Fluzone High-Dose Quadrivalent (Influenza Vaccine), Suspension, for intramuscular injection 2020-2021 Formula
Initial U.S. Approval: 2019

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 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)

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. (5.1)

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. (5.2)

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. (5.3)

5.4 Limitations of Vaccine Effectiveness
Vaccination with Fluzone High-Dose Quadrivalent may not protect all recipients. (5.4)

ADVERSE REACTIONS
6.1 Clinical Trials Experience
The most common solicited systemic adverse event was myalgia (22.7%). (6.1)

8.1 Pregnancy
8.2 Lactation

9 CLINICAL STUDIES
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.

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

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: 07/2020
Fluzone High-Dose Quadrivalent is not approved for use in persons 8 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, octylphenoxy 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 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 2020-2021 influenza season: A/Guangdong-Maonan/SWL1536/2019 (H1N1), A/Hong Kong/2671/2019 (H3N2), B/Phuket/3073/2013 (B Yamagata lineage), and B/Washington/02/2019 (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>Sodium phosphate-buffered isotonic sodium chloride solution</td>
<td>QS² to appropriate volume</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>≤140 mcg</td>
</tr>
<tr>
<td>Octylphenoxy 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 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>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>Percentage</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>Percentage</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>Fever³</td>
<td>0.4</td>
</tr>
</tbody>
</table>

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)].

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 hemagglutinin content 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 been tested for carcinogenicity 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 (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]).

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 (6.8% 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

| Influenza Strain | GMT (N=1679-1680) | GMT Ratio | Met predefined non-inferiority criteria
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>QIV-HD (B1 Victoria)</td>
<td>312 vs. 374 (0.83; 0.932)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>TIV-HD1 (B2 Yamagata)</td>
<td>563 vs. 594 (0.95; 1.096)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>TIV-HD2 (B2 Yamagata)</td>
<td>516 vs. 476 (1.08; 1.224)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>B1 (Victoria)</td>
<td>578 vs. 580 (1.00; 1.129)</td>
<td>Yes</td>
<td></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>QIV-HD (N=1668-1669)</td>
<td>50.4 vs. 53.7</td>
<td>-3.27 (-7.37; 0.86)</td>
<td>Yes</td>
</tr>
<tr>
<td>TIV-HD1 (B1 Victoria)</td>
<td>49.8 vs. 50.5</td>
<td>-0.71 (-4.83; 3.42)</td>
<td>Yes</td>
</tr>
<tr>
<td>TIV-HD2 (B2 Yamagata)</td>
<td>36.5 vs. 39.0</td>
<td>-2.41 (-7.66; 2.70)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### 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

<table>
<thead>
<tr>
<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>Any type/subtype‡</td>
<td>227 (1.43)</td>
<td>300 (1.89)</td>
</tr>
<tr>
<td>Influenza A</td>
<td>190 (1.20)</td>
<td>249 (1.56)</td>
</tr>
<tr>
<td>A (H1N1)</td>
<td>8 (0.05)</td>
<td>9 (0.06)</td>
</tr>
</tbody>
</table>
**Fluzone High-Dose Quadrivalent vaccine**

**What is Fluzone High-Dose Quadrivalent vaccine?**

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

Fluzone High-Dose Quadrivalent vaccine is for people 65 years of age and older.

**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 viruses. 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.

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

Manufactured by: Sanofi Pasteur Inc.

Swiftwater, PA 18370 USA

INHDQ-FPLR-SL-JUL20 Rx Only

**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-like illness (flu).

Fluzone High-Dose Quadrivalent vaccine is for people 65 years of age and older.