Sanofi Pasteur
372 Fluzone® High-Dose

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 Vaccine)
Suspension for Intramuscular Injection
2018-2019 Formula
Initial US Approval: 2009

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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)

DOSAGE AND ADMINISTRATION

• 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)

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 PATIENT COUNSELING INFORMATION and FDA – approved patient labeling.

Revised: 01 2019

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*Sections or subsections omitted from the full prescribing information are not listed.
Table 1 summarizes solicited injection-site reactions and systemic adverse events reported within 7 days after vaccination with Fluzone High-Dose or Fluzone, adults 65 years of age and older.

<table>
<thead>
<tr>
<th></th>
<th>Fluzone High-Dose (N=2569-2572)</th>
<th>Fluzone (N=1258-1260)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percentage</td>
<td>Percentage</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>Moderate</td>
</tr>
<tr>
<td>Injection-Site Pain</td>
<td>35.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Injection-Site Erythema</td>
<td>14.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Injection-Site Swelling</td>
<td>8.9</td>
<td>1.6</td>
</tr>
<tr>
<td>Malaise</td>
<td>21.4</td>
<td>4.2</td>
</tr>
<tr>
<td>Headache</td>
<td>18.0</td>
<td>4.7</td>
</tr>
<tr>
<td>Fever* (≥99.5°F)</td>
<td>3.6</td>
<td>1.1</td>
</tr>
</tbody>
</table>

* NCT00391053  
** N is the number of vaccinated participants with available data for the events listed  
% Moderate - injection-site pain: sufficiently disconcerting 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  
2 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  
3 Fever - 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 (SAE). No deaths were reported within 28 days post-vaccination. A total of 23 deaths were reported during Days 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. These data do not provide evidence for a causal relationship between deaths and vaccination with Fluzone High-Dose.

Within the study surveillance period (approximately 6 to 8 months post-vaccination), 1323 (8.3%) Fluzone High-Dose recipients and 1442 (8.0%) Fluzone recipients experienced an SAE. Within 30 days post-vaccination, 204 (1.3%) Fluzone High-Dose recipients and 200 (1.3%) Fluzone recipients experienced an SAE. The majority of these participants had one or more chronic comorbid illnesses. A total of 167 deaths were reported within 6 to 8 months post-vaccination: 83 (0.5%) among Fluzone High-Dose recipients and 84 (0.5%) among Fluzone recipients. A total of 6 deaths were reported within 30 days post-vaccination: 6 (0.4%) among Fluzone High-Dose recipients and 0 (0%) among Fluzone recipients. These data do not provide evidence for a causal relationship between deaths and vaccination with Fluzone High-Dose.

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 or Fluzone High-Dose.

- **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, vasodilation/flushing**
- **Respiratory, Thoracic and Mediastinal Disorders: Dyspnea, pharyngitis, rhinitis, cough, wheezing, throat tightness**
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
Fluzone High-Dose is not approved for use in persons <65 years of age. There are limited human data and no animal data available to establish whether there is a vaccine-associated risk with use of Fluzone High-Dose in pregnancy.

8.2 Lactation
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/secretion.

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 2018-2019 influenza season: A/Michigan/45/2015 X-275 (H1N1), A/ Singapore/INFIMH-16-0019/2016 IVR-186 (H3N2), and B/ Maryland/15/2016 BX-69A (a B/ Colorado/2007-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>Fluzone High-Dose 0.5 mL Dose</td>
<td>180 mcg HA total</td>
</tr>
<tr>
<td>Active Substance: Split influenza virus, inactivated strains:&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>A (H1N1)</td>
<td>80 mcg HA</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</td>
<td>QS&lt;sup&gt;b&lt;/sup&gt; to appropriate volume</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>

<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 ≥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 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 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 (2006-2007 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 72.9 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 26% 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 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.

### 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>Fluzone High-Dose GMT Ratio</th>
<th>Seroconversion %&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Difference</th>
<th>Met Both Pre-defined Superiority Criteria&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00391053</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A (H1N1)</td>
<td>115.8</td>
<td>67.3</td>
<td>1.7</td>
<td>48.6</td>
</tr>
<tr>
<td></td>
<td>(1.6; 1.8)</td>
<td>(95% CI)</td>
<td>(1.7; 2.0)</td>
<td></td>
</tr>
<tr>
<td>A (H3N2)</td>
<td>608.9</td>
<td>332.5</td>
<td>1.8</td>
<td>69.1</td>
</tr>
<tr>
<td></td>
<td>(1.2; 1.4)</td>
<td>(95% CI)</td>
<td>(1.3; 2.0)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>69.1</td>
<td>52.3</td>
<td>1.3</td>
<td>41.8</td>
</tr>
</tbody>
</table>

<sup>a</sup> NCT00391053

<sup>b</sup> Criteria are fulfilled when the lower limit of the 95% CI of the GMT ratio is greater than 1.50, and when the difference in GMTs for the vaccine groups is greater than 0.67 log2.
In the first year of the study, the influenza B component of the vaccine and the majority of influenza B cases were of the Victoria lineage; in the second year, the influenza B component of the vaccine and the majority of influenza B cases were of the Yamagata lineage.

A secondary endpoint of the study was the occurrence of culture-confirmed influenza caused by viral types/subtypes antigenically similar to those contained in the respective annual vaccine formulations in association with a modified CDC-defined ILI, defined as the occurrence of a temperature >99.0°F (>37.2°C) with cough or sore throat. The efficiency of Fluzone High-Dose relative to Fluzone for this endpoint was 51.1% (95% CI: 16.8; 72.0).

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
Single-dose, prefilled syringe, without needle, 0.5 mL (NDC 49281-403-88) (not made with natural rubber latex). Supplied as package of 10 (NDC 49281-403-65).

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.
- 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).

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