Fluzone High-Dose Quadrivalent (Influenza Vaccine), Suspension, for intramuscular injection
2021-2022 Formula
Initial U.S. Approval: 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. (1)
Fluzone High-Dose Quadrivalent is indicated for use in persons 65 years of age and older. (1)

2 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)

3 DOSAGE FORMS AND STRENGTHS
Suspension for injection in prefilled syringe, 0.7 mL (3)

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

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 Quadrivalent should be based on careful consideration of the potential benefits and risks. (5.1)

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience
The most common reactions occurring after Fluzone High-Dose Quadrivalent administration were injection-site pain (41.3%); the most common solicited systemic adverse event was myalgia (22.7%). (6.1)

6.2 Postmarketing Experience

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
8.2 Lactation

13 NONCLINICAL TOXICOLOGY

17 PATIENT COUNSELING INFORMATION
*Sections or subsections omitted from the full prescribing information are not listed

16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

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

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

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 and may not reflect the rates observed in practice. One clinical study has evaluated the safety of Fluzone High-Dose Quadrivalent. Study 1 (NCT03282240, see https://clinicaltrials.gov) was a randomized, active-controlled, modified double-blind pre-licensure trial conducted in the U.S. The study compared the safety and immunogenicity of Fluzone High-Dose Quadrivalent to those of Fluzone High-Dose (trivalent formulation). The safety analysis set included 1777 Fluzone High-Dose Quadrivalent recipients, 443 Fluzone High-Dose recipients, and 450 investigational Fluzone High-Dose containing the alternate B influenza strain recipients.

The most common reactions occurring after Fluzone High-Dose Quadrivalent administration were injection-site pain (41.3%), myalgia (22.7%), headache (14.4%), and malaise (13.2%). Onset usually occurred within the first 3 days after vaccination. The majority of solicited reactions resolved within three days of vaccination. Table 1 displays solicited adverse reactions for Fluzone High-Dose Quadrivalent compared to Fluzone High-Dose reported within 7 days after vaccination and collected using standardized diary cards.

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 https://vaers.hhs.gov.

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

Revised: 07/2021
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, or Fluzone Quadrivalent. 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.

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.

The Fluzone High-Dose Quadrivalent prefilled syringe presentation is not made with natural rubber latex.

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 virus strains for the influenza season of 2021-2022:

- A/Panama/2007/19 (H1N1) variant, A/California/07/2009 (H1N1) virus, A/Hong Kong/4801/2009 (H1N1) virus, A/Brazil/7/2011 (H1N1) virus
- A/California/07/2009 (H3N2) virus (9.5 mcg HA total)
- B/Brisbane/60/2008 (B Yamagata lineage) virus
- B/Phuket/3073/2013 (B Victoria Lineage) virus

The amounts of HA and other ingredients per dose of vaccine are listed in Table 2.

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)).

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.

Table 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>Event</th>
<th>Fluzone High-Dose Quadrivalent (N=1761-1768) Percentage</th>
<th>Fluzone High-Dose* (N=885-889) Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>Any</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Grade 3</td>
<td>Grade 3</td>
</tr>
<tr>
<td><strong>Local Reactions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>41.3 (per dose)</td>
<td>36.4 (per dose)</td>
</tr>
<tr>
<td>Injection Site Erythema</td>
<td>6.2 (per dose)</td>
<td>5.7 (per dose)</td>
</tr>
<tr>
<td>Injection Site Swelling</td>
<td>4.9 (per dose)</td>
<td>4.7 (per dose)</td>
</tr>
<tr>
<td>Injection Site Induration</td>
<td>3.7 (per dose)</td>
<td>3.5 (per dose)</td>
</tr>
<tr>
<td>Injection Site Bruising</td>
<td>1.3 (per dose)</td>
<td>1.1 (per dose)</td>
</tr>
<tr>
<td><strong>Systemic Reactions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>22.7 (per dose)</td>
<td>18.9 (per dose)</td>
</tr>
<tr>
<td>Headache</td>
<td>14.4 (per dose)</td>
<td>13.6 (per dose)</td>
</tr>
<tr>
<td>Malaise</td>
<td>13.2 (per dose)</td>
<td>13.4 (per dose)</td>
</tr>
<tr>
<td>Shivering</td>
<td>5.4 (per dose)</td>
<td>4.7 (per dose)</td>
</tr>
<tr>
<td>Fever</td>
<td>0.4 (per dose)</td>
<td>0.9 (per dose)</td>
</tr>
</tbody>
</table>

6.2 Postmarketing Experience

The following adverse events have been spontaneously reported during the postmarketing use of Fluzone High-Dose, Fluzone, or Fluzone Quadrivalent and may occur in people receiving Fluzone High-Dose Quadrivalent. 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 High-Dose, Fluzone, or Fluzone Quadrivalent.

- Blood and Lymphatic System Disorders: Thrombocytopenia, lymphopenopathy
- Immunologic 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, vasodilatation
- Respiratory, Thoracic and Mediastinal Disorders: Dyspnea, cough, wheezing, throat tightness, oropharyngeal pain, and rhinorrhea
- Gastrointestinal Disorders: Vomiting
- Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome
- General Disorders and Administration Site Conditions: pruritus, asthena/fatigue, chest pain, chills

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Fluzone High-Dose Quadrivalent is not approved for use in persons <65 years of age.

8.2 Lactation

Fluzone High-Dose Quadrivalent is not approved for use in persons <65 years of age.

8.4 Pediatric Use

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

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

Study 1 (NCT03282240, see http://clinicaltrials.gov) 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.

A total of 2670 adults from 65 years of age were randomized (4:1:1) to receive one dose of either Fluzone High-Dose Quadrivalent or one of two formulations of Fluzone High-Dose (one formulation contained a B strain of the Victoria lineage [TIV-HD1] while the other contained a B strain of the Yamagata lineage [TIV-HD2]), respectively.

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 (TIV-HD1 and TIV-HD2, pooled). The mean age was 72.9 years (range: 65 through 100 years) in the Fluzone High-Dose Quadrivalent group and the mean age was 73.0 years (range: 65 through 95 years) in the Fluzone High-Dose group. The percentage of subjects 75 years of age or older was 35.4% in the Fluzone High-Dose Quadrivalent group and 35.3% in the Fluzone High-Dose group.

Most participants were White (91.2% and 89.7%), followed by Black (6.8% and 8.0%), and Hispanic (2.8% and 2.6%) in the Fluzone High-Dose Quadrivalent and Fluzone High-Dose groups, respectively.

The immunogenicity results of Study 1 are summarized in Table 3 and Table 4 below.

### 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 Ratio</th>
<th>Met Predefined Non-inferiority Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (H1N1)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>312/374</td>
<td>Yes</td>
</tr>
<tr>
<td>A (H3N2)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>563/594</td>
<td>Yes</td>
</tr>
<tr>
<td>B1 (Victoria)</td>
<td>516/476</td>
<td>Yes</td>
</tr>
<tr>
<td>B2 (Yamagata)</td>
<td>578/580</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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

† Predefined noninferiority criterion for the GMT ratio: the lower limit of the 95% CI of the GMT ratio (QIV-HD divided by TIV-HD) is >0.667

‡ Prepandemic noninferiority criterion for seroconversion: the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (QIV-HD minus TIV-HD) is >0.10

§ Predefined noninferiority criterion for seroconversion: the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (QIV-HD minus TIV-HD) is >0.90

¶ Pooled TIV-HD group includes subjects vaccinated with either TIV-HD1 or TIV-HD2 for the A strain comparison

### 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)&lt;sup&gt;†&lt;/sup&gt;</th>
<th>Difference of Seroconversion Rates</th>
<th>Met Predefined Non-inferiority Criteria&lt;sup&gt;‡&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (H1N1)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>50.4/53.7</td>
<td>-3.37 (-7.37; 0.66)</td>
<td>Yes</td>
</tr>
<tr>
<td>A (H3N2)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>49.8/50.5</td>
<td>-0.71 (-4.83; 3.42)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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

† Predefined noninferiority criterion for the GMT ratio: the lower limit of the 95% CI of the GMT ratio (QIV-HD divided by TIV-HD) is >0.667

‡ Prepandemic noninferiority criterion for seroconversion: the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (QIV-HD minus TIV-HD) is >0.10

§ Predefined noninferiority criterion for seroconversion: the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (QIV-HD minus TIV-HD) is >0.90

¶ Pooled TIV-HD group includes subjects vaccinated with either TIV-HD1 or TIV-HD2 for the A strain comparison

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 induced a superior immune response, based on a pre-specified superiority criterion, with respect to the additional B strain than the immune response induced by Fluzone High-Dose formulation that did not contain the additional B strain.

14.2 Efficacy of Fluzone High-Dose in Adults 65 to 85 Years of Age and Older

The efficacy of Fluzone High-Dose (trivalent formulation) is relevant to Fluzone High-Dose Quadrivalent since both vaccines are manufactured according to the same process and have overlapping compositions.

Study 2 (NCT01427309) was a multi-center, double-blind, post-licensure efficacy trial conducted in the U.S. and Canada in which adults 65 years of age and older were randomized (1:1) to receive either Fluzone High-Dose or Fluzone. The study was conducted over two influenza seasons (2011-2012 and 2012-2013); 53% of participants enrolled in the first year of the study were re-enrolled and re-randomized in the second year. The per-protocol analysis set for efficacy assessments included 15,892 Fluzone High-Dose recipients and 15,911 Fluzone recipients. The majority (67%) of participants in the per-protocol analysis set for efficacy had one or more high-risk chronic comorbid conditions.

In the per-protocol analysis set, females accounted for 57.2% of participants in the Fluzone High-Dose group and 56.1% of participants in the Fluzone group. In both groups, the median age was 72.2 years (range 65 through 100 years). Overall, most participants in the study were White (95%); approximately 4% of study participants were Black, and approximately 6% reported Hispanic ethnicity.

The primary endpoint of the study was the occurrence of laboratory-confirmed influenza (as determined by culture or polymerase chain reaction) caused by any influenza viral type/subtype in association with influenza-like illness (ILI), defined as the occurrence of at least one of the following respiratory symptoms: sore throat, cough, chest pain, flushed skin, difficulty breathing; concurrent with at least one of the following systemic signs or symptoms: temperature >99.0°F, chills, tiredness, headaches or myalgia. Participants were monitored for the occurrence of a respiratory illness by both active and passive surveillance, starting 2 weeks post-vaccination for approximately 7 months. After an episode of respiratory illness, nasopharyngeal swab samples were collected for analysis; attack rates and vaccine efficacy were calculated (see Table 5).
Fluzone High-Dose Quadrivalent vaccine is for people 65 years of age and older.

Vaccination with Fluzone High-Dose Quadrivalent vaccine may not protect all people who receive the vaccine.

Why should I get Fluzone High-Dose Quadrivalent vaccine instead of Fluzone?

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

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.

How did Fluzone High-Dose Quadrivalent vaccine work?

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.

Table 5: 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 B</th>
<th>Fluzone High-Dose N=15,892</th>
<th>Fluzone High-Dose N=15,911</th>
<th>Relative Efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>37 (0.23)</td>
<td>51 (0.32)</td>
<td>27.4 (-13.1; 53.8)</td>
</tr>
</tbody>
</table>

NCT01427309

†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

#The prespecified statistical superiority criterion for the primary endpoint (lower limit of the 2-sided 95% CI of the vaccine efficacy of Fluzone High-Dose relative to Fluzone >9.1%) was met

†† 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 efficacy of Fluzone High-Dose relative to Fluzone for this endpoint was 51.1% (95% CI: 16.8; 72.0).