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

2019-2020 Formula

Initial U.S. Approval: 2009

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)

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

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)

WARNINGS AND PRECAUTIONS

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

CONTRAINDICATIONS

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

• 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

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FULL PRESCRIBING INFORMATION

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

2 DOSAGE AND ADMINISTRATION

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 of age and older.

2.2 Administration

Inspect Fluzone High-Dose 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 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

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. The 17B6 strain influenza vaccine was associated with an elevated risk of 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. (See references 1 and 2.)

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 trial(s) of a vaccine cannot be directly compared to rates in the clinical trial(s) of another vaccine.

6.2 Post-Marketing Experience

There has been a case report of Guillain-Barré syndrome (GBS) following vaccination with Fluzone High-Dose. The patient had received the vaccine 4 weeks prior to the onset of GBS symptoms.

6.3 Interactions between Fluzone High-Dose and Other Vaccines

The concurrent use of Fluzone High-Dose with other vaccines is not expected to have any significant impact on the safety or immunogenicity of Fluzone High-Dose.

7 DRUG INTERACTIONS

There are no significant drug interactions known for Fluzone High-Dose.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Fluzone High-Dose is not expected to cause harm to the fetus when administered to a pregnant woman.

8.2 Lactation

It is not known whether Fluzone High-Dose is excreted in breast milk. However, because many drugs are excreted in human milk, caution should be exercised when Fluzone High-Dose is administered to a nursing woman.

8.4 Pediatric Use

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

8.5 Geriatric Use

The safety and effectiveness of Fluzone High-Dose in persons 65 years of age and older have been established.

9 SAFETY INFORMATION

9.1 Serious Adverse Events

Serious adverse events occurring in clinical trials with Fluzone High-Dose included Guillain-Barré syndrome (GBS), myocarditis, and vasculitis.

9.2 Post-Marketing Experience

There have been reports of Guillain-Barré syndrome (GBS) following vaccination with Fluzone High-Dose.

9.3 Other Information

There have been reports of systemic adverse events following vaccination with Fluzone High-Dose.

10 QC0391053 Study

The QC0391053 study 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).

11 DESCRIPTION

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of Fluzone High-Dose is not fully understood. However, it is believed to be related to the induction of specific antibodies against the influenza virus.

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No relevant findings were observed in non-clinical studies of Fluzone High-Dose.

14 CLINICAL STUDIES

There have been two clinical studies that evaluated the safety of Fluzone High-Dose.

Study 1 (NCT00391053) 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: 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>Injection-Site Reaction</th>
<th>Fluzone High-Dose (N=2569-2572) Percentage</th>
<th>Fluzone (N=1258-1260) Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>35.6</td>
<td>24.3</td>
</tr>
<tr>
<td>Severe</td>
<td>3.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Any</td>
<td>7.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

15 REFERENCES

References are not listed in the full prescribing information.
8.1 Pregnancy

Data evaluating the concomitant administration of Fluzone High-Dose with other vaccines are not 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 a 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/02/2016 (H1N1) Subtype and Clade 1, A/Kansas/14/2017 (H3N2), and B/Maryland/12/2016 (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: Sodium phosphate-buffered isotonic sodium chloride solution</td>
<td>≤250 mcg</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>≤100 mcg</td>
</tr>
<tr>
<td>Octylphenol ethoxylate</td>
<td></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 (USPHS) 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 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 (range from 65 through 94 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 criteria were 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>GMT</th>
<th>GMT Ratio</th>
<th>Seroconversion %</th>
<th>Difference</th>
<th>Met Both Pre-defined Superiority Criteriaa</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (H1N1)</td>
<td>115.8</td>
<td>67.3</td>
<td>1.7 (1.6; 1.8)</td>
<td>24.8</td>
<td>23.1</td>
</tr>
<tr>
<td>A (H3N2)</td>
<td>608.9</td>
<td>322.5</td>
<td>1.8 (1.7; 2.0)</td>
<td>69.1</td>
<td>50.7</td>
</tr>
<tr>
<td>B</td>
<td>69.1</td>
<td>52.3</td>
<td>1.3 (1.2; 1.4)</td>
<td>41.8</td>
<td>29.9</td>
</tr>
</tbody>
</table>

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</th>
<th>Fluzone</th>
<th>Relative Efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=15,911 n=15,911</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any type/subtype</td>
<td>227 (1.43)</td>
<td>300 (1.89)</td>
<td>24.2 (9.7; 36.5)b</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 (-159.9; 70.1)</td>
</tr>
</tbody>
</table>

*Aflotoxin B1*