Fluzone Quadrivalent (Influenza Vaccine)  
Suspension for Intramuscular Injection  
2018-2019 Formula  
Initial US Approval (Fluzone Quadrivalent): 2013  

**Indications and Usage**  
Fluzone 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 Quadrivalent is approved for use in persons 6 months of age and older. (1)  

**Contraindications**  
If Guillain-Barré syndrome (GBS) has occurred within 6 weeks following previous influenza vaccination, the decision to give Fluzone Quadrivalent should be based on careful consideration of the potential benefits and risks. (4)  

**Warnings and Precautions**  
• Pregnancy: Pregnancy exposure registry available. Call Sanofi Pasteur Inc. at 1-800-822-2463 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.  

**Adverse Reactions**  
• In children 6 months through 35 months of age, the most common (≥10%) injection-site reactions were pain (5%) or tenderness (47%), erythema (23%), and swelling (13%–22%); the most common solicited systemic adverse reactions were irritability (47%–54%), abnormal crying (33%–41%), malaise (38%), drowsiness (31%–38%), appetite loss (27%–32%), and myalgia (27%), vomiting (10%–15%), and fever (11%–14%). (6.1)  
• In children 3 years through 8 years of age, the most common (≥10%) injection-site reactions were pain (67%), erythema (34%), and swelling (25%); the most common solicited systemic adverse reactions were myalgia (39%), malaise (32%), and headache (23%). (6.1)  
• In adults 18 years and older, the most common (≥10%) injection-site reaction was pain (47%); the most common solicited systemic adverse reactions were myalgia (24%), headache (16%), and malaise (11%). (6.1)  
• In adults 65 years of age and older, the most common (≥10%) injection-site reaction was pain (33%); the most common solicited systemic adverse reactions were myalgia (18%), headache (13%), and malaise (11%). (6.1)  

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Pasteur Inc., at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

**Use in Specific Populations**  
• Pregnancy: Pregnancy exposure registry available. Call Sanofi Pasteur Inc. at 1-800-822-2463.  
• Antibody responses to Fluzone Quadrivalent are lower in persons ≥65 years of age than in younger adults. (8.5)  

See 17 FOR PATIENT COUNSELING INFORMATION and FDA - approved patient labeling.  

**Dosage Forms and Strengths**  
Suspension for injection supplied in 4 presentations: prefilled single-dose syringe (pink plunger rod), 0.25 mL; prefilled single-dose syringe (clear plunger rod), 0.5 mL; single-dose vial, 0.5 mL; multi-dose vial, 5 mL. (3)  

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

**Warnings and Precautions**  
• Pregnancy: Pregnancy exposure registry available. Call Sanofi Pasteur Inc. at 1-800-822-2463 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.  

**Use in Specific Populations**  
• Pregnancy: Pregnancy exposure registry available. Call Sanofi Pasteur Inc. at 1-800-822-2463.  
• Antibody responses to Fluzone Quadrivalent are lower in persons ≥65 years of age than in younger adults. (8.5)  

See 17 FOR PATIENT COUNSELING INFORMATION and FDA - approved patient labeling.
FULL PRESCRIBING INFORMATION:
1 INDICATIONS AND USAGE
Fluzone 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 Quadrivalent is approved for use in persons 6 months of age and older.

2 DOSAGE AND ADMINISTRATION
For intramuscular use only
2.1 Dose and Schedule
The dose and schedule for Fluzone Quadrivalent are presented in Table 1.

Prior to vaccination, always refer to the current Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza vaccines.

Table 1: Dose and Schedule for Fluzone Quadrivalent

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccination Status</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>Not previously vaccinated with influenza vaccine or unknown vaccination history</td>
<td>Two doses, either 0.25 mL or 0.5 mL*</td>
<td>Administer at least 4 weeks apart</td>
</tr>
<tr>
<td>through 35 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previously vaccinated with influenza vaccine</td>
<td>One or two doses, either 0.25 mL or 0.5 mL*</td>
<td>If two doses, administer at least 4 weeks apart</td>
<td></td>
</tr>
<tr>
<td>36 months through 8 years</td>
<td>Not previously vaccinated with influenza vaccine or unknown vaccination history</td>
<td>Two 0.5 mL doses</td>
<td>Administer at least 4 weeks apart</td>
</tr>
<tr>
<td>9 years and older</td>
<td>Previously vaccinated with influenza vaccine</td>
<td>One or two 0.5 mL doses</td>
<td>If two doses, administer at least 4 weeks apart</td>
</tr>
</tbody>
</table>

*The schedule can be completed as two 0.25-mL doses ≥ 4 weeks apart, two 0.5-mL doses ≥ 4 weeks apart, or any combination of 2 doses (either 0.25 mL or 0.5 mL) administered ≥ 4 weeks apart.

2.2 Administration
Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration, whenever solution and container permit. If any of these defects or conditions exist, Fluzone Quadrivalent should not be administered.

Before administering a dose of vaccine, shake the prefilled syringe or vial. Withdraw one dose of vaccine from the single-dose vial using a sterile needle and syringe. Use a separate sterile needle and syringe for each dose withdrawn from the multi-dose vial.

The preferred sites for intramuscular injection are the anterolateral aspect of the thigh in infants 6 months through 11 months of age, the anterolateral aspect of the thigh (or the deltoid muscle if muscle mass is adequate) in persons 12 months through 35 months of age, or the deltoid muscle in persons ≥36 months of age. 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, intradermally, or subcutaneously.

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

3 DOSAGE FORMS AND STRENGTHS
Fluzone Quadrivalent is a suspension for injection.

Fluzone Quadrivalent is supplied in 4 presentations:
1) Prefilled single-dose syringe (pink syringe plunger rod), 0.25 mL, for persons 6 months through 35 months of age.
2) Prefilled single-dose syringe (clear syringe plunger rod), 0.5 mL, for persons 6 months of age and older.
3) Single-dose vial, 0.5 mL, for persons 6 months of age and older.
4) Multi-dose vial, 5 mL, for persons 6 months of age and older.

4 CONTRAINDICATIONS
Do not administer Fluzone Quadrivalent to anyone with a history of 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.

5 WARNINGS AND PRECAUTIONS
5.1 Guillain-Barré Syndrome
The 1976 swine influenza vaccine was associated with an elevated risk of Guillain-Barré syndrome (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 ref. 1) If GBS has occurred within 6 weeks following previous influenza vaccination, the decision to give Fluzone Quadrivalent should be based on careful consideration of the potential benefits and risks.

5.2 Preventing and Managing Allergic Reactions
Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of Fluzone Quadrivalent.

5.3 Altered Immunocompetence
If Fluzone Quadrivalent 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 Quadrivalent may not protect all recipients.

6 ADVERSE REACTIONS
In children 6 months through 35 months of age receiving a 0.25-mL dose of Fluzone Quadrivalent in Study 1 (NCT01240746, see http://clinicaltrials.gov), the most common (≥10%) injection-site reactions were pain (57%) or tenderness (54%), erythema (37%), and swelling (22%), the most common solicited systemic adverse reactions were irritability (54%), abnormal crying (41%), malaise (38%), drowsiness (38%); appetite loss (32%); myalgia (27%); vomiting (15%); and fever (14%). In children 3 years through 8 years of age, the most common (≥10%) injection-site reactions were pain (67%), erythema (34%), and swelling (25%); the most common solicited systemic adverse reactions were myalgia (39%), malaise (32%), and headache (23%). In adults 18 years older, the most common (≥10%) injection-site reaction was pain (47%); the most common solicited systemic adverse reactions were myalgia (34%), headache (16%), and malaise (11%). In adults 65 years of age and older, the most common (≥10%) injection-site reaction was pain (33%); the most common solicited systemic adverse reactions were myalgia (34%), headache (16%), and malaise (11%).

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.

Children 6 Months Through 8 Years of Age
Study 1 (NCT01240746, see http://clinicaltrials.gov) was a single-blind, randomized, active-controlled multi-center safety and immunogenicity study conducted in the US. In this study, children 6 months through 35 months of age received one or two 0.25 mL doses of either Fluzone Quadrivalent or one of two formulations of a comparator trivalent influenza vaccine (TIV-1 or TIV-2), and children 3 years through 8 years of age received one or two 0.5 mL doses of either Fluzone Quadrivalent, TIV-1, or TIV-2. Each of the trivalent formulations contained an influenza type B virus that corresponded to one of the two type B viruses in Fluzone Quadrivalent (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). For participants who received two doses, the doses were administered approximately 4 weeks apart. The safety analysis set included 1841 children 6 months through 35 months of age and 2506 children 3 years through 8 years of age. Among participants 6 months through 8 years of age in the three vaccine groups combined, 49.3% were female (Fluzone Quadrivalent, 49.4%; TIV-1, 49.1%; TIV-2, 49.5%), 58.4% Caucasian (Fluzone Quadrivalent, 58.4%; TIV-1, 58.9%; TIV-2, 57.8%), 20.2% Black (Fluzone Quadrivalent, 20.5%; TIV-1, 19.9%; TIV-2, 19.1%), 14.1% Hispanic (Fluzone Quadrivalent, 14.3%; TIV-1, 13.2%; TIV-2, 14.7%), and 7.3% were of other racial/ethnic groups (Fluzone Quadrivalent, 6.8%; TIV-1, 8.0%; TIV-2, 8.5%). Table 2 and Table 3 summarize solicited injection-site and systemic adverse reactions reported within 7 days post-vaccination via diary cards. Participants were monitored for unsolicited adverse events for 28 days after each dose and serious adverse events (SAEs) during the 6 months following the last dose.

Table 2: Study 1: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 7 Days After Vaccination in Children 6 Months Through 35 Months of Age (Safety Analysis Set)b

<table>
<thead>
<tr>
<th>Injection-site adverse reactions</th>
<th>Fluzone Quadrivalent (N=1223)</th>
<th>TIV-1c,d (B Victoria) (N=310)</th>
<th>TIV-2c,d (B Yamagata) (N=308)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (%)</td>
<td>50.2</td>
<td>53.4</td>
<td>50.3</td>
</tr>
<tr>
<td>Grade 2 (%)</td>
<td>38.1</td>
<td>37.5</td>
<td>38.2</td>
</tr>
<tr>
<td>Grade 3 (%)</td>
<td>11.5</td>
<td>8.3</td>
<td>11.4</td>
</tr>
<tr>
<td>Tenderness (%)</td>
<td>51.4</td>
<td>49.7</td>
<td>50.2</td>
</tr>
<tr>
<td>Erythema (%)</td>
<td>37.4</td>
<td>43.3</td>
<td>37.5</td>
</tr>
<tr>
<td>Swelling (%)</td>
<td>22.6</td>
<td>25.1</td>
<td>22.6</td>
</tr>
</tbody>
</table>

*The Table 1: Dose and Schedule for Fluzone Quadrivalent is shown. The schedule can be completed as two 0.25-mL doses ≥ 4 weeks apart, two 0.5-mL doses ≥ 4 weeks apart, or any combination of 2 doses (either 0.25 mL or 0.5 mL) administered ≥ 4 weeks apart.

To determine if 1 or 2 doses are required, refer to Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza vaccines.

* Indicates information is not applicable.

*b The safety analysis set includes all persons who received at least one dose of study vaccine.

c Fluzone Quadrivalent (0.25 mL) containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage).

d Participants received one or two doses according to ACIP recommendations.

e 2010-2011 Fluzone TIV (0.25 mL) containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

a Assessed in children 24 months through 35 months of age

b Assessed in children 6 months through 23 months of age
were Black, 6.5% were of other racial groups, and 22.0% were Hispanic/Latino.

For participants recommended to receive two doses of influenza vaccine as per Advisory Committee on Immunization Practices (ACIP) guidance, 22.1% were ≥22 years of age (Fluzone Quadrivalent, 23.3%; TIV-1, 20.9%; TIV-2, 24.2%).

The difference in fever rate (Group 2 minus Group 1) was 0.84% (95% CI: -2.13%; 3.80%), meeting the prespecified non-inferiority criterion (upper limit of the 2-sided 95% CI of the difference in fever rates < 5%). Participants were monitored for unsolicited adverse events and SAEs during the 28 days following vaccination. Unsolicited non-serious adverse events were reported in 417 (44%) participants in Group 1 and 394 (40%) participants in Group 2. The most commonly reported unsolicited non-serious adverse events in both groups were cough and rhinorrhea. Ten SAEs were reported during the 28-day follow-up period: 5 (0.5%) in Group 1 and 5 (0.5%) in Group 2.

Adults

In Study 3 (NCT00988143, see http://clinicaltrials.gov), a multi-centered randomized, open-label trial conducted in the US, adults 18 years of age and older received one dose of either Fluzone Quadrivalent or one of two formulations of comparator trivalent influenza vaccine (TIV-1 or TIV-2). Each of the trivalent formulations contained an influenza type B virus that corresponded to one of the two type B viruses in Fluzone Quadrivalent (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The safety analysis set included 570 recipients, half aged 18-60 years and half aged 61 years or older. Among participants in the three vaccine groups combined, 67.2% were female (Fluzone Quadrivalent, 68.4%; TIV-1, 67.9%; TIV-2, 65.2%; TIV-3, 56.4%).

The difference in fever rate (Group 2 minus Group 1) was 0.84% (95% CI: -2.13%; 3.80%), meeting the prespecified non-inferiority criterion (upper limit of the 2-sided 95% CI of the difference in fever rates < 5%). Participants were monitored for unsolicited adverse events and SAEs during the 28 days following vaccination. Unsolicited non-serious adverse events were reported in 417 (44%) participants in Group 1 and 394 (40%) participants in Group 2. The most commonly reported unsolicited non-serious adverse events in both groups were cough and rhinorrhea. Ten SAEs were reported during the 28-day follow-up period: 5 (0.5%) in Group 1 and 5 (0.5%) in Group 2.

Table 3: Study 1*: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 7 Days After Vaccination in Children 3 Years Through 8 Years of Age (Safety Analysis Set)*

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>N</th>
<th>Grade 1 (%)</th>
<th>Grade 2 (%)</th>
<th>Grade 3 (%)</th>
<th>Any (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluzone Quadrivalent</td>
<td>1669</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIV-1 (B Victoria)</td>
<td>424</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIV-2 (B Yamagata)</td>
<td>413</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Study 2*: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 7 Days After Vaccination in Children 6 Months Through 35 Month of Age (Safety Analysis Set)*

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>N</th>
<th>Grade 1 (%)</th>
<th>Grade 2 (%)</th>
<th>Grade 3 (%)</th>
<th>Any (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluzone Quadrivalent</td>
<td>949</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIV-1 (B Victoria)</td>
<td>986</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIV-2 (B Yamagata)</td>
<td>992</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5: Study 3*: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 3 Days After Vaccination in Adults 18 Years of Age and Older (Safety Analysis Set)*

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>N</th>
<th>Grade 1 (%)</th>
<th>Grade 2 (%)</th>
<th>Grade 3 (%)</th>
<th>Any (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluzone Quadrivalent</td>
<td>190</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIV-1 (B Victoria)</td>
<td>190</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIV-2 (B Yamagata)</td>
<td>190</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The safety analysis set includes all persons who received at least one dose of study vaccine.
6.2 Post-Marketing Experience

The following events have been spontaneously reported during the post-approval use of Fluzone (trivalent) or Fluzone 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 (trivalent) 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/flushing
- **Respiratory, Thoracic and Mediastinal Disorders**: Dyspnea, cough, wheezing, throat tightness, oropharyngeal pain, rhinitis
- **Skin and Subcutaneous Tissue Disorders**: Rash, pruritus, and Stevens-Johnson syndrome
- **General Disorders and Administration Site Conditions**: Aesthetic/fatigue, pain in extremities, chest pain
- **Gastrointestinal Disorders**: Vomiting

# USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

### Pregnancy Exposure Registry

Sanofi Pasteur Inc. is maintaining a prospective pregnancy exposure registry to collect data on pregnancy outcomes following vaccination with Fluzone Quadrivalent during pregnancy. Healthcare providers are encouraged to enroll women who receive Fluzone Quadrivalent during pregnancy in Sanofi Pasteur Inc.'s vaccination pregnancy registry by calling 1-800-822-2463.

### Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Available data with Fluzone Quadrivalent use in pregnant women are insufficient to inform vaccine-associated risk of adverse developmental outcomes.

A developmental and reproductive toxicity study was performed in female rabbits given a 0.5 mL/dose of Fluzone Quadrivalent prior to mating and during gestation (a single human dose is 0.5 mL). This study revealed no adverse effects to the fetus or pre-weaning development due to Fluzone Quadrivalent [see Animal Data (8.1)].

### Data

#### Animal Data

In a developmental and reproductive toxicity study female rabbits were administered a 0.5 mL/dose of Fluzone Quadrivalent by intramuscular injection 24 and 10 days before insemination, and on Days 6, 12, and 27 of gestation (a single human dose is 0.5 mL). There were no adverse effects on pre-weaning development or vaccine-related fetal malformations noted in this study.

#### Clinical Considerations

Disease-associated Maternal and/or Embryo/Fetal Risk

Pregnant women are at increased risk of complications associated with influenza infection compared to non-pregnant women. Pregnant women who contract influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

### 8.2 Lactation

Risk Summary

It is not known whether Fluzone Quadrivalent is excreted in human milk. Data are not available to assess the effects of Fluzone Quadrivalent on the breastfed infant or on milk production/excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Fluzone Quadrivalent and any potential adverse effects on the breastfed child from Fluzone Quadrivalent or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to the disease prevented by the vaccine.

### 8.4 Pediatric Use

Safety and effectiveness of Fluzone Quadrivalent in children under the age of 6 months have not been established.

### 8.5 Geriatric Use

Safety and immunogenicity of Fluzone Quadrivalent were evaluated in adults 65 years of age and older. [See Clinical Studies (14.6).] Antibody responses to Fluzone Quadrivalent are lower in persons ≥65 years of age than in younger adults.

#### 11 DESCRIPTION

Fluzone Quadrivalent (Influenza Vaccine) 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 Quadrivalent process uses an additional concentration factor after...
the ultratfiltration step in order to obtain a higher hemagglutinin (HA) antigen concentration. Antigens from the four strains included in the vaccine are produced separately and then combined to make the quadrivalent formulation.

Fluzone Quadrivalent suspension for injection is clear and slightly opalescent in color. Antibiotics are not used in the manufacture of Fluzone Quadrivalent.

The Fluzone Quadrivalent prefilled syringe and vial presentations are not made with natural rubber latex.

Fluzone 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 X-275 (H1N1), A/Singapore/INF-M/16-0019/2016 I6V-186 (H3N2), B/Phuket/3073/2013 (B Yamagata lineage), and B/Maryland/15/2016 BX-69A (a B/Colorado/6/2017-like virus, B Victoria lineage). The amounts of HA and other ingredients per dose of vaccine are listed in Table 7. The single-dose, pre-filled syringe (0.25 mL and 0.5 mL), and the single-dose vial (0.5 mL) are manufactured and formulated without thimerosal or any other preservative. The 5 mL multi-dose vial presentation contains thimerosal, a mercury derivative, added as a preservative. Each 0.5 mL-dose from the multi-dose vial contains 25 mcg mercury. Each 0.25 mL-dose from the multi-dose vial contains 12.5 mcg mercury.

Table 7: Fluzone Quadrivalent Ingredients

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (per dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Substance: Split influenza virus, inactivated strainsa:</td>
<td></td>
</tr>
<tr>
<td>A (H1N1)</td>
<td>30 mcg HA total</td>
</tr>
<tr>
<td>A (H3N2)</td>
<td>15 mcg HA</td>
</tr>
<tr>
<td>B (Victoria lineage)</td>
<td>15 mcg HA</td>
</tr>
<tr>
<td>B (Yamagata lineage)</td>
<td>15 mcg HA</td>
</tr>
<tr>
<td>Other:</td>
<td></td>
</tr>
<tr>
<td>Sodium phosphate-buffered isotonic sodium chloride solution</td>
<td>QSb to appropriate volume</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>≤50 mcg</td>
</tr>
<tr>
<td>Octylphenol ethoxylate</td>
<td>≤125 mcg</td>
</tr>
<tr>
<td>Preservative</td>
<td></td>
</tr>
<tr>
<td>Single-dose presentations</td>
<td>-</td>
</tr>
<tr>
<td>Multi-dose presentation (thimerosal)</td>
<td>12.5 mcg mercury</td>
</tr>
</tbody>
</table>

aUnited States Public Health Service (USPHS) requirement
bQuality Sufficient

- Indicates information is not applicable

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. Since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. Since 2001, two distinct lineages of influenza B (Victoria and Yamagata lineages) have co-circulated worldwide. Protection from influenza virus infection has not been correlated with a specific level of hemagglutination inhibition (HI) antibody titre post-vaccination. However, in some human studies, antibody titers ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects. (See ref. 2) (See ref. 3)

Table 8: Estimated Efficacy of Fluzone (Trivalent Influenza Vaccine) Against Culture-Confirmed Influenza in Children Aged 6 through 24 Months during the 1999-2000 and 2000-2001 Influenza Seasons – Intent-to-Treat Analysis Setb

<table>
<thead>
<tr>
<th>Year</th>
<th>Fluzonec</th>
<th>Placebo</th>
<th>Fluzone vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999-2000</td>
<td>257</td>
<td>65</td>
<td>0.38 (0.18; 0.64)</td>
</tr>
<tr>
<td>2000-2001</td>
<td>252</td>
<td>66</td>
<td>0.32 (0.20; 0.52)</td>
</tr>
</tbody>
</table>

bThe intent-to-treat analysis set includes all enrolled participants who were randomly assigned to receive Fluzone or placebo and vaccinated

cFluzone (0.25 mL); 1999-2000 formulation containing A/Beijing/262/95 (H1N1), A/Sydney/15/97 (H3N2), and B/Yamanashi/166/98 (Yamagata lineage) and 2000-2001 formulation containing A/New Caledonia/2009 (H1N1), A/Panama/2007/99 (H3N2), and B/Yamanashi/166/98 (Yamagata lineage)

dPlacebo: 0.4% NaCl

eIs the number of participants with culture-confirmed influenza for the given year as listed in the first column

14.2 Efficacy of Fluzone (Trivalent Influenza Vaccine) in Adults

A randomized, double-blind, placebo-controlled study was conducted in a single US center during the 2007-2008 influenza season. Participants received one dose of either Fluzone vaccine (N = 813), an active comparator (N = 814), or placebo (N = 325). The intent-to-treat analysis set included 1138 healthy adults who received Fluzone or placebo. Participants were 18 through 49 years of age (mean age was 23.3 years); 63.3% were female, 83.1% were Caucasian, and 16.9% were of other racial/ethnic groups. Cases of influenza were laboratory-confirmed by culture, PCR, or both. Vaccine efficacy against all influenza viral types and subtypes is presented in Table 9.
characteristics was similar to that of the safety analysis set [see Adverse Reactions (6.1)].

HI antibody geometric mean titers (GMTs) and seroconversion rates 28 days following vaccination with Fluzone Quadrivalent were non-inferior to those following each TIV for all four strains, based on pre-specified criteria (see Table 10 and Table 11).

Table 10: Study 1: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by HI Antibody GMTs at 28 Days Post-Vaccination, Persons 6 Months Through 8 Years of Age[Per-protocol Analysis Set]a

<table>
<thead>
<tr>
<th>Antigen Strain</th>
<th>Fluzone Quadrivalentb N=2339</th>
<th>Pooled TVic N=1181</th>
<th>GMT Ratio (95% CI)d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GM Tac</td>
<td>GM Tac</td>
<td></td>
</tr>
<tr>
<td>A (H1N1)</td>
<td>1,124</td>
<td>936</td>
<td>1.03 (0.93; 1.14)</td>
</tr>
<tr>
<td>A (H3N2)</td>
<td>822</td>
<td>826</td>
<td>0.98 (0.91; 1.06)</td>
</tr>
</tbody>
</table>

Fluzone Quadrivalentb was non-inferior to Pooled TVic in GMTs and seroconversion rates 28 days post-vaccination in all three age groups (6 months to 38 months and 3 years to <9 years) examined. In addition, HI antibody GMTs and seroconversion rates following Fluzone Quadrivalent were higher than those following TIV for the B strain not contained in each respective TIV based on pre-specified criteria (the lower limit of the 2-sided 95% CI of the ratio of the GMTs [Fluzone Quadrivalent divided by TIV] >1.5 for each B strain in Fluzone Quadrivalent compared with the corresponding B strain not contained in each TIV and the lower limit of the two 2-sided 95% CI of the difference of the seroconversion rates [Fluzone Quadrivalent minus TIV] >10% for each B strain in Fluzone Quadrivalent compared with the corresponding B strain not contained in each TIV).

14.4 Immunogenicity of the 0.5 mL Dose of Fluzone Quadrivalent in Children 6 Months through 35 Months of Age

In Study 2 (NCT02915302) [see Adverse Reactions (6.1)], 1,027 children, 6 months through 35 months of age, were included in the per-protocol immunogenicity analysis. The distribution of demographic characteristics was similar to that of the safety analysis set [see Adverse Reactions (6.1)].

In this study, children 6 months through 35 months of age received one or two doses of either 0.25 mL or 0.5 mL of Fluzone Quadrivalent. Non-inferiority of the 0.5 mL dose(s) relative to the 0.25 mL dose(s) of Fluzone Quadrivalent was demonstrated for all four strains based on pre-specified criteria (see Table 14). The HI antibody GMTs 21 days following vaccination with Fluzone Quadrivalent were non-inferior to those following each TIV for all four strains, based on pre-specified criteria (see Table 12).

Table 11: Study 1: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by Seroconversion Rates at 28 Days Post-Vaccination, Persons 6 Months Through 8 Years of Age[Per-protocol Analysis Set]a

<table>
<thead>
<tr>
<th>Antigen Strain</th>
<th>Fluzone Quadrivalentb N=2339</th>
<th>Pooled TVic N=1181</th>
<th>Difference of Seroconversion Rates (95% CI)d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serumov (%)</td>
<td>Serumov (%)</td>
<td></td>
</tr>
<tr>
<td>A (H1N1)</td>
<td>92.4</td>
<td>91.4</td>
<td>0.9 (0.0; 3.0)</td>
</tr>
<tr>
<td>A (H3N2)</td>
<td>82</td>
<td>64.2</td>
<td>1.48 (1.0; 2.0)</td>
</tr>
</tbody>
</table>

Fluzone Quadrivalentb was non-inferior to Pooled TVic in seroconversion rates 28 days post-vaccination in all three age groups (6 months to 38 months and 3 years to <9 years) examined. In addition, HI antibody GMTs and seroconversion rates following Fluzone Quadrivalent were higher than those following TIV for the B strain not contained in each respective TIV based on pre-specified criteria (the lower limit of the 2-sided 95% CI of the ratio of the GMTs [Fluzone Quadrivalent divided by TIV] >1.5 for each B strain in Fluzone Quadrivalent compared with the corresponding B strain not contained in each TIV).

14.5 Immunogenicity of Fluzone Quadrivalent in Adults ≥18 Years of Age

In Study 3 (NCT00988143) [see Adverse Reactions (6.1)], 565 adults 18 years of age and older who had received one dose of Fluzone Quadrivalent, TIV-1, or TIV-2 were included in the per-protocol immunogenicity analysis. The distribution of demographic characteristics was similar to that of the safety analysis set [see Adverse Reactions (6.1)].

HI antibody GMTs 21 days following vaccination with Fluzone Quadrivalent were non-inferior to those following each TIV for all four strains, based on pre-specified criteria (see Table 12).

Table 12: Study 3: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by HI Antibody GMTs at 21 Days Post-Vaccination, Adults 18 Years of Age and Older (Per-protocol Analysis Set)b

<table>
<thead>
<tr>
<th>Antigen Strain</th>
<th>Fluzone Quadrivalentb N=190</th>
<th>Pooled TVic N=375</th>
<th>GMT Ratio (95% CI)d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GM Tac</td>
<td>GM Tac</td>
<td></td>
</tr>
<tr>
<td>A (H1N1)</td>
<td>160</td>
<td>151</td>
<td>1.06 (0.87; 1.31)</td>
</tr>
<tr>
<td>A (H3N2)</td>
<td>304</td>
<td>359</td>
<td>0.90 (0.70; 1.15)</td>
</tr>
</tbody>
</table>

Fluzone Quadrivalentb was non-inferior to Pooled TVic in GMTs and seroconversion rates 21 days post-vaccination in all three age groups (6 months to 38 months and 3 years to <9 years) examined. In addition, HI antibody GMTs and seroconversion rates following Fluzone Quadrivalent were higher than those following TIV for the B strain not contained in each respective TIV based on pre-specified criteria (the lower limit of the 2-sided 95% CI of the ratio of the GMTs [Fluzone Quadrivalent divided by TIV] >1.5 for each B strain in Fluzone Quadrivalent compared with the corresponding B strain not contained in each TIV).

14.6 Immunogenicity of Fluzone Quadrivalent in Geriatric Adults ≥65 Years of Age

In Study 4 (NCT01218464) [see Adverse Reactions (6.1)], 660 adults 65 years of age and older were included in the per-protocol immunogenicity analysis. The distribution of demographic characteristics was similar to that of the safety analysis set [see Adverse Reactions (6.1)].

HI antibody GMTs 21 days following vaccination with Fluzone Quadrivalent were non-inferior to those following each TIV for all four strains, based on pre-specified criteria (see Table 13). Seroconversion rates 21 days following Fluzone Quadrivalent were non-inferior to those following TIV for the B strain not contained in each respective TIV, based on pre-specified criteria (the lower limit of the 2-sided 95% CI of the ratio of the GMTs [Fluzone Quadrivalent divided by TIV] >1.5 for each B strain in Fluzone Quadrivalent compared with the corresponding B strain not contained in each TIV).
Table 13: Study 4: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by HI Antibody GMTs at 21 Days Post-Vaccination, Adults 65 Years of Age and Older (Per-protocol Analysis Set)a

<table>
<thead>
<tr>
<th>Antigen Strain</th>
<th>Fluzone Quadrivalent N=220</th>
<th>Pooled TIV N=440</th>
<th>GMT Ratio (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (H1N1)</td>
<td>231</td>
<td>270</td>
<td>0.85 (0.67; 1.09)</td>
</tr>
<tr>
<td>A (H3N2)</td>
<td>501</td>
<td>324</td>
<td>1.55 (1.25; 1.92)</td>
</tr>
</tbody>
</table>

Fluzone Quadrivalent N=220, TIV-1 (B Victoria) N=219, TIV-2 (B Yamagata) N=221

GMT Ratio (95% CI)b

<table>
<thead>
<tr>
<th>GMT</th>
<th>GMTC</th>
<th>GMTc</th>
</tr>
</thead>
<tbody>
<tr>
<td>69.09</td>
<td>54.8</td>
<td>18.72</td>
</tr>
<tr>
<td>1.27 (1.05; 1.55)</td>
<td>(8.60)</td>
<td>0.85 (0.67; 1.09)</td>
</tr>
</tbody>
</table>

Fluzone Quadrivalent N=221, TIV-1 (B Victoria) N=219, TIV-2 (B Yamagata) N=221

GMT Ratio (95% CI)b

<table>
<thead>
<tr>
<th>GMT</th>
<th>GMTC</th>
<th>GMTc</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.91 (1.96; 17.70)</td>
<td>6.32 (1.32; 2.66)</td>
<td>3.86 (1.96; 7.67)</td>
</tr>
</tbody>
</table>

aNCT01218646
bPer-protocol analysis set included all persons who had no study protocol deviations
cFluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)
dN is the number of participants in the per-protocol analysis set
ePooled TIV group includes participants vaccinated with either TIV-1 or TIV-2
fNon-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio of GMTs (Fluzone Quadrivalent divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >0.66

2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed

TIV-2 did not contain B/Florida/60/2008

TIV-1 did not contain B/Florida/04/2006

Table 14: Study 4: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by Seroconversion Rates at 21 Days Post-Vaccination, Adults 65 Years of Age and Older (Per-protocol Analysis Set)a

<table>
<thead>
<tr>
<th>Antigen Strain</th>
<th>Fluzone Quadrivalent N=220</th>
<th>Pooled TIV N=440</th>
<th>Seroconversion (%a)</th>
<th>Difference of Seroconversion Rate (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (H1N1)</td>
<td>65.91</td>
<td>69.77</td>
<td>3.86 (-11.50; 3.56)</td>
<td></td>
</tr>
<tr>
<td>A (H3N2)</td>
<td>69.09</td>
<td>59.32</td>
<td>9.77 (1.96; 17.20)</td>
<td></td>
</tr>
</tbody>
</table>

Fluzone Quadrivalent N=220, TIV-1 (B Victoria) N=219, TIV-2 (B Yamagata) N=221

Seroconversion (%a) | Difference of Seroconversion Rate (95% CI)b |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>28.64</td>
<td>18.72</td>
</tr>
<tr>
<td>(9.13)c</td>
<td>31.22</td>
</tr>
</tbody>
</table>

9.91 (1.96; 17.70) | 6.32 (1.32; 2.66) | 3.86 (1.96; 7.67) |

aNCT01218646
bPer-protocol analysis set included all persons who had no study protocol deviations
cFluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)
dN is the number of participants in the per-protocol analysis set
ePooled TIV group includes participants vaccinated with either TIV-1 or TIV-2
fNon-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference in seroconversion rates (Fluzone Quadrivalent minus pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >10%
gSeroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination titer ≥1:40 or a minimum 4-fold increase for participants with pre-vaccination titer ≥1:10
h2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed
iInvestigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed
jTIV-2 did not contain B/Florida/60/2008
kTIV-1 did not contain B/Florida/04/2006

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
Single-dose, prefilled syringe (pink plunger rod), without needle, 0.25 mL (NDC 49281-518-00) (not made with natural rubber latex). Supplied as package of 10 (NDC 49281-518-25).

Single-dose, prefilled syringe (clear plunger rod), without needle, 0.5 mL (NDC 49281-418-00) (not made with natural rubber latex). Supplied as package of 10 (NDC 49281-418-50).

Single-dose vial, 0.5 mL (NDC 49281-418-50) (not made with natural rubber latex). Supplied as package of 10 (NDC 49281-418-10).

Multi-dose vial, 5 mL (NDC 49281-629-78) (not made with natural rubber latex). Supplied as package of 1 (NDC 49281-629-15). A maximum of ten doses can be withdrawn from the multi-dose vial.

16.2 Storage and Handling
Store all Fluzone Quadrivalent presentations refrigerated at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Discard if vaccine has been frozen.

Do not use after the expiration date shown on the label.

17 PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling (Patient Information). Inform the vaccine recipient or guardian:

• Fluzone Quadrivalent contains killed viruses and cannot cause influenza.
• Fluzone Quadrivalent stimulates the immune system to protect against influenza, but does not prevent other respiratory infections.
• Annual influenza vaccination is recommended.
• Report adverse reactions to their healthcare provider and/or to the Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967.
• Sanofi Pasteur Inc. is maintaining a prospective pregnancy exposure registry to collect data on pregnancy outcomes and newborn health status following vaccination with Fluzone Quadrivalent during pregnancy. Women who receive Fluzone Quadrivalent during pregnancy are encouraged to contact Sanofi Pasteur Inc. directly or have their healthcare provider contact Sanofi Pasteur Inc. at 1-800-922-2463.

Vaccine Information Statements must be provided to vaccine recipients or their guardians, as required by the National Childhood Vaccine Injury Act of 1986 prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

Fluzone is a registered trademark of Sanofi Pasteur Inc.