HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Fluzone® High-Dose Quadrivalent (Influenza Vaccine), Suspension, for intramuscular injection

2018-2019 Formula

Initial U.S. Approval: 2019

INDICATIONS AND USAGE

Fluzone High-Dose Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. (1)

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

DOSAGE AND ADMINISTRATION

For intramuscular use only

A single 0.7 mL dose for intramuscular injection in adults 65 years of age and older (2.1)

CONTRAINDICATIONS

A severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

FDA-APPROVED PATIENT LABELING

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

Revised: 11/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Fluzone High-Dose Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

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

2 DOSAGE AND ADMINISTRATION

For intramuscular use only

2.1 Dose and Schedule

Fluzone High-Dose Quadrivalent should be administered as a single 0.7 mL injection by the intramuscular route in adults 65 years of age and older.

2.2 Administration

Inspect Fluzone High-Dose Quadrivalent visually for particulate matter and/or discoloration prior to administration. If either of these conditions exists 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.

Fluzone High-Dose Quadrivalent should not be combined through reconstitution or mixed with any other vaccine.

3 DOSAGE FORMS AND STRENGTHS

Fluzone High-Dose Quadrivalent is a suspension for injection. Fluzone High-Dose Quadrivalent is supplied in prefilled syringes, 0.7 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 Quadrivalent.

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

If Guillain-Barré syndrome (GBS) has occurred within 6 weeks following any previous influenza vaccination, the decision to give Fluzone High-Dose Quadrivalent should be based on careful consideration of the potential benefits and risks. The 1976 swine 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. GBS has also been temporally associated with influenza disease. (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 Quadrivalent is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be lower than expected.

5.4 Limitations of Vaccine Effectiveness

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

6 ADVERSE REACTIONS

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6.2 Postmarketing Experience

6.3 Lab Test Abnormalities

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16.2 Storage and Handling

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VAERS at 1-800-822-7967 or https://vaers.hhs.gov.

Table 1 displays solicited adverse reactions for Fluzone High-Dose Quadrivalent compared to study groups. The safety analysis set included 1777 Fluzone High-Dose Quadrivalent recipients, 443 Fluzone High-Dose recipients, and 450 investigational dose Quadrivalent recipients, 443 Fluzone High-Dose recipients, and 450 investigational dose Quadrivalent recipients, 443 Fluzone High-Dose recipients, and 450 investigational dose Quadrivalent recipients, 443 Fluzone High-Dose recipients, and 450 investigational dose Quadrivalent recipients,
Fluzone High-Dose Quadrivalent is not approved for use in persons <65 years of age and older.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Fluzone High-Dose Quadrivalent is not approved for use in persons <65 years of age. There are limited human data on Fluzone High-Dose and no animal data available on Fluzone High-Dose Quadrivalent to establish whether there is a vaccine-associated risk with use of Fluzone High-Dose Quadrivalent in pregnancy.

8.2 Lactation
Fluzone High-Dose Quadrivalent 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 Quadrivalent on the breastfeeding infant or on milk production/excretion.

8.4 Pediatric Use
Safety and effectiveness of Fluzone High-Dose Quadrivalent in children younger than 18 years of age have not been established.

8.5 Geriatric Use
Safety, immunogenicity, and efficacy of Fluzone High-Dose Quadrivalent 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 Quadrivalent 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 Quadrivalent process uses an additional concentration factor after the ultrafiltration step in order to obtain a higher hemagglutinin (HA) antigen concentration.

For Fluzone High-Dose Quadrivalent suspension for injection is clear and slightly opalescent in color. Neither antibiotics nor preservatives are used in the manufacture of Fluzone High-Dose Quadrivalent.

Fluzone High-Dose Quadrivalent is standardized according to United States Public Health Service requirements and is formulated to contain HA of each of the following four influenza strains recommended for the 2018-2019 influenza season: A/Michigan/45/2015 (H1N1), A/Singapore/INFIMH-16-0019/2016 (H3N2), B/Phuket/3073/2013 (B/Yamagata lineage), and B/Maryland/19/2016 (B/Colorado/6/2017-like virus, B/Yamagata lineage). The amounts of HA and other ingredients per dose of vaccine are listed in Table 2.

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

<table>
<thead>
<tr>
<th></th>
<th>Fluzone High-Dose Quadrivalent (N=1761-1768)</th>
<th>Fluzone High-Dose (N=885-889)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Reactions</td>
<td>Any Grade 3</td>
<td>Any Grade 3</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>41.3 0.7</td>
<td>36.4 0.2</td>
</tr>
<tr>
<td>Injection Site Erythema</td>
<td>6.2 0.6</td>
<td>5.7 0.2</td>
</tr>
<tr>
<td>Injection Site Swelling</td>
<td>4.9 0.3</td>
<td>4.7 0.1</td>
</tr>
<tr>
<td>Injection Site Induration</td>
<td>3.7 0.2</td>
<td>3.5 0.1</td>
</tr>
<tr>
<td>Injection Site Blisters</td>
<td>1.3 0.0</td>
<td>1.1 0.0</td>
</tr>
<tr>
<td>Systemic Reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>22.7 0.9</td>
<td>18.9 0.7</td>
</tr>
<tr>
<td>Headache</td>
<td>14.4 0.6</td>
<td>13.6 0.4</td>
</tr>
<tr>
<td>Malaise</td>
<td>13.2 0.7</td>
<td>13.4 0.4</td>
</tr>
<tr>
<td>Shivering</td>
<td>5.4 0.3</td>
<td>4.7 0.3</td>
</tr>
<tr>
<td>Fever</td>
<td>0.4 0.2</td>
<td>0.9 0.2</td>
</tr>
</tbody>
</table>

%NCT03282240

N is the number of vaccinated participants with available data for the events listed.

Safety results for the Fluzone High-Dose and investigational Fluzone High-Dose containing the alternate B influenza strain recipients were pooled for the analysis.

Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Grade 3: ≥100 mm

Based on data from Fluzone High-Dose, solicited injection site reactions and systemic adverse reactions were slightly more frequent after vaccination with Fluzone High-Dose compared to a standard-dose vaccine.

Table 2: Fluzone High-Dose Quadrivalent Ingredients

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (per dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium phosphate-buffered isotonic sodium chloride solution</td>
<td>QS³ to appropriate volume</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>≤140 mcg</td>
</tr>
<tr>
<td>Octylphenol ethoxylate</td>
<td>≤350 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 (USPHS) requirement

Table 12: Fluzone High-Dose Quadrivalent 0.7 mL Dose

Active Substance: Split influenza virus, inactivated strains:

- A (H1N1)                                           240 mcg HA total
- A (H3N2)                                           60 mcg HA
- B (Victoria Lineage)                               60 mcg HA
- B (Yamagata Lineage)                               60 mcg HA

Other:

- Sodium phosphate-buffered isotonic sodium chloride solution
- Formaldehyde
- Octylphenol ethoxylate
- Gelatin
- Preservative

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Influenza illness and its complications may follow influenza infection. Global surveillance of influenza viruses identifies yearly antigenic variants. 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 U.S. during the influenza season.

Fluzone High-Dose Quadrivalent stimulates the immune system to produce antibodies that help prevent influenza disease.

13 NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Fluzone High-Dose Quadrivalent has not been evaluated for carcinogenic or mutagenic potential or for impairment of fertility.
14 CLINICAL STUDIES

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

Study 1 (NCT03282240) was a randomized, active-controlled, modified double-blind trial in adults 65 years of age and older conducted in the US. The study compared the safety and immunogenicity of Fluzone High-Dose Quadrivalent to those of Fluzone High-Dose. The objective was to demonstrate immunologic non-inferiority of Fluzone High-Dose Quadrivalent to Fluzone High-Dose, as assessed by HAI geometric mean antibody titers (GMTs) at Day 28 and seroconversion rates, to strains common to formulations of both vaccines, based on pre-specified criteria. The per-protocol (PP) analysis set included 15,892 subjects, with 7,946 and 7,946 vaccinated with Fluzone High-Dose Quadrivalent and Fluzone High-Dose, respectively. The immunogenicity results of Study 1 are summarized in Table 3 and Table 4 below. Females accounted for 58.2% of participants in the Fluzone High-Dose Quadrivalent group and 57.4% of participants in the Fluzone High-Dose group.

Fluzone High-Dose Quadrivalent was as immunogenic as Fluzone High-Dose for GMTs and seroconversion rates for the common influenza strains. Fluzone High-Dose Quadrivalent was as immunogenic as Fluzone High-Dose for GMTs and seroconversion rates for the common influenza strains. Fluzone High-Dose Quadrivalent was as immunogenic as Fluzone High-Dose for GMTs and seroconversion rates for the common influenza strains. Fluzone High-Dose Quadrivalent was as immunogenic as Fluzone High-Dose for GMTs and seroconversion rates for the common influenza strains. Fluzone High-Dose Quadrivalent was as immunogenic as Fluzone High-Dose for GMTs and seroconversion rates for the common influenza strains.

### Table 3: Study 1: Post-vaccination HAI Antibody GMTs and Analyses of Non-inferiority of Fluzone High-Dose Quadrivalent Relative to Fluzone High-Dose, Adults 65 Years of Age and Older, Per-Protocol Analysis Set

<table>
<thead>
<tr>
<th>Influenza Strain</th>
<th>GMT</th>
<th>GMTRatio</th>
<th>Met Predefined Non-Inferiority Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B1 (Victoria)</strong></td>
<td>516</td>
<td>476</td>
<td>--</td>
</tr>
<tr>
<td><strong>B2 (Yamagata)</strong></td>
<td>578</td>
<td>--</td>
<td>1.00 (0.881; 1.129)</td>
</tr>
</tbody>
</table>

### Table 4: Study 1: Seroconversion Rates and Analyses of Non-inferiority of Fluzone High-Dose Quadrivalent Relative to Fluzone High-Dose, Adults 65 Years of Age and Older, Per-Protocol Analysis Set

<table>
<thead>
<tr>
<th>Influenza Strain</th>
<th>Seroconversion Rates (Percentage)</th>
<th>Difference of Seroconversion Rates</th>
<th>Met Predefined Non-Inferiority Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B1 (Victoria)</strong></td>
<td>50.4</td>
<td>-3.7</td>
<td>-7.37 (-10.0; -4.60)</td>
</tr>
<tr>
<td><strong>B2 (Yamagata)</strong></td>
<td>49.8</td>
<td>-0.71</td>
<td>-3.42 (-5.73; -1.10)</td>
</tr>
</tbody>
</table>

### Table 4: Study 1: Seroconversion Rates and Analyses of Non-inferiority of Fluzone High-Dose Quadrivalent Relative to Fluzone High-Dose, Adults 65 Years of Age and Older, Per-Protocol Analysis Set (continued)

<table>
<thead>
<tr>
<th>Strain</th>
<th>Seroconversion Rates (Percentage)</th>
<th>Difference of Seroconversion Rates</th>
<th>Met Predefined Non-Inferiority Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B1 (Victoria)</strong></td>
<td>36.5</td>
<td>-2.41</td>
<td>-7.61 (-10.2; -4.96)</td>
</tr>
<tr>
<td><strong>B2 (Yamagata)</strong></td>
<td>46.6</td>
<td>-1.75</td>
<td>-7.04 (-9.62; -4.47)</td>
</tr>
</tbody>
</table>

NCT03282240

1Predefined noninferiority criterion for GMT ratio: the lower limit of the 95% CI of the GMT ratio (QIV-HD divided by TIV-HD) is >0.667
2Predefined noninferiority criterion for GMT ratio: the lower limit of the 95% CI of the GMT ratio (QIV-HD divided by TIV-HD) is >0.667
3Predefined noninferiority criterion for GMT ratio: the lower limit of the 95% CI of the GMT ratio (QIV-HD divided by TIV-HD) is >0.667
4Predefined noninferiority criterion for GMT ratio: the lower limit of the 95% CI of the GMT ratio (QIV-HD divided by TIV-HD) is >0.667
5Predefined noninferiority criterion for GMT ratio: the lower limit of the 95% CI of the GMT ratio (QIV-HD divided by TIV-HD) is >0.667
6Predefined noninferiority criterion for GMT ratio: the lower limit of the 95% CI of the GMT ratio (QIV-HD divided by TIV-HD) is >0.667
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8Predefined noninferiority criterion for GMT ratio: the lower limit of the 95% CI of the GMT ratio (QIV-HD divided by TIV-HD) is >0.667
9Predefined noninferiority criterion for GMT ratio: the lower limit of the 95% CI of the GMT ratio (QIV-HD divided by TIV-HD) is >0.667
10Predefined noninferiority criterion for GMT ratio: the lower limit of the 95% CI of the GMT ratio (QIV-HD divided by TIV-HD) is >0.667

### Table 5: Study 2: Relative Efficacy Against Laboratory-Confirmed Influenza

<table>
<thead>
<tr>
<th>Strain</th>
<th>Relative Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fluzone High-Dose</strong></td>
<td>227 (1.43)</td>
</tr>
<tr>
<td><strong>Fluzone High-Dose</strong></td>
<td>300 (1.89)</td>
</tr>
<tr>
<td><strong>Fluzone High-Dose</strong></td>
<td>24.2 (9.7; 36.5)</td>
</tr>
<tr>
<td><strong>Fluzone High-Dose</strong></td>
<td>190 (1.20)</td>
</tr>
<tr>
<td><strong>Fluzone High-Dose</strong></td>
<td>249 (1.56)</td>
</tr>
<tr>
<td><strong>Fluzone High-Dose</strong></td>
<td>23.6 (7; 37.1)</td>
</tr>
<tr>
<td><strong>Fluzone High-Dose</strong></td>
<td>8 (0.05)</td>
</tr>
<tr>
<td><strong>Fluzone High-Dose</strong></td>
<td>9 (0.06)</td>
</tr>
<tr>
<td><strong>Fluzone High-Dose</strong></td>
<td>11.0 (-159.9; 70.1)</td>
</tr>
<tr>
<td><strong>Fluzone High-Dose</strong></td>
<td>171 (1.08)</td>
</tr>
<tr>
<td><strong>Fluzone High-Dose</strong></td>
<td>222 (1.40)</td>
</tr>
<tr>
<td><strong>Fluzone High-Dose</strong></td>
<td>22.9 (5.4; 37.2)</td>
</tr>
</tbody>
</table>
Fluzone High-Dose Quadrivalent vaccine contains 4 killed flu virus strains. There is no live flu virus in Fluzone High-Dose Quadrivalent. Fluzone High-Dose Quadrivalent cannot cause the flu. Inactive ingredients include formaldehyde and octylphenol ethoxylate.

Who should not get Fluzone High-Dose Quadrivalent vaccine? You should not get Fluzone High-Dose Quadrivalent 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 Quadrivalent vaccine given? Fluzone High-Dose Quadrivalent vaccine is a shot given into the muscle of the arm.

What are the possible side effects of Fluzone High-Dose Quadrivalent vaccine? The most common side effects of Fluzone High-Dose Quadrivalent vaccine are:
- pain, redness, and swelling where you got the shot
- muscle ache
- tiredness
- headache

These are not all of the possible side effects of Fluzone High-Dose Quadrivalent 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 https://vaers.hhs.gov.

Why should I get Fluzone High-Dose Quadrivalent vaccine instead of a standard-dose quadrivalent influenza vaccine? Among persons 65 years of age and older, Fluzone High-Dose Quadrivalent generated a similar immune response to Fluzone High-Dose and is expected to provide better protection against influenza compared to standard-dose quadrivalent influenza vaccines. What are the ingredients in Fluzone High-Dose Quadrivalent vaccine? Fluzone High-Dose Quadrivalent vaccine contains 4 killed flu virus strains. There is no live flu virus in Fluzone High-Dose Quadrivalent. Fluzone High-Dose Quadrivalent cannot cause the flu. Inactive ingredients include formaldehyde and octylphenol ethoxylate.

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

INHQD-FPLR-SL-NOV19Rx Only