AFLURIA QUADRIVALENT, Influenza Vaccine
Suspension for Intramuscular Injection
18-2019 Season
Initial U.S. Approval (AFLURIA QUADRIVALENT): 2016

Indications and Usage (1) 07/2017
Dosage and Administration (2) 07/2017

- 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 5 years of age and older. (1)

For intramuscular injection only, by needle and syringe (5 years of age and older) or by PharmaJet® Stratis® Needle-Free Injection System (18 through 64 years of age). Administer as a single 0.5 mL dose. (2)

<table>
<thead>
<tr>
<th>Age</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years</td>
<td>One dose or two doses</td>
</tr>
<tr>
<td>8 years</td>
<td>at least 1 month apart*</td>
</tr>
<tr>
<td>9 years and older</td>
<td>One dose</td>
</tr>
</tbody>
</table>

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

Dosage and Administration (2)

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

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)

Adverse Reactions

AFLURIA QUADRIVALENT administered by needle and syringe:

- 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)

AFLURIA (trivalent formulation) administered by the PharmaJet Strati 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 5 years of age have not been established in clinical trials. (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: 04/2018
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 5 years of age and older.

2 DOSAGE AND ADMINISTRATION
For intramuscular (IM) use only.
• By needle and syringe (5 years of age and older)
• By Pharmalea® Stratis® Needle-Free Injection System (18 through 64 years of age)

Administer as a single 0.5 mL dose.

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

Table 1: AFLURIA QUADRIVALENT Schedule

<table>
<thead>
<tr>
<th>Age</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years through</td>
<td>One dose or two doses</td>
</tr>
<tr>
<td>8 years</td>
<td>at least 1 month apart</td>
</tr>
<tr>
<td>9 years and older</td>
<td>One dose</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.

The preferred site for intramuscular injection is the deltoid muscle of the upper arm. When using the multi-dose vial, shake the vial thoroughly before withdrawing each dose. Use small syringes (0.5 mL or 1 mL) to minimize product loss.

To use the Pharmalea Stratis Needle-Free Injection System, refer to the Instructions for Use for the Pharmalea Stratis Needle-Free Injection System.

3 DOSAGE FORMS AND STRENGTHS
AFLURIA QUADRIVALENT is a sterile suspension for intramuscular injection (see Description [11]).

AFLURIA QUADRIVALENT is supplied in two presentations:
• 0.5 mL pre-filled syringe (single dose).
• 5 mL multi-dose vial (ten 0.5 mL doses).

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 reactions observed in clinical studies with AFLURIA QUADRIVALENT administered by needle and syringe were pain (≥50%), redness (≥10%), swelling (≥10%), and headache (≥10%). The most common systemic adverse events were myalgia, malaise, and fatigue (≥10%).

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%).

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.

Adul ts
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. Unsolicted adverse events were collected for 28 days post-vaccination. Serious adverse events (SAEs), including deaths, were collected for 180 days post-vaccination.

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>Percentage (%) of Subjects in each Age Cohort Reporting an Event</th>
<th>Subjects 18 through 64 years</th>
<th>Subjects 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFLURIA Quadrivalent N= 854</td>
<td>TIV-1 N= 428</td>
<td>TIV-2 N= 430</td>
</tr>
<tr>
<td>Any</td>
<td>Gr 3</td>
<td>Any</td>
</tr>
<tr>
<td>Headache</td>
<td>21.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Malaise</td>
<td>8.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Chills</td>
<td>4.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Fever</td>
<td>1.1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Loc al Adverse Reactions:
• Pain: 47.9% (% of Subjects 18 through 64 years; 43.7% of Subjects 65 years).
• Swelling/Lump: 3.7% (2.1% of Subjects 18 through 64 years; 2.3% of Subjects 65 years).
• Redness: 2.9% (2.8% of Subjects 18 through 64 years; 2.8% of Subjects 65 years).

Systemic Adverse Events:
• Maliga (muscle ache): 25.5% (1.9% of Subjects 18 through 64 years; 23.4% of Subjects 65 years).
• Headache: 21.7% (1.7% of Subjects 18 through 64 years; 15.2% of Subjects 65 years).
• Malaise: 8.9% (0.7% of Subjects 18 through 64 years; 9.1% of Subjects 65 years).
• Chills: 4.8% (0.6% of Subjects 18 through 64 years; 7.6% of Subjects 65 years).
• Vomiting: 1.5% (0.4% of Subjects 18 through 64 years; 0.9% of Subjects 65 years).
• Fever: 1.1% (0.4% of Subjects 18 through 64 years; 0.9% of Subjects 65 years).

Abbreviations: Gr 3, Grade 3.

* NCT02214225

1 Proportion of subjects reporting each solicited local adverse reaction or systemic adverse event by study vaccine group based on the number of subjects contributing any follow up safety information for at least one data value of an individual sign/symptom.

2 N = number of subjects in the Safety Population for each study vaccine group.

3 Local adverse reactions: Grade 3 pain is that which prevents daily activity; Swelling/Lump and redness: any ≥ 20 mm diameter; Grade 3 = ≥ 100 mm diameter.

4 Systemic adverse events: Fever: any ≥ 100.4°F; Grade 3 = ≥ 102.2°F; Grade 3 for all other adverse events is that which prevents daily activity.

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) administration using the Pharmatek Stratis Needle-Free Injection System (Study 2). Study 2 included 1,247 subjects for safety analysis, ages 18 through 64 years, randomized to receive AFLURIA by either the Pharmatek Stratis 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). All solicited local adverse reactions and systemic adverse events following any vaccination (first or second dose) are presented in Table 4.

### 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 Pharmatek Stratis Needle-Free Injection System or Needle and Syringe (Study 2)

<table>
<thead>
<tr>
<th>Local Adverse Reactions</th>
<th>AFLURIA (trivalent formulation)</th>
<th>Needle and Syringe</th>
<th>Any</th>
<th>Grade 3</th>
<th>Any</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenderness</td>
<td>89.4</td>
<td>2.1</td>
<td>77.9</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swelling</td>
<td>64.8</td>
<td>1.7</td>
<td>19.7</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>64.4</td>
<td>0.8</td>
<td>49.3</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Redness</td>
<td>60.1</td>
<td>1.3</td>
<td>19.2</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iching</td>
<td>28.0</td>
<td>0.0</td>
<td>9.5</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruising</td>
<td>17.6</td>
<td>0.2</td>
<td>5.3</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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>AFLURIA QUADRIVALENT</td>
<td>Comparator</td>
</tr>
<tr>
<td>N=828-829</td>
<td>N=979-792</td>
</tr>
<tr>
<td>Any</td>
<td>Gr 3</td>
</tr>
<tr>
<td>Pain</td>
<td>51.3</td>
</tr>
<tr>
<td>Redness</td>
<td>19.4</td>
</tr>
<tr>
<td>Swelling/Lump</td>
<td>15.3</td>
</tr>
</tbody>
</table>

### Table 6: 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 immunizations generally or influenza immunizations specifically; 2) are potentially serious; or 3) have been reported frequently. There are no 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.
confirmed by postmarketing studies.

**Vaccine was associated with increased rates of fever and febrile seizures, predominantly in children below the age of 5 years as compared to previous years, in postmarketing reports confirmed by postmarketing studies.**

**Skin and subcutaneous tissue disorders**

Pruritus, urticaria, and rash

**General disorders and administration site conditions**

Cellulitis and large injection site swelling

**7 DRUG INTERACTIONS**

**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 no 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 Embry-o-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 and 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 or the effects on milk production.

**8.4 Pediatric Use**

The safety and effectiveness of AFLURIA QUADRIVALENT in persons less than 5 years have not been established in clinical trials.

**Administration of Seqirus’ (formerly CSL) 2010 Southern Hemisphere trivalent influenza vaccine was associated with increased rates of fever and febrile seizures, predominantly in children below the age of 5 years as compared to previous years, in postmarketing reports confirmed by postmarketing studies.**
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 4, a randomized, observer-blind, placebo-controlled study conducted in 15,044 subjects. Healthy subjects 18 through 64 years of age were randomized 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 45.4 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 5).

Table 5: AFLURIA (trivalent formulation): Laboratory-Confirmed Influenza Infection Rate and Vaccine Efficacy in Adults 18 through 64 Years of Age (Study 4)*

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Labo-</th>
<th>Influenza Infection Rate</th>
<th>Vaccine Efficacy</th>
<th>Lower Limit of the 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N</td>
<td>n/N %</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Vaccine-matched Strains</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFLURIA</td>
<td>9889</td>
<td>58</td>
<td>0.59</td>
<td>60</td>
</tr>
<tr>
<td>Placebo</td>
<td>4960</td>
<td>73</td>
<td>1.47</td>
<td>41</td>
</tr>
<tr>
<td>Any Influenza Virus Strain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFLURIA</td>
<td>9889</td>
<td>222</td>
<td>2.24</td>
<td>42</td>
</tr>
<tr>
<td>Placebo</td>
<td>4960</td>
<td>192</td>
<td>3.87</td>
<td>28</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval.
* NCT00562484
† 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 via 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 virus strains 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 vaccination. Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the GMT ratio (AFLURIA QUADRIVALENT/TIV-1 or TIV-2) 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 6). Superiority of the immune response to each of the influenza B strains contained in AFLURIA QUADRIVALENT was shown relative to the antibody response after 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 6: 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 Ratio†</th>
<th>Seroconversion %‡</th>
<th>Difference</th>
<th>Met both pre-defined non-inferiority criteria?§</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFLURIA Quadrivalent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria)</td>
<td>423.7</td>
<td>402.8</td>
<td>0.93* (0.85, 1.02)</td>
<td>51.3</td>
<td>49.1</td>
</tr>
<tr>
<td>AFLURIA Quadrivalent N=1691</td>
<td>569.1</td>
<td>515.1</td>
<td>0.91* (0.83, 0.99)</td>
<td>56.3</td>
<td>51.7</td>
</tr>
<tr>
<td>AFLURIA Quadrivalent N=1691</td>
<td>92.3</td>
<td>79.3</td>
<td>0.86* (0.76, 0.97)</td>
<td>45.7</td>
<td>41.3</td>
</tr>
<tr>
<td>AFLURIA Quadrivalent N=1691</td>
<td>110.7</td>
<td>95.2</td>
<td>0.86* (0.76, 0.98)</td>
<td>57.6</td>
<td>53.0</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; GMT, geometric mean titer.
* NCT0214225
† GMT ratio was calculated 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 ≥ 1:10.
§ 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)/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)/AFLURIA Quadrivalent should not exceed 10%.
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 across 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 7: Baseline and Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of Non-Inferiority of AFLURIA (trivalent formulation) Administered by Pharamaceutic Stratix 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</th>
<th>Seroconversion %</th>
<th>Difference</th>
<th>Met both pre-defined non-inferiority criteria?</th>
</tr>
</thead>
<tbody>
<tr>
<td>AH1N1</td>
<td>79.5</td>
<td>83.7</td>
<td>280.6</td>
<td>282.9</td>
<td>0.99</td>
<td>(0.88, 1.12)</td>
</tr>
<tr>
<td>AH3N2</td>
<td>75.4</td>
<td>68.1</td>
<td>265.9</td>
<td>247.3</td>
<td>1.08</td>
<td>(0.96, 1.21)</td>
</tr>
<tr>
<td>8</td>
<td>12.6</td>
<td>13.5</td>
<td>39.7</td>
<td>42.5</td>
<td>0.94</td>
<td>(0.83, 1.06)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strain</th>
<th>AFLURIA Quadrivalent N=1605</th>
<th>Comparator N=528</th>
<th>Serovaccine %</th>
<th>SCR difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A(H1N1)</td>
<td>952.6 (n=1604)</td>
<td>958.8</td>
<td>1.03 (1.09)</td>
<td>-3.1 (1.8) Yes</td>
</tr>
<tr>
<td>A(H3N2)</td>
<td>886.4 (n=1604)</td>
<td>930.6</td>
<td>1.05 (1.15)</td>
<td>-4.5 (5.3) Yes</td>
</tr>
</tbody>
</table>

### 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 2278 subjects were randomized 3:1 to receive one or two doses of AFLURIA QUADRIVALENT (N=1709) or a U.S.-licensed comparator quadrivalent influenza vaccine (N=569). 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 influenza 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 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 8). 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.

### 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>33332-318-01</td>
<td>• Ten 0.5 mL single-dose syringes fitted with a Luer-Lok™ attachment without needles [NDC 33332-318-02]</td>
</tr>
<tr>
<td>Multi-Dose Vial</td>
<td>33332-418-10</td>
<td>• One 5 mL vial, which contains ten 0.5 mL doses [NDC 33332-418-11]</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.
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.