AFLURIA QUADRIVALENT, Influenza Vaccine
Suspension for Intramuscular Injection

Initial U.S. Approval (AFLURIA QUADRIVALENT): 2016

Dosage and Administration

AFLURIA QUADRIVALENT is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. (1)

AFLURIA QUADRIVALENT is approved for use in persons 6 months of age and older. (1)

**DOSE AND ADMINISTRATION**

For intramuscular injection only, by needle and syringe (6 months and older) or by PharmaJet®Stratis® Needle-Free Injection System (18 through 64 years). (2)

**Age**  |  **Dose**  |  **Schedule**
--- | --- | ---
6 months through 35 months  |  One or two doses*, 0.25 mL each  |  If 2 doses, administer at least 1 month apart
36 months through 59 months  |  One or two doses*, 0.5 mL each  |  If 2 doses, administer at least 1 month apart
9 years and older  |  One dose, 0.5 mL  |  Not Applicable

*1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines. (U)

**DOSE FORMS AND STRENGTHS**

AFLURIA QUADRIVALENT is a suspension for injection supplied in three presentations:

- 0.25 mL pre-filled syringe (single dose) (3, 11)
- 0.5 mL pre-filled syringe (single dose) (3, 11)
- 5 mL multi-dose vial (0.25 mL or 0.5 mL) (3, 11)

**CONTRAINDICATIONS**

- Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine including egg protein, or to a previous dose of any influenza vaccine. (4, 11)
- If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give AFLURIA QUADRIVALENT should be based on careful consideration of the potential benefits and risks. (S.1)

**WARNINGS AND PRECAUTIONS**

- Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. (5.2)

**ADVERSE REACTIONS**

- In adults 18 through 64 years, the most commonly reported injection-site adverse reaction was pain (≥ 40%). The most common systemic adverse events were myalgia and headache (≥ 20%), (6.1)
- In adults 65 years of age and older, the most commonly reported injection-site adverse reaction was pain (≥ 20%). The most common systemic adverse event was myalgia (≥ 10%). (6.1)
- In children 5 through 8 years, the most commonly reported injection-site adverse reactions were pain (≥ 50%), redness and swelling (≥ 10%). The most common systemic adverse event was headache (≥ 10%). (6.1)
- In children 9 through 17 years, the most commonly reported injection-site adverse reactions were pain (≥ 50%), redness and swelling (≥ 10%). The most common systemic adverse events were headache, myalgia, and malaise and fatigue (≥ 10%). (6.1)
- In children 6 months through 35 months of age, the most commonly reported injection-site reaction were pain and redness (≥ 20%). The most common systemic adverse events were irritability (≥ 30%), diarrhea and loss of appetite (≥ 20%). (6.1)
- In children 36 through 59 months of age, the most commonly reported injection site reactions were pain (≥ 30%) and redness (≥ 20%). The most commonly reported systemic adverse events were malaise and fatigue, and diarrhea (≥ 10%). (6.1)

AFLURIA (trivalent formulation) administered by the PharmaJet Stratis Needle-Free Injection System:

- In adults 18 through 64 years of age, the most commonly reported injection-site adverse reactions were tenderness (≥ 80%), swelling, pain, redness (≥ 60%), itching (≥ 20%) and bruising (≥ 10%). The most common systemic adverse events were myalgia, malaise (≥ 30%), and headache (≥ 20%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Seqirus USA Inc. at 1-855-358-8966 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

**USE IN SPECIFIC POPULATIONS**

- The safety and effectiveness of AFLURIA QUADRIVALENT in persons less than 6 months of age have not been established. (8.4)
- Antibody responses were lower in geriatric subjects than in younger adults. (8.5)
- Pregnancy: There is a pregnancy exposure registry that monitors outcomes in women exposed to AFLURIA QUADRIVALENT during pregnancy. Enroll in the pregnancy registry by calling 1-855-358-8966 or sending an email to us.medicalinformation@seqirus.com. (8.1).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2020

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
AFLURIA® QUADRIVALENT is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

AFLURIA QUADRIVALENT is approved for use in persons 6 months of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular (IM) use only.
- By needle and syringe (6 months of age and older)
- By PharmaJet® Stratis® Needle-Free Injection System (18 through 64 years of age)

The dose and schedule for AFLURIA QUADRIVALENT are presented in Table 1.

Table 1: AFLURIA QUADRIVALENT Dosage and Schedule

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months through 35 months</td>
<td>One or two doses*, 0.25 mL each</td>
<td>If 2 doses, administer at least 1 month apart</td>
</tr>
<tr>
<td>36 months through 8 years</td>
<td>One or two doses*, 0.5 mL each</td>
<td>If 2 doses, administer at least 1 month apart</td>
</tr>
<tr>
<td>9 years and older</td>
<td>One dose, 0.5mL</td>
<td>Not Applicable</td>
</tr>
</tbody>
</table>

*1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines.

Immediately before use, shake thoroughly and inspect visually. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever suspension and container permit. If either of these conditions exists, the vaccine should not be administered.

When using the single-dose pre-filled syringe, shake the syringe thoroughly and administer the dose immediately.

When using the multi-dose vial, shake the vial thoroughly before withdrawing each dose, and administer the dose immediately. The number of needle punctures should not exceed 20 per multi-dose vial.

- Needle and Syringe: Draw up the exact dose using a separate sterile needle and syringe for each individual patient. It is recommended that small syringes (0.5 mL or 1 mL) be used to minimize any product loss.
- PharmaJet Stratis Needle-Free Injection System: For instructions on withdrawal of a 0.5 mL dose and use of the PharmaJet Stratis Needle-Free Injection System, refer to the Instructions For Use for the PharmaJet Stratis Needle-Free Injection System.

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 of the upper arm if muscle mass is adequate) in persons 12 months through 35 months of age, or the deltoid muscle of the upper arm in persons ≥ 36 months of age.

3 DOSAGE FORMS AND STRENGTHS

AFLURIA QUADRIVALENT is a sterile suspension for intramuscular injection (see Description [11]).

AFLURIA QUADRIVALENT is supplied in three presentations:
- 0.25 mL pre-filled syringe (single dose, for persons 6 months through 35 months of age)
- 0.5 mL pre-filled syringe (single dose, for persons 36 months of age and older)
- 5 mL multi-dose vial (for persons 6 months of age and older).

4 CONTRAINDICATIONS

AFLURIA QUADRIVALENT is contraindicated in individuals with known severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine including egg protein, or to a previous dose of any influenza vaccine (see Description [11]).

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give AFLURIA QUADRIVALENT should be based on careful consideration of the potential benefits and risks.

The 1976 swine influenza vaccine was associated with an increased frequency of GBS. Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear. If influenza vaccine does pose a risk, it is probably slightly more than one additional case per 1 million persons vaccinated.

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 AFLURIA QUADRIVALENT is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

5.4 Limitations of Vaccine Effectiveness

Vaccination with AFLURIA QUADRIVALENT may not protect all individuals.

6 ADVERSE REACTIONS

In adults 18 through 64 years of age, the most commonly reported injection-site adverse reaction observed in clinical studies with AFLURIA QUADRIVALENT administered by needle and syringe was pain (≥ 40%). The most common systemic adverse events observed were myalgia and headache (≥ 20%).

In adults 65 years of age and older, the most commonly reported injection-site adverse reaction observed in clinical studies with AFLURIA QUADRIVALENT administered by needle and syringe was pain (≥ 20%). The most common systemic adverse event observed was myalgia (≥ 10%).

The safety experience with AFLURIA (trivalent formulation) is relevant to AFLURIA QUADRIVALENT because both vaccines are manufactured using the same process and have overlapping compositions (see Description [11]).

In adults 18 through 64 years of age, the most commonly reported injection-site adverse reactions observed in a clinical study with AFLURIA (trivalent formulation) using the PharmaJet Stratis Needle-Free Injection System were tenderness (≥ 80%), swelling, pain, redness (≥ 60%), itching (≥ 20%) and bruising (≥ 10%). The most common systemic adverse events were myalgia, malaise (≥ 30%) and headache (≥ 20%).

In children 5 through 8 years, the most commonly reported injection-site adverse reactions when AFLURIA QUADRIVALENT was administered by needle and syringe were pain (≥ 50%) and redness and swelling (≥ 10%). The most common systemic adverse event was headache (≥ 10%).

In children 9 through 17 years, the most commonly reported injection-site adverse reactions when AFLURIA QUADRIVALENT was administered by needle and syringe were pain (≥ 50%) and redness and swelling (≥ 10%). The most common systemic adverse events were headache, myalgia, and malaise and fatigue (≥ 10%).

In children 6 months through 35 months of age, the most frequently reported injection-site reactions in the clinical study with AFLURIA QUADRIVALENT administered by needle and syringe were pain and redness (≥ 20%). The most common systemic adverse events were irritability (≥ 30%), diaphoresis and loss of appetite (≥ 20%).

In children 36 through 59 months of age, the most commonly reported injection-site reactions were pain (≥ 30%) and redness (≥ 20%). The most commonly reported systemic adverse events were malaise and fatigue, and diarrhea (≥ 10%).

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a vaccine cannot be directly compared to rates in the clinical studies of another vaccine and may not reflect the rates observed in clinical practice.

Adults

Clinical safety data for AFLURIA QUADRIVALENT in adults have been collected in one clinical trial, Study 1, a randomized, double-blind, active-controlled trial conducted in the U.S. in 3449 subjects ages 18 years and older. Subjects in the safety population received one dose of either AFLURIA QUADRIVALENT (N=1721) or one of two formulations of comparator trivalent influenza vaccine (AFLURIA, TIV-1 N=864 or TIV-2 N=864) each containing an influenza type B virus that corresponded to one of the two B viruses in AFLURIA QUADRIVALENT (a type B virus of the Yamagata lineage or a type B virus of the Victoria lineage), respectively. The mean age of the population was 58 years, 57% were female, and racial groups consisted of 82% White, 16% Black, and 2% other; 5% of subjects were Hispanic/Latino. The age sub-groups were 18 through 64 years and 65 years and older with mean ages of 43 years and 73 years, respectively. In this study, AFLURIA QUADRIVALENT and comparator trivalent influenza vaccines were administered by needle and syringe (see Clinical Studies [14]).

Local (injection-site) adverse reactions and systemic adverse events were solicited for 7 days post-vaccination (Table 2). Injection site cellulitis, cellulitis-like reactions (defined as concurrent Grade 3 pain, redness, and swelling/lump), and Grade 3 swelling/lump were monitored for 28 days post-vaccination. Unsolicited adverse events were collected for 28 days post-vaccination. Serious adverse events (SAEs), including deaths, were collected for 180 days post-vaccination.
In the 28 days following vaccination, no subject experienced cellulitis or a cellulitis-like reaction. All Grade 3 swelling/lump reactions began within 7 days of vaccination and are included in Table 2. In the 28 days following vaccination, 20.5%, 20.1%, and 20.7% of adults 18 through 64 years and 20.3%, 24.1%, and 20.0% of adults ≥ 65 years who received AFLURIA QUADRIVALENT, TIV-1, and TIV-2, respectively, reported unsolicited adverse events. Rates of individual events were similar between treatment groups, and most events were mild to moderate in severity. In the 180 days following vaccination, 2.3%, 1.6%, and 1.5% of all subjects who received AFLURIA QUADRIVALENT, TIV-1, and TIV-2, respectively, experienced SAEs, including six deaths, five in the AFLURIA QUADRIVALENT group and one in the TIV-2 group. The majority of SAEs occurred after Study Day 28 and in subjects ≥ 65 years of age who had co-morbid illnesses. No SAEs or deaths appeared related to the study vaccines.

Safety information has also been collected in a clinical study of AFLURIA (trivalent formulation) administered using the PharmaJet Strats Needle-Free Injection System (Study 2). Study 2 included 1,247 subjects for safety analysis, aged 18 through 64 years, randomized to receive AFLURIA by either the PharmaJet Strats Needle-Free Injection System (624 subjects) or needle and syringe (623 subjects). No deaths or vaccine-related serious adverse events were reported in Study 2. Local (injection-site) adverse reactions and systemic adverse events were solicited for 7 days post-vaccination (Table 3).

### Table 2: Proportion of Subjects Per Age Cohort with Any Solicited Local Adverse Reactions or Systemic Adverse Events within 7 Days after Administration of AFLURIA QUADRIVALENT or Trivalent Influenza Vaccine (Study 1)

<table>
<thead>
<tr>
<th>Local Adverse Reactions</th>
<th>Subjects 18 through 64 years</th>
<th>Subjects ≥ 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFLURIA Quadrivalent</td>
<td>N=854 c</td>
<td>N=428 a</td>
</tr>
<tr>
<td>Pain</td>
<td>47.9 0.7</td>
<td>43.7 1.0</td>
</tr>
<tr>
<td>Swelling/Lump</td>
<td>3.7 0.1</td>
<td>2.3 0.2</td>
</tr>
<tr>
<td>Redness</td>
<td>2.9 0.2</td>
<td>2.8 0.2</td>
</tr>
<tr>
<td>Myalgia (muscle ache)</td>
<td>25.5 1.9</td>
<td>23.5 1.4</td>
</tr>
<tr>
<td>Head-ache</td>
<td>21.7 1.7</td>
<td>15.2 0.9</td>
</tr>
<tr>
<td>Malaise</td>
<td>8.9 0.7</td>
<td>9.1 0.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.9 0.6</td>
<td>7.7 0.5</td>
</tr>
<tr>
<td>Chills</td>
<td>4.8 0.6</td>
<td>4.4 0.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.5 0.4</td>
<td>0.9 0.2</td>
</tr>
<tr>
<td>Fever</td>
<td>1.1 0.4</td>
<td>0.9 0.5</td>
</tr>
</tbody>
</table>

Local Adverse Reactions & Systemic Adverse Events within 7 Days after Administration of AFLURIA (trivalent formulation) by PharmaJet Strats Needle-Free Injection System or Needle and Syringe (Study 2)

### Table 3: Proportion of Subjects 18 through 64 Years of Age with Solicited Local Adverse Reactions or Systemic Adverse Events within 7 Days after Administration of AFLURIA (trivalent formulation) by PharmaJet Strats Needle-Free Injection System or Needle and Syringe

<table>
<thead>
<tr>
<th>Systemic Adverse Events</th>
<th>Subjects 18 through 64 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFLURIA (trivalent formulation)</td>
<td>N=540-616 c</td>
</tr>
<tr>
<td>Tenderness</td>
<td>89.4 0.8</td>
</tr>
<tr>
<td>Swelling</td>
<td>64.8 1.7</td>
</tr>
<tr>
<td>Malaise</td>
<td>31.2 0.7</td>
</tr>
<tr>
<td>Headache</td>
<td>24.7 1.3</td>
</tr>
<tr>
<td>Chills</td>
<td>7.0 0.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.6 0.2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.3 0.2</td>
</tr>
<tr>
<td>Fever</td>
<td>0.3 0.0</td>
</tr>
</tbody>
</table>

Abbreviations: Gr 3, Grade 3.

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a) NCT01688921
b) Proportion of subjects reporting each local adverse reaction or systemic adverse event by study vaccine group based on the number of subjects contributing at least one data value for an individual sign/symptom.

### Abbreviations

- N = number of subjects in the Safety Population for each study vaccine group.
- NCT02214225
- N = number of subjects in the Safety Population for each treatment group. Denominators for the PharmaJet Strats Needle-Free Injection System group were: N=540 for itching and N=450-616 for all other parameters. Denominators for the needle and syringe group were: N=572 for itching and N=599-606 for all other parameters.
- Local adverse reactions: Grade 3 pain, tenderness or itching that prevents daily activity; swelling, redness or bruising: any = ≥ 25mm diameter, Grade 3 = >100mm diameter.
- Systemic adverse events: Fever: any = ≥ 100.4°F (Oral), Grade 3 = ≥ 102.2°F (Oral); Grade 3 for all other adverse events is that which prevents daily activity.
- Myalgia (muscle ache) is that which prevents daily activity.
- Itching: any = ≥ 25mm diameter, Grade 3 = >100mm diameter.
- Head-ache
- Malaise
- Nausea
- Chills
- Vomiting
- Fever

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**Children 5 Years Through 17 Years of Age**

Clinical safety data for AFLURIA QUADRIVALENT in older children and adolescents have been collected in one clinical trial, Study 3, a randomized, observer-blinded, comparator-controlled trial conducted in the U.S. in 2278 subjects aged 5 through 17 years. Subjects were stratified into one of two age cohorts of 5 through 8 years or 9 through 17 years (51.2% and 48.8% of the study population, respectively). The mean age of the population was 9.5 years, 52.1% were male, and racial groups consisted of 73.3% White, 20.7% Black, 0.8% Asian, 0.3% American Indian/Native American, and 0.7% Native Hawaiian/Pacific Islander; 23.8% of subjects were Hispanic/Latino. The mean ages of subjects aged 5 through 8 years and 9 through 17 years were 7.6 and 12.5 years, respectively. Subjects in the safety population (N=2252) received either AFLURIA QUADRIVALENT (N=1692) or a U.S.-licensed comparator quadrivalent influenza vaccine (N=560). Study subjects were scheduled to receive either a single vaccination or two vaccinations 28 days apart based on their previous vaccination history. In this study, AFLURIA QUADRIVALENT and comparator vaccine were administered by needle and syringe (see Clinical Studies [14]). Local (injection site) adverse reactions and systemic adverse events were solicited for 7 days post-vaccination. Cellulitis-like reactions (defined as concurrent Grade 3 pain, redness, and swelling/lump) at the injection site were monitored for 28 days post-vaccination. Subjects were instructed to report and return to clinic within 24 hours in the event of a cellulitis-like reaction. Unsolicited adverse events were collected for 28 days post-vaccination. All solicited local adverse reactions and systemic adverse events following any vaccination (first or second dose) are presented in Table 4.
Table 4: Proportion of Subjects Per Age Cohort with Any Solicited Local Adverse Reactions or Systemic Adverse Events within 7 Days after Administration of AFLURIA QUADRIVALENT or Comparator (Study 3)*

<table>
<thead>
<tr>
<th>Subjects 5 through 8 years</th>
<th>Subjects 9 through 17 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AFLURIA QUADRIVALENT</strong></td>
<td><strong>Comparator</strong></td>
</tr>
<tr>
<td>N= 828-829</td>
<td>N= 273-274</td>
</tr>
<tr>
<td><strong>AFLURIA QUADRIVALENT</strong></td>
<td><strong>Comparator</strong></td>
</tr>
<tr>
<td>N= 790-792</td>
<td>N= 261</td>
</tr>
</tbody>
</table>

**Local Adverse Reactions**

<table>
<thead>
<tr>
<th>Event</th>
<th>Gr 3</th>
<th>Gr 3</th>
<th>Gr 3</th>
<th>Gr 3</th>
<th>Gr 3</th>
<th>Gr 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>51.3</td>
<td>0.8</td>
<td>49.6</td>
<td>0.7</td>
<td>51.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Redness</td>
<td>19.4</td>
<td>3.5</td>
<td>18.6</td>
<td>1.8</td>
<td>14.8</td>
<td>1.9</td>
</tr>
<tr>
<td>Swelling/Lump</td>
<td>15.3</td>
<td>3.4</td>
<td>12.4</td>
<td>2.2</td>
<td>12.2</td>
<td>2.0</td>
</tr>
</tbody>
</table>

**Systemic Adverse Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Gr 3</th>
<th>Gr 3</th>
<th>Gr 3</th>
<th>Gr 3</th>
<th>Gr 3</th>
<th>Gr 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>12.2</td>
<td>0.1</td>
<td>10.6</td>
<td>0.4</td>
<td>18.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Myalgia</td>
<td>9.8</td>
<td>0.1</td>
<td>11.3</td>
<td>0.4</td>
<td>16.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Malaise and Fatigue</td>
<td>8.8</td>
<td>0.4</td>
<td>5.8</td>
<td>0.0</td>
<td>10.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Nausea</td>
<td>7.1</td>
<td>0.1</td>
<td>8.4</td>
<td>0.0</td>
<td>7.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.2</td>
<td>0.6</td>
<td>3.6</td>
<td>0.4</td>
<td>5.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Fever</td>
<td>4.5</td>
<td>1.2</td>
<td>3.6</td>
<td>0.7</td>
<td>2.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.4</td>
<td>0.2</td>
<td>4.4</td>
<td>0.8</td>
<td>1.8</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Abbreviations: Gr 3, Grade 3 (severe); Comparator, Comparator quadrivalent influenza vaccine [Fluarix® Quadrivalent (Sanofi Pasteur)]

Table 5: Proportion of Subjects Per Age Cohort with Any Solicited Local Adverse Reactions or Systemic Adverse Events within 7 Days after Administration of AFLURIA QUADRIVALENT or Comparator QIV (Study 4)*

<table>
<thead>
<tr>
<th>Subjects 6 through 35 months</th>
<th>Subjects 36 through 59 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AFLURIA QUADRIVALENT</strong></td>
<td><strong>Comparator</strong></td>
</tr>
<tr>
<td>N= 688-689</td>
<td>N= 226-227</td>
</tr>
<tr>
<td><strong>AFLURIA QUADRIVALENT</strong></td>
<td><strong>Comparator</strong></td>
</tr>
<tr>
<td>N= 947-949</td>
<td>N= 317-318</td>
</tr>
</tbody>
</table>

**Local Adverse Reactions**

<table>
<thead>
<tr>
<th>Event</th>
<th>Gr 3</th>
<th>Gr 3</th>
<th>Gr 3</th>
<th>Gr 3</th>
<th>Gr 3</th>
<th>Gr 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>20.8</td>
<td>0.1</td>
<td>25.6</td>
<td>0.4</td>
<td>35.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Redness</td>
<td>20.8</td>
<td>0.6</td>
<td>17.6</td>
<td>1.8</td>
<td>22.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Swelling/Lump</td>
<td>6.1</td>
<td>0.4</td>
<td>6.2</td>
<td>0.9</td>
<td>10.1</td>
<td>1.7</td>
</tr>
</tbody>
</table>

**Systemic Adverse Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Gr 3</th>
<th>Gr 3</th>
<th>Gr 3</th>
<th>Gr 3</th>
<th>Gr 3</th>
<th>Gr 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritability</td>
<td>32.9</td>
<td>0.7</td>
<td>28.2</td>
<td>0.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24.2</td>
<td>0.1</td>
<td>25.6</td>
<td>0.4</td>
<td>12.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Loss of Appetite</td>
<td>20.0</td>
<td>0.3</td>
<td>19.4</td>
<td>0.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nasal Obstruction</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>14.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Myalgia</td>
<td>-</td>
<td>-</td>
<td>9.9</td>
<td>0.1</td>
<td>9.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>9.4</td>
<td>0.7</td>
<td>11.0</td>
<td>0.0</td>
<td>9.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Headache</td>
<td>-</td>
<td>-</td>
<td>6.2</td>
<td>0.4</td>
<td>5.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Fever 1</td>
<td>7.2</td>
<td>2.5</td>
<td>11.9</td>
<td>2.6</td>
<td>4.8</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Abbreviations: Gr 3, Grade 3 (severe); Comparator, Comparator quadrivalent influenza vaccine [Fluzone® Quadrivalent (Sanofi Pasteur)]

References:
[1] NCT02545543
[2] NCT02914275
[3] NCT02914275
[4] NCT02914275
[5] NCT02914275
[6] NCT02914275
[7] NCT02914275
[8] NCT02914275
[9] NCT02914275
[10] NCT02914275

6.2 Postmarketing Experience

Because postmarketing reporting of adverse events is voluntary and from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. The adverse events described have been included in this section because they: 1) represent reactions that are known to occur following vaccinations generally or influenza immunizations specifically; 2) are potentially serious; or 3) have been reported frequently. There are limited postmarketing data available for AFLURIA QUADRIVALENT. The adverse events listed below reflect experience in both children and adults and include those identified during post-approval use of AFLURIA (trivalent formulation) outside the U.S. since 1985.
The post-marketing experience with AFLURIA (trivalent formulation) included the following:

**Blood and lymphatic system disorders**
Thrombocytopenia

**Immune system disorders**
Allergic or immediate hypersensitivity reactions including anaphylactic shock and serum sickness

**Nervous system disorders**
Neuralgia, paresthesia, convulsions (including febrile seizures), encephalomyelitis, encephalopathy, neuritis or neuropathy, transverse myelitis, and GBS

**Vascular disorders**
Vasculitis which may be associated with transient renal involvement

**Skin and subcutaneous tissue disorders**
Pruritus, urticaria, and rash

General disorders and administration site conditions
Cellulitis and large injection site swelling

**Influenza-like illness**

7 **DRUG INTERACTIONS**
No interaction studies have been performed on interaction between influenza vaccines in general and other vaccines or medications.

8 **USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy

**Pregnancy Exposure Registry**
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to AFLURIA QUADRIVALENT during pregnancy. Women who are vaccinated with AFLURIA QUADRIVALENT during pregnancy are encouraged to enroll in the registry by calling 1-855-358-8966 or sending an email to Seqirus at us.medicalinformation@seqirus.com.

**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. Data for AFLURIA (trivalent formulation) administered to pregnant women are relevant to AFLURIA QUADRIVALENT because both vaccines are manufactured using the same process and have overlapping compositions (see Description [11]). There are limited data for AFLURIA QUADRIVALENT administered to pregnant women, and available data for AFLURIA (trivalent formulation) administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

There were no developmental toxicity studies of AFLURIA QUADRIVALENT performed in animals. A developmental toxicity study of AFLURIA (trivalent formulation) has been performed in female rats administered a single human dose (0.5 mL (divided)) of AFLURIA (trivalent formulation) prior to mating and during gestation. This study revealed no evidence of harm to the fetus due to AFLURIA (trivalent formulation) (see 8.1 Data).

**Clinical Considerations**

**Disease-associated Maternal and/or Embryo-Fetal Risk**
Pregnant women are at increased risk for severe illness due to influenza compared to non-pregnant women. Pregnant women with influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

**Data**

**Animal Data**
In a developmental toxicity study, female rats were administered a single human dose [0.5 mL (divided)] of AFLURIA (trivalent formulation) by intramuscular injection 21 days and 7 days prior to mating, and on gestation day 6. Some rats were administered an additional dose on gestation day 20. No vaccine-related fetal malformations or variations or no adverse effects on pre-weaning development were observed in the study.

8.2 Lactation

**Risk Summary**
It is not known whether AFLURIA QUADRIVALENT is excreted in human milk. Data are not available to assess the effects of AFLURIA 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 AFLURIA QUADRIVALENT and any potential adverse effects on the breastfed child from AFLURIA QUADRIVALENT or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

The safety and effectiveness of AFLURIA QUADRIVALENT in persons less than 6 months of age have not been established. The Pharmalet Stratis Needle-Free Injection System is not approved as a method of administering AFLURIA QUADRIVALENT to children and adolescents less than 18 years of age due to lack of adequate data supporting safety and effectiveness in this population.

8.5 Geriatric Use

In clinical studies, AFLURIA QUADRIVALENT has been administered to, and safety information collected for, 867 subjects aged 65 years and older (see Adverse Reactions [6]). The 65 years and older age group included 539 subjects 65 through 74 years and 328 subjects 75 years and older. After administration of AFLURIA QUADRIVALENT, hemagglutination-inhibiting antibody responses were non-inferior to comparator trivalent influenza (TIV-1 and TIV-2) in persons 65 years of age and older, but were lower than younger adult subjects (see Clinical Studies [14]).

The Pharmalet Stratis Needle-Free Injection System is not approved as a method of administering AFLURIA QUADRIVALENT to adults 65 years of age and older due to lack of adequate data supporting safety and effectiveness in this population.

11 DESCRIPTION

AFLURIA QUADRIVALENT, Influenza Vaccine for intramuscular injection, is a sterile, clear, colorless to slightly opalescent suspension with some sediment that resuspends upon shaking to form a homogeneous suspension. AFLURIA QUADRIVALENT is prepared from influenza virus propagated in the allantoic fluid of embryonated chicken eggs. Following harvest, the virus is purified in a sucrose density gradient using continuous flow zonal centrifugation. The purified virus is inactivated with beta-propiolactone, and the virus particles are disrupted using sodium taurodeoxycholate to produce a “split virion”. The disrupted virus is further purified and suspended in a phosphate buffered isotonic solution.

AFLURIA QUADRIVALENT is standardized according to USP8 requirements for the 2020-2021 influenza season and is formulated to contain 60 mcg hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 mcg HA for each of the four influenza strains recommended for the 2020-2021 Northern Hemisphere influenza season: A/Victoria/2454/2019 (H1N1) pdm09-like virus, A/Hong Kong/2671/2019 (H1N1) (H3N2)-like virus, B/Victoria/705/2018 BVR-1 (A/B/Washington/02/2019-like virus) and B/Phuket/3073/2013 BVR-18 (B/Phuket/3073/2013-like virus). A 0.25 mL dose contains 7.5 mcg HA of each of the same four influenza strains.

Thimerosal, a mercury derivative, is not used in the manufacturing process for the single dose presentation. This presentation does not contain preservative. The multi-dose presentation contains thimerosal added as a preservative; each 0.5 mL dose contains 24.5 mcg of mercury and each 0.25 mL dose contains 12.25 mcg of mercury.

A single 0.5 mL dose of AFLURIA QUADRIVALENT contains sodium chloride (4.1 mg), monobasic sodium phosphate (80 mcg), dibasic sodium phosphate (300 mcg), monobasic potassium phosphate (20 mcg), potassium chloride (20 mcg), and calcium chloride (0.5 mcg). From the manufacturing process, each 0.5 mL dose may also contain residual amounts of sodium taurodeoxycholate (≤ 10 ppm), ovalbumin (< 1 mcg), sucrose (< 10 mcg), neomycin sulfate (< 81.8 nanograms [ng]), polymyxin B (≤ 14 ng), beta-propiolactone (≤ 1.5 ng) and hydrocortisone (≤ 0.56 ng). A single 0.25 mL dose of AFLURIA QUADRIVALENT contains half of these quantities. The rubber tip cap and plunger used for the preservative-free, single-dose syringes and the rubber stoppers used for the multi-dose vial were not made with natural rubber latex.

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. For example, since 1977 antigenic variants of influenza A (H1N1 and H3N2) 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. Specific levels of hemagglutination inhibition (HI) antibody titers post-vaccination with inactivated influenza vaccine have not been correlated with protection from influenza virus. In some human studies, antibody titers of 1:40 or greater have been associated with protection from influenza illness in up to 50% of subjects.1,2 Antibody against one influenza virus type or subtype confers limited or no protection against another. Furthermore, antibody 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 to one or more new strains in each year’s influenza vaccine. Therefore, inactivated influenza vaccines are standardized to contain the HA of four strains (i.e., typically two type A and two type B) representing the influenza viruses likely to be circulating in the U.S. during the upcoming winter.

Annual revaccination with the current vaccine is recommended because immunity declines year to year.1

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

AFLURIA QUADRIVALENT has not been evaluated for carcinogenic or mutagenic potential, or male infertility in animals. A developmental toxicity study conducted in rats vaccinated with AFLURIA (trivalent formulation) revealed no impact on female fertility (see Pregnancy [8.1]).

14 CLINICAL STUDIES

14.1 Efficacy Against Laboratory-Confirmed Influenza

The efficacy of AFLURIA (trivalent formulation) is relevant to AFLURIA QUADRIVALENT because both vaccines are manufactured using the same process and have overlapping compositions (see Description [11]).

The efficacy of AFLURIA (trivalent formulation) was demonstrated in Study 5, a randomized, observer-blind, placebo-controlled study conducted in 15,044 subjects. Healthy subjects 18 through 64 years of age were randomly assigned in a 2:1 ratio to receive a single dose of AFLURIA (trivalent formulation) (enrolled subjects: 10,033; evaluable subjects: 9,889) or placebo (enrolled subjects: 5,011; evaluable subjects: 4,960). The mean age of all randomized
subjects was 35.5 years. 54.4% were female and 90.2% were White. Laboratory-confirmed influenza was assessed by active and passive surveillance of influenza-like illness (ILI) beginning 2 weeks post-vaccination until the end of the influenza season, approximately 6 months post-vaccination. ILI was defined as at least one respiratory symptom (e.g., cough, sore throat, nasal congestion) and at least one systemic symptom (e.g., oral temperature of 100.0°F or higher, feverishness, chills, body aches). Nasal and throat swabs were collected from subjects who presented with an ILI for laboratory confirmation by viral culture and real-time reverse transcription polymerase chain reaction. Influenza virus strain was further characterized using gene sequencing and pyrosequencing.

Attack rates and vaccine efficacy, defined as the relative reduction in the influenza infection rate for AFLURIA (trivalent formulation) compared to placebo, were calculated using the per protocol population. Vaccine efficacy against laboratory-confirmed influenza infection due to influenza A or B virus strains contained in the vaccine was 60% with a lower limit of the 95% CI of 41% (Table 6).

Table 6: AFLURIA (trivalent formulation): Laboratory-Confirmed Influenza Infection Rate and Vaccine Efficacy in Adults 18 through 64 Years of Age (Study 5)*

<table>
<thead>
<tr>
<th>Subjects†</th>
<th>Laboratory-Confirmed Influenza Cases</th>
<th>Influenza Infection Rate</th>
<th>Vaccine Efficacy‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N</td>
<td>n/N %</td>
<td>%</td>
</tr>
<tr>
<td>Vaccine-matched Strains</td>
<td>AFLURIA 9889</td>
<td>58</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>Placebo 4960</td>
<td>73</td>
<td>1.47</td>
</tr>
<tr>
<td>Any Influenza Virus Strain</td>
<td>AFLURIA 9889</td>
<td>222</td>
<td>2.24</td>
</tr>
<tr>
<td></td>
<td>Placebo 4960</td>
<td>192</td>
<td>3.87</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval. *M.T.00062484 †The Per Protocol Population was identical to the Evaluable Population in this study. ‡Vaccine efficacy = 1 minus the ratio of AFLURIA (trivalent formulation)/placebo infection rates. The objective of the study was to demonstrate that the lower limit of the CI for vaccine efficacy was greater than 40%.

14.2 Immunogenicity of AFLURIA QUADRIVALENT in Adults and Older Adults Administered by Needle and Syringe

Study 1 was a randomized, double-blind, active-controlled trial conducted in the U.S. in adults aged 18 years of age and older. Subjects received one dose of either AFLURIA QUADRIVALENT (N=1691) or one of two formulations of comparator trivalent influenza vaccine (AFLURIA, TIV-1 N=854 or TIV-2 N=850) each containing an influenza type B virus that corresponded to one of the two B viruses in AFLURIA QUADRIVALENT (a type B virus of the Yamagata lineage or a type B virus of the Victoria lineage, respectively).

Post-vaccination immunogenicity was evaluated on sera obtained 21 days after administration of a single dose of AFLURIA QUADRIVALENT or TIV comparator. The co-primary endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted for baseline HI titers) and the difference in seroconversion rates for each vaccine strain, 21 days after vaccination. Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the GMT ratio (TIV/AFLURIA QUADRIVALENT) did not exceed 1.5 and the upper bound of the 2-sided 95% CI of the seroconversion rate difference (TIV minus AFLURIA QUADRIVALENT) did not exceed 10.0% for each strain.

Serum HI antibody responses to AFLURIA QUADRIVALENT were non-inferior to both TIVs for all influenza strains for subjects 18 years of age and older. Additionally, non-inferiority was demonstrated for both endpoints in both age sub-groups, adults aged 18 through 64 years and 65 years and older, for all strains (Table 7). Superiority of the immune response to each of the influenza B strains contained in AFLURIA QUADRIVALENT was shown relative to the antibody response to vaccination with TIV formulations not containing that B lineage strain for subjects 18 years of age and older. Superiority against the alternate B strain was also demonstrated for each of the influenza B strains in both age sub-groups; 18 through 64 years and 65 years and older. Post-hoc analyses of immunogenicity endpoints by gender did not demonstrate meaningful differences between males and females. The study population was not sufficiently diverse to assess differences between races or ethnicities.

Table 7: Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of Non-Inferiority of AFLURIA QUADRIVALENT Relative to Trivalent Influenza Vaccine (TIV) by Age Cohort (Study 1)*

<table>
<thead>
<tr>
<th>Strain</th>
<th>Post-vaccination GMT</th>
<th>GMT Ratiob</th>
<th>Seroconversion %c</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFLURIA Quadrivalent</td>
<td>Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria)</td>
<td>0.93 (0.85, 1.02)</td>
<td>51.3</td>
<td>-2.1% (4.9, 2.7)</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>0.91 (0.83, 0.99)</td>
<td>56.3</td>
<td>-4.6% (9.0, 0.2)</td>
</tr>
<tr>
<td>B/Massachusetts/2/2012 (B Yamagata)</td>
<td>92.3</td>
<td>79.3</td>
<td>0.86 (0.76, 0.97)</td>
<td>45.7</td>
</tr>
<tr>
<td>B/Brisbane/60/2008 (B Victoria)</td>
<td>110.7</td>
<td>95.2</td>
<td>0.86 (0.76, 0.98)</td>
<td>57.6</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; GMT, geometric mean titer. *M.T.00341225 †GMT ratio was computed after fitting a multi-variable model on the post-vaccination titers including sex, vaccination history, pre-vaccination HI titers and other factors. ‡Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer ≥ 1:10 or an increase in titer from < 1:10 to ≥ 1:40. §Non-inferiority (NI) criterion for the GMT ratio: upper bound of 2-sided 95% CI on the GMT ratio of Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria)/AFLURIA QUADRIVALENT should not exceed 1.5. NI criterion for the SCR difference: upper bound of 2-sided 95% CI on the difference between SCR Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria) minus AFLURIA QUADRIVALENT should not exceed 10%.

14.3 Immunogenicity of AFLURIA (trivalent formulation) Administered by Pharmaset Stratis Needle-Free Injection System

Study 2 was a randomized, comparator-controlled, non-inferiority study that enrolled 1,250 subjects 18 through 64 years of age. This study compared the immune response following administration of AFLURIA (trivalent formulation) when delivered intramuscularly using either the Pharmaset Stratis Needle-Free Injection System or needle and syringe. Immunogenicity assessments were performed prior to vaccination and at 28 days after vaccination in the immunogenicity population (1130 subjects, 562 Pharmaset Stratis Needle-Free Injection System group, 568 needle and syringe group). The co-primary endpoints were HI GMT ratios for each vaccine strain and the absolute difference in seroconversion rates for each vaccine strain 28 days after vaccination. As shown in Table 8, non-inferiority of administration of AFLURIA (trivalent formulation) by the Pharmaset Stratis Needle-Free Injection System compared to administration of AFLURIA (trivalent formulation) by needle and syringe was demonstrated in the immunogenicity population for all strains. Post-hoc analyses of immunogenicity by age showed that younger subjects (18 through 49 years) elicited higher immunological responses than older subjects (50 through 64 years). Post-hoc analyses of immunogenicity according to sex and body mass
index did not reveal significant influences of these variables on immune responses. The study population was not sufficiently diverse to assess immunogenicity by race or ethnicity.

### Table 8: Baseline and Post-Vaccination HI Antibody GMTs, Serumconversion Rates, and Analyses of Non-Inferiority of AFLURIA (trivalent formulation) Administered by Pharmatek Stratis Needle-Free Injection System or Needle and Syringe, Adults 18 through 64 Years of Age (Study 2)*

<table>
<thead>
<tr>
<th>Strain</th>
<th>Baseline GMT</th>
<th>Post-vaccination GMT</th>
<th>GMT Ratio a</th>
<th>Serumconversion % b</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needle and Syringe N=568</td>
<td>70.8</td>
<td>79.2</td>
<td>1.12</td>
<td>38.4</td>
<td>37.5</td>
</tr>
<tr>
<td>Needle and Syringe N=562</td>
<td>70.8</td>
<td>79.2</td>
<td>1.12</td>
<td>38.4</td>
<td>37.5</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; GMT, geometric mean titer.

* NCT0188921

The co-primary endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted for baseline HI titers and other covariates) and seroconversion rates for each vaccine strain, 28 days after the last vaccination. Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the GMT ratio (Comparator/AFLURIA QUADRIVALENT) did not exceed 1.5. NI criterion for the GMT ratio: upper bound of 2-sided 95% CI on the GMT ratio of Needle and Syringe/PharmaJet Stratis Needle-Free Injection System should not exceed 10.0.

14.4 Immunogenicity of AFLURIA QUADRIVALENT in Children 5 through 17 Years Administered via Needle and Syringe

Study 3 was a randomized, observer-blinded, comparator-controlled trial conducted in the U.S. in children 5 through 17 years of age. A total of 2274 children were randomized 2:1 to receive one or two doses of AFLURIA QUADRIVALENT (N=1137) or a U.S.-licensed comparator quadrivalent influenza vaccine (N=1137). Subjects 5 through 8 years of age were eligible to receive a second dose at least 28 days after the first dose depending on their vaccination history, consistent with the 2015-2016 recommendations of the Advisory Committee on Immunization Practices (ACIP) for Prevention and Control of Seasonal Influenza with Vaccines. Approximately 25% of subjects in each treatment group in the 5 through 8 years of age sub-group received two vaccine doses.

Baseline serology for HI assessment was collected prior to vaccination. Post-vaccination immunogenicity was evaluated by HI assay on sera obtained 28 days after the last vaccination dose.

The primary objective was to demonstrate that vaccination with AFLURIA QUADRIVALENT elicits an immune response that is not inferior to that of a comparator vaccine containing the same recommended virus strains. The Per Protocol Population (AFLURIA QUADRIVALENT n=1605, Comparator n=528) was used for the primary endpoint analyses. The co-primary endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted for baseline HI titers and other covariates) and seroconversion rates for each vaccine strain, 28 days after the last vaccination. Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the GMT ratio (Comparator/AFLURIA QUADRIVALENT) did not exceed 1.5. NI criterion for the GMT ratio: upper bound of 2-sided 95% CI on the difference between SCR Needle and Syringe – SCR PharmaJet Stratis Needle-Free Injection System should not exceed 10.

### Table 9: Post-Vaccination HI Antibody GMTs, SRCS, and Analyses of Non-Inferiority of AFLURIA QUADRIVALENT Relative to a U.S.-Licensed Comparator Quadrivalent Influenza Vaccine for each Strain 28 Days after Last Vaccination Among a Pediatric Population 5 through 17 Years of Age (Per Protocol Population) (Study 3)*

<table>
<thead>
<tr>
<th>Strain</th>
<th>Post-vaccination GMT</th>
<th>GMT Ratio c</th>
<th>Seroconversion % d</th>
<th>SCR Difference *</th>
<th>Met both pre-defined non-inferiority criteria? b</th>
</tr>
</thead>
<tbody>
<tr>
<td>A(H1N1)</td>
<td>95.2 (n=1604)</td>
<td>1.01 (0.93, 1.09)</td>
<td>66.4 (64.0, 68.7)</td>
<td>63.3 (59.0, 67.4)</td>
<td>-3.1 (-8.0, 1.8)</td>
</tr>
<tr>
<td>A(H3N2)</td>
<td>88.6 (n=1604)</td>
<td>1.05 (0.96, 1.15)</td>
<td>82.9 (81.0, 84.7)</td>
<td>83.3 (79.9, 86.4)</td>
<td>0.4 (-0.5, 3.3)</td>
</tr>
<tr>
<td>B/Phuket/07/2013 (B/Yamagata)</td>
<td>60.9 (n=1604)</td>
<td>0.89 (0.81, 0.98)</td>
<td>58.5 (56.0, 60.9)</td>
<td>55.1 (50.8, 59.4)</td>
<td>-3.4 (-8.3, 1.5)</td>
</tr>
<tr>
<td>B/Brisbane/60/2008 (B/Victoria)</td>
<td>145.0 (n=1604)</td>
<td>0.92 (0.83, 1.02)</td>
<td>72.1 (69.8, 74.2)</td>
<td>70.1 (66.0, 74.4)</td>
<td>2.0 (-6.9, 2.9)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; Comparator, Comparator quadrivalent influenza vaccine (Fluarix® Quadrivalent Influenza Vaccine [GlaxoSmithKline Biologicals]); GMT (adjusted), geometric mean titer; SCR, seroconversion rate.

* NCT02345543

The Per-Protocol Population comprised all subjects in the Evaluable Population who did not have any protocol violations that were medically assessed as potentially impacting on immunogenicity results.

1 GMT Ratio = Comparator/AFLURIA QUADRIVALENT. Adjusted analysis model: Log-transformed Post-Vaccination HI Titer-Vaccine = Age Strata (5-8, 9-17) + Gender + Vaccination History (yes) + Log-transformed Pre-Vaccination HI Titer + Site + Number of Doses (1 vs 2) + Age Strata*Vaccine. The Age Strata*Vaccine interaction term was excluded from the model fit for the strains B/Yamagata and B/Victoria as the interaction result was non-significant (p>0.05). Least square means were back transformed.

2 Seroconversion rate was defined as the percentage of subjects with either a pre-vaccination HI titer ≤ 1:10 and a post-vaccination HI titer > 1:40 or a pre-vaccination HI titer > 1:10 and a 4-fold increase in post-vaccination HI titer.

3 Seroconversion rate difference = Comparator SCR percentage minus AFLURIA QUADRIVALENT SCR percentage.

4 NI criterion for the GMT ratio: upper bound of two-sided 95% CI on the GMT ratio of Comparator AFLURIA QUADRIVALENT should not exceed 1.5. NI criterion for the SCR difference: upper bound of two-sided 95% CI on the difference between SCR Comparator - AFLURIA QUADRIVALENT should not exceed 10.

5 Subject 840394-0046 was excluded from the Per-Protocol Population for the adjusted GMT analysis for the GMT ratio since the subject did not have information on all covariates (unknown pre-vaccination history).

14.5 Immunogenicity of AFLURIA QUADRIVALENT in Children 6 Months through 59 Months Administered by Needle and Syringe

Study 4 was a randomized, observer-blind, comparator-controlled trial conducted in the U.S. children 6 months through 59 months of age. A total of 2247 children were randomized 3:1 to receive AFLURIA QUADRIVALENT (N=1124) or a U.S.-licensed comparator quadrivalent influenza vaccine (N=1123). Children 6 months through 35 months received one or two 0.25 mL doses and children 36 months through 59 months received one or two 0.5 mL doses. Subjects were eligible to receive a second dose at least 28 days after the first dose depending on their influenza vaccination history, consistent with the 2016-2017 recommendations of the Advisory Committee on Immunization Practices (ACIP) for Prevention and Control of Seasonal Influenza with Vaccines. Approximately 40% of subjects in each treatment group received two vaccine doses.

Baseline serology for HI assessment was collected prior to vaccination. Postvaccination immunogenicity was evaluated by HI assay on sera obtained 28 days after the last vaccination dose.

The primary objective was to demonstrate that vaccination with AFLURIA QUADRIVALENT elicits an immune response that is not inferior to that of a comparator vaccine containing the same recommended virus strains. The Per Protocol Population (AFLURIA QUADRIVALENT n=1456, Comparator n=484) was used for the primary endpoint analyses. The co-primary endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted for baseline HI titers and other covariates) and seroconversion rates for each vaccine strain, 28 days after the last vaccination. Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the GMT ratio (Comparator/AFLURIA QUADRIVALENT) did not exceed 1.5 and the upper bound of the 2-sided 95% CI of the seroconversion rate difference (Comparator minus AFLURIA QUADRIVALENT) did not exceed 10.0% for each strain. Serum HI antibody responses to AFLURIA QUADRIVALENT were non-inferior for both GMT ratio and seroconversion rates relative to the comparator vaccine for all influenza strains (Table 10). Analyses of immunogenicity endpoints by gender did not demonstrate meaningful differences between males and females. The study population was not sufficiently diverse to assess differences among races or ethnicities.
Table 10: Post-Vaccination HI Antibody GMTs, SCRs, and Analyses of Non-Inferiority of AFLURIA QUADRIVALENT Relative to a U.S.-Licensed Comparator Quadrivalent Influenza Vaccine for each Strain 28 Days after Last Vaccination Among a Pediatric Population 6 through 59 Months of Age (Per Protocol Population) (Study 4)\(^a\)

<table>
<thead>
<tr>
<th>Strain</th>
<th>Post-vaccination GMT</th>
<th>GMT Ratio (^a)</th>
<th>Seroconversion % &lt;b&gt;(^a)</th>
<th>SCR Difference &lt;b&gt;(^a)</th>
<th>Met both pre-defined non-inferiority criteria? &lt;i&gt;(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A(H1N1)</td>
<td>353.5 (n=1455 (^a))</td>
<td>0.79 (0.72, 0.88)</td>
<td>79.1 (76.9, 81.1) (n=1456)</td>
<td>68.8 (64.5, 72.9) (n=1484)</td>
<td>-10.2 (-15.4, -5.1) Ye</td>
</tr>
<tr>
<td>A(H3N2)</td>
<td>393.0 (n=1454 (^a))</td>
<td>1.27 (1.15, 1.42)</td>
<td>82.3 (80.2, 84.2) (n=1455)</td>
<td>84.9 (81.4, 88.0) (n=1484)</td>
<td>2.6 (-2.5, 7.8) Ye</td>
</tr>
<tr>
<td>B/Phuket/2073/2013 B/Tamagawa</td>
<td>23.7 (n=1455 (^a))</td>
<td>1.12 (1.01, 1.24)</td>
<td>38.9 (36.4, 41.4) (n=1456)</td>
<td>41.9 (37.5, 46.5) (n=1484)</td>
<td>3.1 (-2.1, 8.2) Ye</td>
</tr>
<tr>
<td>B/Brisbane/60/2008 (B/Victoria)</td>
<td>54.6 (n=1455 (^a))</td>
<td>0.97 (0.86, 1.09)</td>
<td>60.2 (57.6, 62.7) (n=1456)</td>
<td>61.1 (56.6, 65.4) (n=1483)</td>
<td>0.9 (-4.2, 6.1) Ye</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; Comparator, Comparator quadrivalent influenza vaccine (Fluzone Quadrivalent [Sanofi Aventis]); GMT (adjusted), geometric mean titer; SCR, seroconversion rate.
\(^a\) The Per-Protocol Population comprised all subjects (6 through 35 months of age receiving one or two 0.25 mL doses and 36 through 59 months of age receiving one or two 0.5 mL doses) in the Evaluable Population who did not have any protocol deviations that were medically assessed as potentially impacting on immunogenicity results.
\(^b\) GMT Ratio = Comparator / AFLURIA QUADRIVALENT. Adjusted analysis model: Log-transformed Post-Vaccination HI Titer + Vaccine + Age Cohort (6 through 35 months or 36 through 59 months) + Gender + Vaccination History (+y/n) + Log-transformed Pre-Vaccination HI Titer + Site + Number of Doses (1 vs 2) + Age Cohort \[6 through 35 months or 36 through 59 months\] + Gender + Vaccination History. The Age Cohort*Vaccine interaction term was excluded from the model fit for the strains A(H1N1), A(H3N2) and B/Tamagawa as the interaction result was non-significant (p>0.05). Least square means were back-transformed.
\(^c\) Seroconversion rate was defined as the percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer ≥ 1:40 or a prevaccination HI titer ≥ 1:10 and a 4-fold increase in postvaccination HI titer.
\(^d\) Seroconversion rate difference = Comparator SCR percentage – AFLURIA QUADRIVALENT SCR percentage.
\(^e\) Noninferiority (NI) criterion for the GMT ratio: upper bound of two-sided 95% CI on the GMT ratio of Comparator / AFLURIA QUADRIVALENT should not exceed 1.5. NI criterion for the SCR difference: upper bound of two-sided 95% CI on the difference between SCR Comparator – AFLURIA QUADRIVALENT should not exceed 10%.
\(^f\) Subject 840402-0073 was excluded from the Per-Protocol Population for the adjusted GMT analysis for the GMT ratio because the subject did not have information on all covariates (unknown prevaccination history).
\(^g\) Subject 840402-0074 had missing A/H1N2 post-vaccination titer.

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 HOW SUPPLIED
Each product presentation includes a package insert and the following components:

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Carton NDC Number</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Filled Syringe</td>
<td>33332-220-20</td>
<td>• Ten 0.5 mL single-dose syringes fitted with a Luer-Lok™ attachment without needles [NDC 33332-220-21]</td>
</tr>
<tr>
<td>Pre-Filled Syringe</td>
<td>33332-320-01</td>
<td>• Ten 0.5 mL single-dose syringes fitted with a Luer-Lok™ attachment without needles [NDC 33332-320-02]</td>
</tr>
<tr>
<td>Multi-Dose Vial</td>
<td>33332-420-10</td>
<td>• One 5 mL vial [NDC 33332-420-11]</td>
</tr>
</tbody>
</table>

16.2 Storage and Handling
• Store refrigerated at 2–8°C (36–46°F).
• Do not freeze. Discard if product has been frozen.
• Protect from light.
• Do not use AFLURIA QUADRIVALENT beyond the expiration date printed on the label.
• Between uses, return the multi-dose vial to the recommended storage conditions.
• Once the stopper of the multi-dose vial has been pierced the vial must be discarded within 28 days.
• The number of needle punctures should not exceed 20 per multi-dose vial.

17 PATIENT COUNSELING INFORMATION
• Inform the vaccine recipient or guardian of the potential benefits and risks of immunization with AFLURIA QUADRIVALENT.
• Inform the vaccine recipient or guardian that AFLURIA QUADRIVALENT is an inactivated vaccine that cannot cause influenza but stimulates the immune system to produce antibodies that protect against influenza, and that the full effect of the vaccine is generally achieved approximately 3 weeks after vaccination.
• Instruct the vaccine recipient or guardian to report any severe or unusual adverse reactions to their healthcare provider.
• Encourage women who receive AFLURIA QUADRIVALENT while pregnant to enroll in the pregnancy registry. Pregnant women can enroll in the pregnancy registry by calling 1-855-358-8966 or sending an email to Seqirus at us.medicalinformation@seqirus.com.
• Provide the vaccine recipient Vaccine Information Statements prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).
• Instruct the vaccine recipient that annual revaccination is recommended.

Manufactured by:
Seqirus Pty Ltd, Parkville, Victoria, 3052, Australia
U.S. License No. 2044

Distributed by:
Seqirus USA Inc. 25 Deforest Avenue, Summit, NJ 07901, USA
1-855-358-8966

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