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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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.

ADVERSE REACTIONS

In adults ≥65 years of age, the most common (>10%) injection-site reaction was pain (41.3%); the most common solicited systemic adverse reactions were myalgia (22.7%), headache (14.4%) and malaise (13.2%).

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

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

Revised: 11/2023
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.

Table 1: Study 1: Frequency of Solicited-Injection-Site Systemic Adverse Reactions 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>Fluzone High-Dose Quadrivalent (N=1761-1768)</th>
<th>Fluzone High-Dose (N=885-889)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage</td>
<td>Percentage</td>
</tr>
<tr>
<td>Local Reactions</td>
<td></td>
</tr>
<tr>
<td>Injection Site Pain§</td>
<td>41.3</td>
</tr>
<tr>
<td>Injection Site Erythema§</td>
<td>6.2</td>
</tr>
<tr>
<td>Injection Site Swelling§</td>
<td>4.9</td>
</tr>
<tr>
<td>Injection Site Induration§</td>
<td>3.7</td>
</tr>
<tr>
<td>Injection Site Bruising§</td>
<td>1.3</td>
</tr>
<tr>
<td>Systemic Reactions</td>
<td></td>
</tr>
<tr>
<td>Myalgia§</td>
<td>22.7</td>
</tr>
<tr>
<td>Headache§</td>
<td>14.4</td>
</tr>
<tr>
<td>Malaise§</td>
<td>13.2</td>
</tr>
<tr>
<td>Shivering§</td>
<td>5.4</td>
</tr>
<tr>
<td>Fever§</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*TNC03282240
†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: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
©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: > 102.1°F (39.0°C)

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. Unsolicited non-serious adverse events were reported in 279 (15.7%) recipients in the Fluzone High-Dose Quadrivalent group and 140 (15.7%) recipients in the Fluzone High-Dose group. The most commonly reported unsolicited adverse event was cough. Within 180 days post-vaccination, 80 (4.5%) Fluzone High-Dose Quadrivalent recipients and 48 (5.4%) Fluzone High-Dose recipients experienced a serious adverse event (SAE). None of the SAEs were assessed as related to the study vaccines.

6.2 Postmarketing Experience

The following additional 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 Fluzone High-Dose, Fluzone, or Fluzone Quadrivalent.

- **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, vasodilatation
- **Respiratory, Thoracic and Mediastinal Disorders**: Dyspnea, cough, wheezing, throat tightness, onopharyngeal pain, and rhinorrhea
- **Gastrointestinal Disorders**: Vomiting
- **Skin and Subcutaneous Tissue Disorders**: Stevens-Johnson syndrome
- **General Disorders and Administration Site Conditions**: pruritus, asthenia/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. 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.

8.3 Pediatric Use

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

8.4 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.

Fluzone High-Dose Quadrivalent suspension for injection is a colorless opalescent liquid. Neither antibiotics nor preservative 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 strains recommended for the 2023-2024 influenza season: A/Victoria/4897/2022 (H1N1), A/Darwin/9/2021 (H3N2), B/Phuket/3073/2013 (B Yamagata lineage), and B/Michigan/01/2011 (a B/Australia/3954/2011-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 Quadrivalent 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>240 mcg HA total</td>
</tr>
<tr>
<td>A (H1N1)</td>
<td>60 mcg HA</td>
</tr>
<tr>
<td>A (H3N2)</td>
<td>60 mcg HA</td>
</tr>
<tr>
<td>B (Victoria Lineage)</td>
<td>60 mcg HA</td>
</tr>
<tr>
<td>B (Yamagata Lineage)</td>
<td>60 mcg HA</td>
</tr>
<tr>
<td>Other: Sodium phosphate-buffered isotonic sodium chloride solution</td>
<td>QS° 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
°Quantity sufficient

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 titers 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 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 hemag-
glutinins 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, 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 (GMIs) at Day 28 and seroconversion rates, to strains common to formulations of both vaccines, based on pre-specified criteria.

A total of 2,070 adults from 65 years of age were randomized (1:1:1) 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]). 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 (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 35.8% in the Fluzone High-Dose group. Most participants were White (91.2% and 89.7%), followed by Black (6.5% 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 GMIs 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>GMT Ratio</th>
<th>Met Defined Non-inferiority Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>QIV-HD</td>
<td>N=1679-1680</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIV-HD1 (B1 Victoria) N=423</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIV-HD2 (B2 Yamagata) N=430</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A (H1N1)</td>
<td>312</td>
<td>374</td>
<td>0.83 (0.74; 0.932)</td>
</tr>
<tr>
<td>A (H3N2)</td>
<td>563</td>
<td>594</td>
<td>0.95 (0.842; 1.068)</td>
</tr>
<tr>
<td>B1 (Victoria)</td>
<td>516</td>
<td>476</td>
<td>1.08 (1.035; 1.024)</td>
</tr>
<tr>
<td>B2 (Yamagata)</td>
<td>578</td>
<td>580</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 (continued)

<table>
<thead>
<tr>
<th>Influenza Strain</th>
<th>Seroconversion Rates (Percentage)</th>
<th>Difference of Seroconversion Rates</th>
<th>Met Defined Non-inferiority Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (H1N1)</td>
<td>QIV-HD N=1688-1689</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIV-HD1 (B1 Victoria) N=420-421</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIV-HD2 (B2 Yamagata) N=428</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50.4</td>
<td>53.7</td>
<td>-3.27 (-7.37; 0.86)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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

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

Study 2 (NCT03282240) 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 (1:1:1) 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 (defined 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, sputum production, wheezing, or difficulty breathing; concurrent with at least one of the following systemic signs or symptoms: temperature ≥99°F, chills, tremors, 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).

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

<table>
<thead>
<tr>
<th>Influenza A</th>
<th>Relative Efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (H1N1)</td>
<td>227 (1.43)</td>
</tr>
<tr>
<td>A (H3N2)</td>
<td>300 (1.89)</td>
</tr>
<tr>
<td>Any type/subtype*</td>
<td>24.2 (9.7, 36.5)</td>
</tr>
</tbody>
</table>

Fluzone High-Dose N=15,892 n% (95% CI)
occurrence of a temperature
of at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheeze, 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.

†Laboratory-confirmed: culture or polymerase-chain-reaction–confirmed

‡In the first year of the study the influenza B component of the vaccine and the majority of influenza B cases were of the Yamagata lineage; in the second year the influenza B component of the vaccine and the majority of influenza B cases were of the Victoria 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

Patient Information Sheet
Fluzone® High-Dose Quadrivalent
Influenza Vaccine

Please read this information sheet before getting Fluzone High-Dose Quadrivalent vaccine. This summary is not intended to take the place of talking with your healthcare provider. If you have questions or would like more information, please talk with your healthcare provider.

What is Fluzone High-Dose Quadrivalent vaccine?
Fluzone High-Dose Quadrivalent is a vaccine that helps protect against influenza illness (flu).

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.

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.

• 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.

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 where you got the shot

• muscle ache

• tiredness

• headache

These side effects usually go away after a few days. 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.