DOSAGE AND ADMINISTRATION**

Suspension for injection in prefilled syringe (gray plunger rod), 0.5 mL, for adults 65 years of age and older. (2.1)

- For intramuscular use only
  A single 0.5 mL dose for intramuscular injection in adults 65 years of age and older. (2.1)

**WARNINGS AND PRECAUTIONS**

**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 following 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 myalgia, malaise, and headache (>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.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 07/2019

**FULL PRESCRIBING INFORMATION: CONTENTS**

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Dose and Schedule

2.2 Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

13 NON-CLINICAL TOXICOLOGY

14 CLINICAL STUDIES

14.1 Immunogenicity of Fluzone High-Dose in Adults 65 Years of Age and Older

14.2 Efficacy of Fluzone High-Dose in Adults 65 Years of Age and Older

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

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

**FULL PRESCRIBING INFORMATION**

**Fluzone High-Dose** 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 High-Dose is approved for use in persons 65 years of age and older. (1)

- **For intramuscular use only**
  A single 0.5 mL dose for intramuscular injection in adults 65 years of age and older. (2.1)

**Dosage Forms and Strengths**

Suspension for injection in prefilled syringe (gray plunger rod), 0.5 mL. (3)

**Dosage and Administration**

Suspension for injection in prefilled syringe (gray plunger rod), 0.5 mL, for adults 65 years of age and older. (2.1)

- **For intramuscular use only**
  A single 0.5 mL dose for intramuscular injection in adults 65 years of age and older. (2.1)

**Indications and Usage**

Fluzone High-Dose 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 High-Dose is approved for use in persons 65 years of age and older. (1)

**Preventing and Managing Allergic Reactions**

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

**Altered Immunocompetence**

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

**Limitations of Vaccine Effectiveness**

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

**Adverse Reactions**

**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.

Two clinical studies have evaluated the safety of Fluzone High-Dose.

- **Study 1 (NCT00391053, see http://clinicaltrials.gov)** was a multi-center, double-blind pre-licensure trial conducted in the US. In this study, adults 65 years of age and older were randomized to receive either Fluzone High-Dose or Fluzone (2006-2007 formulation). The study compared the safety and immunogenicity of Fluzone High-Dose to those of Fluzone. 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: Study 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**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Fluzone High-Dose (N=2569-2572)</th>
<th>Fluzone (N=1258-1260)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection-Site Pain</td>
<td>Any</td>
<td>Moderate1</td>
</tr>
<tr>
<td>Pain</td>
<td>35.6</td>
<td>3.7</td>
</tr>
</tbody>
</table>

- **Sections or subsections omitted from the full prescribing information are not listed**
Fluzone High-Dose is not approved for use in persons <65 years of age. No human or animal data are available to assess the effects of Fluzone High-Dose on the breastfed infant or on milk production/excretion.

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, immunogenicity, and efficacy 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 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 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 2019-2020 influenza season: A/Brisbane/02/2018/IVR-190 (H1N1), A/Kansas/14/2017 X-327 (H3N2), and B/Maryland15/2016 BX-69A (a B/Colorado/2017-like virus, B Victoria lineage). The amounts of HA and other ingredients per dose of vaccine are listed in Table 2.

2.5 LACTATION
Safety, immunogenicity, and efficacy 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 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 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 2019-2020 influenza season: A/Brisbane/02/2018/IVR-190 (H1N1), A/Kansas/14/2017 X-327 (H3N2), and B/Maryland15/2016 BX-69A (a B/Colorado/2017-like virus, B Victoria lineage). The amounts of HA and other ingredients per dose of vaccine are listed in Table 2.

Table 2: Fluzone High-Dose Ingredients

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (per dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Substance: Split influenza virus, inactivated strains:</td>
<td></td>
</tr>
<tr>
<td>A (H1N1)</td>
<td>180 mcg HA total</td>
</tr>
<tr>
<td>A (H3N2)</td>
<td>60 mcg HA</td>
</tr>
<tr>
<td>B</td>
<td>60 mcg HA</td>
</tr>
<tr>
<td>Other:</td>
<td></td>
</tr>
<tr>
<td>Sodium phosphate-buffered isotonic sodium chloride solution Q5 to appropriate volume</td>
<td></td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>≤100 mcg</td>
</tr>
<tr>
<td>Octylphenol ethoxylate</td>
<td>≤250 mcg</td>
</tr>
<tr>
<td>Gelatin</td>
<td>None</td>
</tr>
<tr>
<td>Preservative</td>
<td>None</td>
</tr>
</tbody>
</table>

* per United States Public Health Service (USP)S requirement
† 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 participants. [See references 3 and 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 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 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 Adults 65 Years of Age and Older
Study 1 (NCT00391053) was a multi-center, double-blind pre-licensure trial conducted in the US in which adults 65 years of age and older were randomized to receive either Fluzone High-Dose or Fluzone (2005-2007 formulation). The study compared the safety and immunogenicity of Fluzone High-Dose to those of Fluzone. 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 72.8 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 White (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 criterion 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 (H2N2), 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.

Table 3: Study 1: 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

<table>
<thead>
<tr>
<th>Influenza Strain</th>
<th>GMT</th>
<th>Difference</th>
<th>Met Both Pre-defined Superiority Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (H1N1)</td>
<td>115.8 to 67.3</td>
<td>1.7 (1.6; 1.8)</td>
<td>24.3 (22.4; 26.5)</td>
</tr>
<tr>
<td>A (H2N2)</td>
<td>608.9 to 322.5</td>
<td>1.8 (1.7; 2.0)</td>
<td>50.7 (18.4; 21.7)</td>
</tr>
<tr>
<td>B</td>
<td>69.1 to 52.3</td>
<td>1.3 (1.2; 1.4)</td>
<td>29.9 (11.8; 15.0)</td>
</tr>
</tbody>
</table>

‡ Predefined superiority criterion for seroconversion: the lower limit of the two-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%).

§ N is the number of vaccinated participants with available data for the immunologic endpoint listed.

14.2 Efficacy of Fluzone High-Dose in Adults 65 Years of Age and Older

Table 4: Study 2: Relative Efficacy Against Laboratory-Confirmed Influenza† Regardless of Similarity to the Vaccine Components, Associated with Influenza-Like Illness‡, Adults 65 Years of Age and Older (continued)

<table>
<thead>
<tr>
<th>Influenza Strain</th>
<th>Fluzone High-Dose N°=15,892 n (%)</th>
<th>Fluzone N°=15,911 n (%)</th>
<th>Relative Efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any type/subtype</td>
<td>227 (1.43)</td>
<td>300 (1.89)</td>
<td>24.2 (9.7; 36.5)⁷</td>
</tr>
<tr>
<td>Influenza A</td>
<td>190 (1.20)</td>
<td>249 (1.56)</td>
<td>23.6 (7.4; 37.1)</td>
</tr>
<tr>
<td>A (H1N1)</td>
<td>8 (0.05)</td>
<td>9 (0.06)</td>
<td>11.0 (-159.8; 70.1)</td>
</tr>
</tbody>
</table>

†Laboratory-confirmed: culture- or polymerase-chain-reaction-confirmed
‡ Occurrence of at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrent with at least one of the following systemic signs or symptoms: temperature >99.0°F, chills, tiredness, headaches or myalgia
§ N is the number of vaccinated participants in the per-protocol analysis set for efficacy assessments
¶ Fluzone High-Dose divided by Fluzone is > 1.5

15 REFERENCES


16 HOW SUPPLIED/STORAGE AND HANDLING

5.1 How Supplied

Single-dose, prefilled syringe, without needle. 0.5 mL (NDC 49281-405-88) (not made with natural rubber latex). Supplied as package of 10 (NDC 49281-405-65).

6.2 Storage and Handling

Store Fluzone High-Dose refrigerated at 2°C to 8°C (35°F 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.

Among persons aged 65 years and older, Fluzone High-Dose stimulates the immune system to produce antibodies that help protect against influenza.

Among persons aged 65 years and older, Fluzone High-Dose offers better protection against influenza as compared to Fluzone.

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).

Fluzone is a registered trademark of Sanofi Pasteur Inc.

Manufactured by:
Sanofi Pasteur Inc.
Swiftwater PA 18370 USA
7439