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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AFLURIA® QUADRIVALENT safely and effectively. See full prescribing information for AFLURIA QUADRIVALENT.

**AFLURIA QUADRIVALENT, Influenza Vaccine
Suspension for Intramuscular Injection
2020-2021 Formula
Initial U.S. Approval (AFLURIA QUADRIVALENT): 2016**

RECENT MAJOR CHANGES

Dosage and Administration (2) XX/2020

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

DOSAGE 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 ^a , 0.25 mL each	If 2 doses, administer at least 1 month apart
36 months through 8 years	One or two doses ^a , 0.5 mL each	If 2 doses, administer at least 1 month apart
9 years and older	One dose, 0.5 mL	Not Applicable

^a1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines. (2)

DOSAGE 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 doses) (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)

WARNINGS AND PRECAUTIONS

- 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. (5.1)
- Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. (5.2)

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)
- In children 6 months through 35 months of age, the most commonly reported injection-site reactions 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: 07/2020

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1 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

Age	Dose	Schedule
6 months through 35 months	One or two doses ^a , 0.25 mL each	If 2 doses, administer at least 1 month apart
36 months through 8 years	One or two doses ^a , 0.5 mL each	If 2 doses, administer at least 1 month apart
9 years and older	One dose, 0.5mL	Not Applicable

^a1 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.

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32 The preferred sites for intramuscular injection are the anterolateral aspect of the thigh in
33 infants 6 months through 11 months of age, the anterolateral aspect of the thigh (or the deltoid
34 muscle of the upper arm if muscle mass is adequate) in persons 12 months through 35 months
35 of age, or the deltoid muscle of the upper arm in persons \geq 36 months of age.

36 **3 DOSAGE FORMS AND STRENGTHS**

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

39 AFLURIA QUADRIVALENT is supplied in three presentations:

- 40 • 0.25 mL pre-filled syringe (single dose, for persons 6 months through 35 months of
41 age)
- 42 • 0.5 mL pre-filled syringe (single dose, for persons 36 months of age and older).
- 43 • 5 mL multi-dose vial (for persons 6 months of age and older).

44 **4 CONTRAINDICATIONS**

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

48 **5 WARNINGS AND PRECAUTIONS**

49 **5.1 Guillain-Barré Syndrome**

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

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

57 **5.2 Preventing and Managing Allergic Reactions**

58 Appropriate medical treatment and supervision must be available to manage possible
59 anaphylactic reactions following administration of the vaccine.

60 **5.3 Altered Immunocompetence**

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

63 **5.4 Limitations of Vaccine Effectiveness**

64 Vaccination with AFLURIA QUADRIVALENT may not protect all individuals.

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6 ADVERSE REACTIONS

65
66 In adults 18 through 64 years of age, the most commonly reported injection-site adverse reaction
67 observed in clinical studies with AFLURIA QUADRIVALENT administered by needle and
68 syringe was pain ($\geq 40\%$). The most common systemic adverse events observed were myalgia
69 and headache ($\geq 20\%$).

70 In adults 65 years of age and older, the most commonly reported injection-site adverse reaction
71 observed in clinical studies with AFLURIA QUADRIVALENT administered by needle and
72 syringe was pain ($\geq 20\%$). The most common systemic adverse event observed was myalgia (\geq
73 10%).

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

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

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

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

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

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

96

6.1 Clinical Trials Experience

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

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

115 Local (injection-site) adverse reactions and systemic adverse events were solicited for 7 days
116 post-vaccination (Table 2). Injection site cellulitis, cellulitis-like reactions (defined as
117 concurrent Grade 3 pain, redness, and swelling/lump), and Grade 3 swelling/lump were
118 monitored for 28 days post-vaccination. Unsolicited adverse events were collected for 28 days
119 post-vaccination. Serious adverse events (SAEs), including deaths, were collected for 180 days
120 post-vaccination.

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

	Percentage (%) ^b of Subjects in each Age Cohort Reporting an Event											
	Subjects 18 through 64 years						Subjects ≥ 65 years					
	AFLURIA Quadrivalent N= 854 ^c		TIV-1 N= 428 ^c		TIV-2 N= 430 ^c		AFLURIA Quadrivalent N= 867 ^c		TIV-1 N= 436 ^c		TIV-2 N= 434 ^c	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
Local Adverse Reactions ^d												
Pain	47.9	0.7	43.7	1.4	50.7	1.2	24.6	0.1	22.7	0	21.0	0.2
Swelling/Lump	3.7	0.1	2.3	0	3.5	0.2	3.2	0.5	1.8	0	1.6	0
Redness	2.9	0	2.8	0	2.8	0	4.2	0.3	2.1	0	2.5	0.2
Systemic Adverse Events ^e												
Myalgia (muscle ache)	25.5	1.9	23.4	1.4	24.2	1.2	12.7	0.3	14.0	0.7	12.2	0.5
Headache	21.7	1.7	15.2	0.9	19.1	1.2	8.4	0	7.1	0.2	7.8	0.7
Malaise	8.9	0.7	9.1	0	9.3	0.7	4.4	0.5	5.0	0.2	5.1	0.2
Nausea	6.9	0.6	7.7	0.5	6.3	1.2	1.6	0	1.8	0	2.1	0.2
Chills	4.8	0.6	4.4	0.2	4.7	0.5	2.0	0	2.1	0.5	1.4	0.2
Vomiting	1.5	0.4	0.9	0	2.3	0.7	0.5	0.1	0	0	0.7	0.2
Fever	1.1	0.4	0.9	0	0.5	0	0.2	0	0.9	0	0.5	0.2

124 Abbreviations: Gr 3, Grade 3.

125 ^a NCT02214225

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

129 ^c N = number of subjects in the Safety Population for each study vaccine group.

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

132 ^e Systemic adverse events: Fever: any = ≥ 100.4°F (Oral), Grade 3 = ≥ 102.2°F (Oral); Grade 3 for all other adverse events is
133 that which prevents daily activity.

134 In the 28 days following vaccination, no subject experienced cellulitis or a cellulitis-like reaction.
135 All Grade 3 swelling/lump reactions began within 7 days of vaccination and are included in
136 Table 2.

137 In the 28 days following vaccination, 20.5%, 20.1%, and 20.7% of adults 18 through 64 years
138 and 20.3%, 24.1%, and 20.0% of adults ≥ 65 years who received AFLURIA QUADRIVALENT,
139 TIV-1, and TIV-2, respectively, reported unsolicited adverse events. Rates of individual events
140 were similar between treatment groups, and most events were mild to moderate in severity.

141 In the 180 days following vaccination, 2.3%, 1.6%, and 1.5% of all subjects who received
142 AFLURIA QUADRIVALENT, TIV-1, and TIV-2, respectively, experienced SAEs, including

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143 six deaths, five in the AFLURIA QUADRIVALENT group and one in the TIV-2 group. The
144 majority of SAEs occurred after Study Day 28 and in subjects ≥ 65 years of age who had co-
145 morbid illnesses. No SAEs or deaths appeared related to the study vaccines.

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

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153 **Table 3: Proportion of Subjects 18 through 64 Years of Age with Solicited Local Adverse**
 154 **Reactions or Systemic Adverse Events within 7 Days after Administration of**
 155 **AFLURIA (trivalent formulation) by PharmaJet Stratis Needle-Free Injection**
 156 **System or Needle and Syringe (Study 2)^a**

	Percentage ^b of Subjects Reporting Event			
	Subjects 18 through 64 years			
	AFLURIA (trivalent formulation)			
	PharmaJet Stratis Needle-Free Injection System N=540-616 ^c		Needle and Syringe N=599-606 ^c	
	Any	Grade 3	Any	Grade 3
Local Adverse Reactions ^d				
Tenderness	89.4	2.1	77.9	1.0
Swelling	64.8	1.7	19.7	0.2
Pain	64.4	0.8	49.3	0.7
Redness	60.1	1.3	19.2	0.3
Itching ^f	28.0	0.0	9.5	0.2
Bruising	17.6	0.2	5.3	0.0
Systemic Adverse Events ^e				
Myalgia	36.4	0.8	35.5	1.0
Malaise	31.2	0.7	28.4	0.5
Headache	24.7	1.3	22.1	1.3
Chills	7.0	0.2	7.2	0.2
Nausea	6.6	0.2	6.5	0.0
Vomiting	1.3	0.0	1.8	0.2
Fever	0.3	0.0	0.3	0.0

157 ^a NCT01688921

158 ^b Proportion of subjects reporting each local adverse reaction or systemic adverse event by treatment group based on the number
 159 of subjects contributing at least one data value for an individual sign/symptom (individual event denominators).

160 ^c N = number of subjects in the Safety Population for each treatment group. Denominators for the PharmaJet Stratis Needle-Free
 161 Injection System group were: N=540 for itching and N=605-616 for all other parameters. Denominators for the needle and
 162 syringe group were: N=527 for itching and N=599-606 for all other parameters.

163 ^d Local adverse reactions: Grade 3 is pain, tenderness or itching that prevents daily activity; Swelling, redness or bruising: any =
 164 ≥ 25mm diameter, Grade 3 = > 100mm diameter.

165 ^e Systemic adverse events: Fever: any = ≥ 100.4°F (Oral), Grade 3 = ≥ 102.2°F (Oral); Grade 3 for all other adverse events is
 166 that which prevents daily activity.

167 ^f A total of 155 subjects (approximately randomly distributed between PharmaJet Stratis Needle-Free Injection System and
 168 needle and syringe groups) received Diary Cards without itching listed as a solicited symptom.

169 In adults 18 through 64 years who received AFLURIA (trivalent formulation) administered by
 170 PharmaJet Stratis Needle-Free Injection System, commonly reported unsolicited adverse events
 171 were headache (4.2%), injection site hematoma (1.8%), injection site erythema (1.1%), myalgia
 172 (1.0%) and nausea (1.0%).

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

174 Clinical safety data for AFLURIA QUADRIVALENT in older children and adolescents have
175 been collected in one clinical trial, Study 3, a randomized, observer-blinded, comparator-
176 controlled trial conducted in the U.S. in 2278 subjects aged 5 through 17 years. Subjects were
177 stratified into one of two age cohorts of 5 through 8 years or 9 through 17 years (51.2% and
178 48.8% of the study population, respectively). The mean age of the population was 9.5 years,
179 52.1% were male, and racial groups consisted of 73.3% White, 20.7% Black, 0.8% Asian, 0.3%
180 American Indian/Native American, and 0.7% Native Hawaiian/Pacific Islander; 23.8% of
181 subjects were Hispanic/Latino. The mean ages of subjects 5 through 8 years and 9 through 17
182 years were 6.7 years and 12.5 years, respectively. Subjects in the safety population (N=2252)
183 received either AFLURIA QUADRIVALENT (N=1692) or a U.S.-licensed comparator
184 quadrivalent influenza vaccine (N=560). Study subjects were scheduled to receive either a single
185 vaccination or two vaccinations 28 days apart based on their previous vaccination history. In
186 this study, AFLURIA QUADRIVALENT and comparator vaccine were administered by needle
187 and syringe (see *Clinical Studies [14]*).

188 Local (injection site) adverse reactions and systemic adverse events were solicited for 7 days
189 post-vaccination. Cellulitis-like reactions (defined as concurrent Grade 3 pain, redness, and
190 swelling/lump) at the injection site were monitored for 28 days post-vaccination. Subjects
191 were instructed to report and return to clinic within 24 hours in the event of a cellulitis-like
192 reaction. Unsolicited adverse events were collected for 28 days post-vaccination. All solicited
193 local adverse reactions and systemic adverse events following any vaccination (first or second
194 dose) are presented in Table 4.

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195 **Table 4: Proportion of Subjects Per Age Cohort with Any Solicited Local Adverse**
196 **Reactions or Systemic Adverse Events within 7 Days after Administration of**
197 **AFLURIA QUADRIVALENT or Comparator (Study 3)^a**

	Percentage (%) ^b of Subjects in each Age Cohort Reporting an Event							
	Subjects 5 through 8 years				Subjects 9 through 17 years			
	AFLURIA Quadrivalent N= 828-829 ^c		Comparator N= 273-274 ^c		AFLURIA Quadrivalent N= 790-792 ^c		Comparator N= 261 ^c	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
Local Adverse Reactions ^d								
Pain	51.3	0.8	49.6	0.7	51.5	0.3	45.2	0.4
Redness	19.4	3.5	18.6	1.8	14.8	1.9	16.1	1.9
Swelling/Lump	15.3	3.4	12.4	2.2	12.2	2.0	10.7	1.9
Systemic Adverse Events ^e								
Headache	12.3	0.1	10.6	0.4	18.8	0.4	14.6	0.4
Myalgia	9.8	0.1	11.3	0.4	16.7	0.3	11.1	0.4
Malaise and Fatigue	8.8	0.4	5.8	0	10.0	0.4	7.7	0
Nausea	7.1	0.1	8.4	0	7.7	0	8.0	0
Diarrhea	5.2	0	3.6	0	5.4	0	4.2	0
Fever	4.5	1.2	3.6	0.7	2.1	0.5	0.8	0
Vomiting	2.4	0.2	4.4	0	1.8	0	2.3	0

198 Abbreviations: Gr 3, Grade 3 (severe); Comparator, Comparator quadrivalent influenza vaccine [Fluarix[®] Quadrivalent
199 (GlaxoSmithKline Biologicals)]

200 ^aNCT02545543

201 ^bPercent (%) is derived from the number of subjects that reported the event divided by the number of subjects in the Solicited
202 Safety Population with non-missing data for each age cohort, treatment group, and each solicited parameter.

203 ^cN = number of subjects in the Solicited Safety Population (subjects who were vaccinated and provided any solicited safety data)
204 for each study vaccine group.

205 ^dLocal adverse reactions: Grade 3 pain is that which prevents daily activity; swelling/lump and redness: any = > 0mm diameter,
206 Grade 3 = > 30mm diameter.

207 ^eSystemic adverse events: Fever: any = $\geq 100.4^{\circ}\text{F}$ (Oral), Grade 3 = $\geq 102.2^{\circ}\text{F}$ (Oral); Grade 3 for all other adverse events is
208 that which prevents daily activity or requires significant medical intervention.
209

210 In subjects 5 through 8 years of age, all solicited local adverse reactions and systemic adverse
211 events were reported at lower frequencies after the second vaccination than after the first
212 vaccination with AFLURIA QUADRIVALENT with the exception of vomiting (which occurred
213 at the same rate of 2.2% after each vaccination).

214 One subject, 8 years of age, experienced a cellulitis-like reaction at the injection site after
215 vaccination with AFLURIA QUADRIVALENT.

216 The most commonly reported unsolicited adverse events in the 28 days following the first or
217 second dose of AFLURIA QUADRIVALENT in subjects 5 through 8 years of age were cough
218 (2.4%), pyrexia (1.8%), rhinorrhea (1.2%), and headache (1.0%), and were similar to the
219 comparator.

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220 For subjects ages 9 through 17 years who received AFLURIA QUADRIVALENT, the most
221 commonly reported unsolicited adverse events in the 28 days following vaccination were
222 oropharyngeal pain (1.6%), cough (1.3%), and upper respiratory tract infection (1.0%), and were
223 similar to the comparator.

224 No deaths were reported in Study 3. In the 180 days following vaccinations, AFLURIA
225 QUADRIVALENT and comparator vaccine recipients experienced similar rates of serious
226 adverse events (SAEs). None of the SAEs appeared related to the study vaccines except for one
227 case of influenza B infection (considered a vaccine failure) in an AFLURIA QUADRIVALENT
228 recipient.

229 Children 6 Months Through 59 Months of Age

230 Clinical safety data for AFLURIA QUADRIVALENT in infants and young children have been
231 collected in one clinical trial, Study 4, a randomized, observer-blind, comparator-controlled trial
232 conducted in the U.S. in 2247 subjects aged 6 through 59 months. Subjects were stratified into
233 one of two age cohorts of 6 through 35 months or 36 through 59 months (41.6% and 58.4% of
234 the study population, respectively). The mean age of the population was 36.6 months, 51.6%
235 were male, and racial groups consisted of 71.0% White, 21.5% Black, 1.1% Asian, 0.7% Native
236 Hawaiian/Pacific Islander, and 0.3% American Indian/Native American; 26.4% of subjects were
237 Hispanic/Latino. The mean ages of subjects 6 through 35 months and 36 through 59 months
238 were 21.7 months and 47.1 months, respectively. Subjects in the safety population (N=2232)
239 received either AFLURIA QUADRIVALENT (N=1673) or a U.S.-licensed comparator
240 quadrivalent influenza vaccine (N=559). Study subjects were scheduled to receive either a single
241 vaccination or two vaccinations 28 days apart based on their previous vaccination history. In
242 this study, AFLURIA QUADRIVALENT and comparator vaccine were administered by needle
243 and syringe (see *Clinical Studies [14]*).

244 Local (injection site) adverse reactions and systemic adverse events were solicited for 7 days
245 post-vaccination. Cellulitis-like reactions (defined as concurrent Grade 3 pain, redness, and
246 swelling/lump) at the injection site were monitored for 28 days post-vaccination. Subjects were
247 instructed to report and return to clinic within 24 hours in the event of a cellulitis-like reaction.
248 Unsolicited adverse events were collected for 28 days post-vaccination, and SAEs for 6 months
249 following the last vaccination. All solicited local adverse reactions and systemic adverse events
250 following any vaccination (first or second dose) are presented in Table 5.

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

	Percentage (%) ^b of Subjects in each Age Cohort Reporting an Event							
	6 through 35 months				36 through 59 months			
	AFLURIA Quadrivalent N= 668-669 ^c		Comparator N= 226-227 ^c		AFLURIA Quadrivalent N= 947-949 ^c		Comparator N= 317-318 ^c	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
Local Adverse Reactions ^d								
Pain	20.8	0.1	25.6	0.4	35.5	0	31.4	0.6
Redness	20.8	0.6	17.6	1.8	22.4	2.3	20.8	5.3
Swelling/Lump	6.1	0.4	6.2	0.9	10.1	1.7	12.9	2.5
Systemic Adverse Events ^e								
Irritability	32.9	0.7	28.2	0.4	-	-	-	-
Diarrhea	24.2	0.1	25.6	0.4	12.1	0.1	8.8	0.6
Loss of Appetite	20.0	0.3	19.4	0.4	-	-	-	-
Malaise and Fatigue	-	-	-	-	14.3	0.5	13.2	0.3
Myalgia	-	-	-	-	9.9	0.1	9.4	0
Nausea and/or vomiting	9.4	0.7	11.0	0	9.2	0.4	6.6	0.3
Headache	-	-	-	-	6.2	0.4	5.0	0
Fever ^f	7.2	2.5	11.9	2.6	4.8	1.2	6.0	0.9

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

256 ^a NCT02914275

257 ^b Percent (%) is derived from the number of subjects that reported the event divided by the number of subjects in the Solicited
258 Safety Population with non-missing data for each age cohort, treatment group, and each solicited parameter.

259 ^c N = number of subjects in the Solicited Safety Population (subjects who were vaccinated and provided any solicited safety
260 data) for each study vaccine group.

261 ^d Local adverse reactions: Grade 3 pain is that which prevents daily activity (36 through 59 month subjects); or cried when limb
262 was moved or spontaneously painful (6 through 35 month subjects); Swelling/Lump and redness: any = ≥ 0mm diameter, Grade
263 3 = ≥ 30mm diameter.

264 ^e Systemic adverse events: Fever: any = ≥ 99.5°F (Axillary), Grade 3 = ≥ 101.3°F (Axillary); Grade 3 for all other adverse events
265 is that which prevents daily activity; Irritability, Loss of Appetite, Malaise and Fatigue, Myalgia and Headache are age specific
266 systemic adverse events, where “-” denotes event was not applicable to that age cohort.

267 ^f Prophylactic antipyretics (acetaminophen or ibuprophen-containing medications) were not permitted. Antipyretics used to treat
268 fever were permitted and rates of use were as follows: 6 through 35 months (Afluria QIV 5.9%, Comparator QIV 9.0%); 36
269 through 59 months (Afluria QIV 3.7%, Comparator QIV 2.5%).

270 In subjects 6 through 35 months of age, all solicited local adverse reactions and systemic adverse
271 events were reported at lower frequencies after the second vaccination than after the first
272 vaccination with AFLURIA QUADRIVALENT.

273 In subjects 36 through 59 months of age, all solicited local adverse reactions and systemic adverse
274 events were reported at lower frequencies after the second vaccination than after the first
275 vaccination with AFLURIA QUADRIVALENT.

276 The most commonly reported unsolicited adverse events in the 28 days following the first or
277 second dose of AFLURIA QUADRIVALENT in subjects 6 through 35 months of age were
278 rhinorrhea (11.2%), cough (10.4%), pyrexia (6.3%), upper respiratory tract infection (4.8%),

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279 diarrhea (3.7%), otitis media (2.4%), vomiting (2.4%), nasal congestion (2.4%), nasopharyngitis
280 (1.9%), irritability (1.7%), ear infection (1.6%), croup infectious (1.4%), teething (1.3%), rash
281 (1.2%), influenza like illness (1.0%) and fatigue (1.0%), and were similar to comparator.

282 The most commonly reported unsolicited adverse events in the 28 days following the first or
283 second dose of AFLURIA QUADRIVALENT in subjects 36 through 59 months of age were
284 cough (7.7%), rhinorrhea (4.9%), pyrexia (3.7%), upper respiratory tract infection (2.5%),
285 vomiting (2.1%), nasal congestion (1.6%), nasopharyngitis (1.7%), oropharyngeal pain (1.2%)
286 diarrhea (1.1%) and fatigue (1.1%), and were similar to the comparator.

287 No deaths were reported in Study 4. In the 180 days following vaccinations, AFLURIA
288 QUADRIVALENT and comparator vaccine recipients experienced similar rates of serious
289 adverse events (SAEs), none of which were related to study vaccines. No vaccine-related febrile
290 seizures occurred in Study 4. Unrelated SAEs of febrile seizures occurred in two AFLURIA
291 QUADRIVALENT recipients (6 through 35 months age group) at 43 and 104 days post-
292 vaccinations.

293

294 6.2 Postmarketing Experience

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

304 The post-marketing experience with AFLURIA (trivalent formulation) included the following:

305 Blood and lymphatic system disorders

306 Thrombocytopenia

307 Immune system disorders

308 Allergic or immediate hypersensitivity reactions including anaphylactic shock and serum
309 sickness

310 Nervous system disorders

311 Neuralgia, paresthesia, convulsions (including febrile seizures), encephalomyelitis,
312 encephalopathy, neuritis or neuropathy, transverse myelitis, and GBS

313 Vascular disorders

314 Vasculitis which may be associated with transient renal involvement

315 Skin and subcutaneous tissue disorders

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316 Pruritus, urticaria, and rash

317 **General disorders and administration site conditions**

318 Cellulitis and large injection site swelling

319 Influenza-like illness

320 **7 DRUG INTERACTIONS**

321 No interaction studies have been performed on interaction between influenza vaccines in general
322 and other vaccines or medications.

323 **8 USE IN SPECIFIC POPULATIONS**

324 **8.1 Pregnancy**

325 Pregnancy Exposure Registry

326 There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to
327 AFLURIA QUADRIVALENT during pregnancy. Women who are vaccinated with AFLURIA
328 QUADRIVALENT during pregnancy are encouraged to enroll in the registry by calling 1-855-
329 358-8966 or sending an email to Seqirus at us.medicalinformation@seqirus.com.

330

331 Risk summary

332 All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general
333 population, the estimated background risk of major birth defects and miscarriage in clinically
334 recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Data for AFLURIA
335 (trivalent formulation) administered to pregnant women are relevant to AFLURIA
336 QUADRIVALENT because both vaccines are manufactured using the same process and have
337 overlapping compositions (see [Description \[11\]](#)). There are limited data for AFLURIA
338 QUADRIVALENT administered to pregnant women, and available data for AFLURIA
339 (trivalent formulation) administered to pregnant women are insufficient to inform vaccine-
340 associated risks in pregnancy.

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

346 Clinical Considerations

347 *Disease-associated Maternal and/or Embryo-Fetal Risk*

348 Pregnant women are at increased risk for severe illness due to influenza compared to non-
349 pregnant women. Pregnant women with influenza may be at increased risk for adverse
350 pregnancy outcomes, including preterm labor and delivery.

351 Data

352 *Animal Data*

Package insert

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

358 8.2 Lactation**359 Risk Summary**

360 It is not known whether AFLURIA QUADRIVALENT is excreted in human milk. Data are
361 not available to assess the effects of AFLURIA QUADRIVALENT on the breastfed infant or
362 on milk production/excretion.

363 The developmental and health benefits of breastfeeding should be considered along with the
364 mother's clinical need for AFLURIA QUADRIVALENT and any potential adverse effects on
365 the breastfed child from AFLURIA QUADRIVALENT or from the underlying maternal
366 condition. For preventive vaccines, the underlying maternal condition is susceptibility to
367 disease prevented by the vaccine.

368 8.4 Pediatric Use

369 The safety and effectiveness of AFLURIA QUADRIVALENT in persons less than 6 months of
370 age have not been established.

371 The PharmaJet Stratis Needle-Free Injection System is not approved as a method of
372 administering AFLURIA QUADRIVALENT to children and adolescents less than 18 years of
373 age due to lack of adequate data supporting safety and effectiveness in this population.

374 8.5 Geriatric Use

375 In clinical studies, AFLURIA QUADRIVALENT has been administered to, and safety
376 information collected for, 867 subjects aged 65 years and older (*see Adverse Reactions [6]*). The
377 65 years and older age group included 539 subjects 65 through 74 years and 328 subjects 75
378 years and older. After administration of AFLURIA QUADRIVALENT, hemagglutination-
379 inhibiting antibody responses were non-inferior to comparator trivalent influenza (TIV-1 and
380 TIV-2) in persons 65 years of age and older, but were lower than younger adult subjects (*see*
381 *Clinical Studies [14]*).

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

385 11 DESCRIPTION

386 AFLURIA QUADRIVALENT, Influenza Vaccine for intramuscular injection, is a sterile, clear,
387 colorless to slightly opalescent suspension with some sediment that resuspends upon shaking to
388 form a homogeneous suspension. AFLURIA QUADRIVALENT is prepared from influenza

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389 virus propagated in the allantoic fluid of embryonated chicken eggs. Following harvest, the virus
390 is purified in a sucrose density gradient using continuous flow zonal centrifugation. The purified
391 virus is inactivated with beta-propiolactone, and the virus particles are disrupted using sodium
392 taurodeoxycholate to produce a “split virion”. The disrupted virus is further purified and
393 suspended in a phosphate buffered isotonic solution.

394 AFLURIA QUADRIVALENT is standardized according to USPHS requirements for the 2020-
395 2021 influenza season and is formulated to contain 60 mcg hemagglutinin (HA) per 0.5 mL dose
396 in the recommended ratio of 15 mcg HA for each of the four influenza strains recommended for
397 the 2020-2021 Northern Hemisphere influenza season:

398 A/Victoria/2454/2019 IVR-207 (an A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09-like
399 virus), A/Hong Kong/2671/2019 IVR-208 (an A/Hong Kong/2671/2019 (H3N2)-like virus),
400 B/Victoria/705/2018 BVR-11 (a B/Washington/02/2019-like virus) and B/Phuket/3073/2013
401 BVR-1B (a B/Phuket/3073/2013-like virus). A 0.25 mL dose contains 7.5 mcg HA of each of
402 the same four influenza strains.

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

407 A single 0.5 mL dose of AFLURIA QUADRIVALENT contains sodium chloride (4.1 mg),
408 monobasic sodium phosphate (80 mcg), dibasic sodium phosphate (300 mcg), monobasic
409 potassium phosphate (20 mcg), potassium chloride (20 mcg), and calcium chloride (0.5 mcg).
410 From the manufacturing process, each 0.5 mL dose may also contain residual amounts of sodium
411 taurodeoxycholate (≤ 10 ppm), ovalbumin (< 1 mcg), sucrose (< 10 mcg), neomycin sulfate
412 (≤ 81.8 nanograms [ng]), polymyxin B (≤ 14 ng), beta-propiolactone (≤ 1.5 ng) and
413 hydrocortisone (≤ 0.56 ng). A single 0.25 mL dose of AFLURIA QUADRIVALENT contains
414 half of these quantities.

415 The rubber tip cap and plunger used for the preservative-free, single-dose syringes and the
416 rubber stoppers used for the multi-dose vial were not made with natural rubber latex.

417 12 CLINICAL PHARMACOLOGY**418 12.1 Mechanism of Action**

419 Influenza illness and its complications follow infection with influenza viruses. Global
420 surveillance of influenza identifies yearly antigenic variants. For example, since 1977 antigenic
421 variants of influenza A (H1N1 and H3N2) and influenza B viruses have been in global
422 circulation. Since 2001, two distinct lineages of influenza B (Victoria and Yamagata lineages)
423 have co-circulated worldwide. Specific levels of hemagglutination inhibition (HI) antibody titers
424 post-vaccination with inactivated influenza vaccine have not been correlated with protection
425 from influenza virus. In some human studies, antibody titers of 1:40 or greater have been
426 associated with protection from influenza illness in up to 50% of subjects.^{2,3}

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427 Antibody against one influenza virus type or subtype confers limited or no protection against
428 another. Furthermore, antibody to one antigenic variant of influenza virus might not protect
429 against a new antigenic variant of the same type or subtype. Frequent development of antigenic
430 variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for
431 the usual change to one or more new strains in each year's influenza vaccine. Therefore,
432 inactivated influenza vaccines are standardized to contain the HA of four strains (i.e., typically
433 two type A and two type B) representing the influenza viruses likely to be circulating in the U.S.
434 during the upcoming winter.

435 Annual revaccination with the current vaccine is recommended because immunity declines
436 during the year after vaccination and circulating strains of influenza virus change from year to
437 year.¹

438 13 NONCLINICAL TOXICOLOGY**439 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

443 14 CLINICAL STUDIES**444 14.1 Efficacy Against Laboratory-Confirmed Influenza**

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

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

462 Attack rates and vaccine efficacy, defined as the relative reduction in the influenza infection rate
463 for AFLURIA (trivalent formulation) compared to placebo, were calculated using the per
464 protocol population. Vaccine efficacy against laboratory-confirmed influenza infection due to

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465 influenza A or B virus strains contained in the vaccine was 60% with a lower limit of the 95%
466 CI of 41% (Table 6).

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

	Subjects ^b	Laboratory-Confirmed Influenza Cases	Influenza Infection Rate	Vaccine Efficacy ^c	
	N	N	n/N %	%	Lower Limit of the 95% CI
Vaccine-matched Strains					
AFLURIA	9889	58	0.59	60	41
Placebo	4960	73	1.47		
Any Influenza Virus Strain					
AFLURIA	9889	222	2.24	42	28
Placebo	4960	192	3.87		

469 Abbreviations: CI, confidence interval.

470 ^aNCT00562484

471 ^b The Per Protocol Population was identical to the Evaluable Population in this study.

472 ^c Vaccine efficacy = 1 minus the ratio of AFLURIA (trivalent formulation) /placebo infection rates. The objective of the study
473 was to demonstrate that the lower limit of the CI for vaccine efficacy was greater than 40%.

474 **14.2 Immunogenicity of AFLURIA QUADRIVALENT in Adults and Older Adults**
475 **Administered by Needle and Syringe**

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

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

490 Serum HI antibody responses to AFLURIA QUADRIVALENT were non-inferior to both TIVs
491 for all influenza strains for subjects 18 years of age and older. Additionally, non-inferiority was
492 demonstrated for both endpoints in both age sub-groups, adults aged 18 through 64 years and 65
493 years and older, for all strains (Table 7). Superiority of the immune response to each of the
494 influenza B strains contained in AFLURIA QUADRIVALENT was shown relative to the



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495 antibody response after vaccination with TIV formulations not containing that B lineage strain
496 for subjects 18 years of age and older. Superiority against the alternate B strain was also
497 demonstrated for each of the influenza B strains in both age sub-groups; 18 through 64 years and
498 65 years and older. Post-hoc analyses of immunogenicity endpoints by gender did not
499 demonstrate meaningful differences between males and females. The study population was not
500 sufficiently diverse to assess differences between races or ethnicities.

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

Strain	Post-vaccination GMT		GMT Ratio ^b	Seroconversion % ^c		Difference	Met both pre-defined non-inferiority criteria? ^d
	AFLURIA Quadrivalent	Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria)	Pooled TIV or TIV-1 or TIV-2 over AFLURIA Quadrivalent (95% CI)	AFLURIA Quadrivalent N=1691	Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria)	Pooled TIV or TIV-1 or TIV-2 minus AFLURIA Quadrivalent (95% CI)	
18 through 64 years	AFLURIA Quadrivalent N=835, Pooled TIV N=845, TIV-1 N=424, TIV-2 N=421						
A(H1N1)	432.7	402.8	0.93 ^e (0.85, 1.02)	51.3	49.1	-2.1 ^h (-6.9, 2.7)	Yes
A(H3N2)	569.1	515.1	0.91 ^e (0.83, 0.99)	56.3	51.7	-4.6 ^h (-9.4, 0.2)	Yes
B/Massachusetts/2/2012 (B Yamagata)	92.3	79.3	0.86 ^f (0.76, 0.97)	45.7	41.3	-4.5 ⁱ (-10.3, 1.4)	Yes
B/Brisbane/60/2008 (B Victoria)	110.7	95.2	0.86 ^g (0.76, 0.98)	57.6	53.0	-4.6 ^j (-10.5, 1.2)	Yes
≥ 65 years	AFLURIA Quadrivalent N=856, Pooled TIV N=859, TIV-1 N=430, TIV-2 N=429						
A(H1N1)	211.4	199.8	0.95 ^e (0.88, 1.02)	26.6	26.4	-0.2 ^h (-5.0, 4.5)	Yes
A(H3N2)	419.5	400.0	0.95 ^e (0.89, 1.02)	25.9	27.0	1.1 ^h (-3.7, 5.8)	Yes
B/Massachusetts/2/2012 (B Yamagata)	43.3	39.1	0.90 ^f (0.84, 0.97)	16.6	14.4	-2.2 ⁱ (-8.0, 3.6)	Yes
B/Brisbane/60/2008 (B Victoria)	66.1	68.4	1.03 ^g (0.94, 1.14)	23.5	24.7	1.2 ^j (-4.6, 7.0)	Yes

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

505 ^a NCT02214225

506 ^b GMT ratio was computed after fitting a multi-variable model on the post-vaccination titers including sex, vaccination history,
507 pre-vaccination HI titers and other factors.

508 ^c Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer $\geq 1:10$ or an
509 increase in titer from $< 1:10$ to $\geq 1:40$.

510 ^d 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
511 Yamagata) or TIV-2 (B Victoria)/AFLURIA Quadrivalent should not exceed 1.5. NI criterion for the SCR difference: upper
512 bound of 2-sided 95% CI on the difference between SCR Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria) minus
513 AFLURIA Quadrivalent should not exceed 10%.

514 ^e Pooled TIV/AFLURIA Quadrivalent

515 ^f TIV-1 (B Yamagata)/AFLURIA Quadrivalent

516 ^g TIV-2 (B Victoria)/AFLURIA Quadrivalent

517 ^h Pooled TIV – AFLURIA Quadrivalent

518 ⁱ TIV-1 (B Yamagata) - AFLURIA Quadrivalent

519 ^j TIV-2 (B Victoria) - AFLURIA Quadrivalent

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14.3 Immunogenicity of AFLURIA (trivalent formulation) Administered by PharmaJet 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 PharmaJet 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 PharmaJet 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 PharmaJet 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, Seroconversion Rates, and Analyses of Non-Inferiority of AFLURIA (trivalent formulation) Administered by PharmaJet Stratis Needle-Free Injection System or Needle and Syringe, Adults 18 through 64 Years of Age (Study 2)^a

Strain	Baseline GMT		Post-vaccination GMT		GMT Ratio ^b	Seroconversion % ^c		Difference	Met both pre-defined non-inferiority criteria? ^d
	Needle and Syringe N=568	PharmaJet Stratis Needle-Free Injection System N=562	Needle and Syringe N=568	PharmaJet Stratis Needle-Free Injection System N=562	Needle and Syringe over PharmaJet Stratis Needle-Free Injection System (95% CI)	Needle and Syringe N=568	PharmaJet Stratis Needle-Free Injection System N=562	Needle and Syringe minus PharmaJet Stratis Needle-Free Injection System (95% CI)	
A(H1N1)	79.5	83.7	280.6	282.9	0.99 (0.88, 1.12)	38.4	37.5	0.8 (-4.8, 6.5)	Yes
A(H3N2)	75.4	68.1	265.9	247.3	1.08 (0.96, 1.21)	45.1	43.8	1.3 (-4.5, 7.1)	Yes
B	12.6	13.5	39.7	42.5	0.94 (0.83, 1.06)	35.2	34.9	0.3 (-5.2, 5.9)	Yes

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

^a NCT01688921

^b GMT ratio is defined as post-vaccination GMT for Needle and Syringe/PharmaJet Stratis Needle-Free Injection System.

^c Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer $\geq 1:10$ or an increase in titer from $< 1:10$ to $\geq 1:40$.

^d Non-inferiority (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 1.5. NI criterion for the seroconversion rate (SCR) difference: 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%.

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551 14.4 Immunogenicity of AFLURIA QUADRIVALENT in Children 5 through 17
552 Years Administered by Needle and Syringe

553 Study 3 was a randomized, observer-blinded, comparator-controlled trial conducted in the U.S.
554 in children 5 through 17 years of age. A total of 2278 subjects were randomized 3:1 to receive
555 one or two doses of AFLURIA QUADRIVALENT (N=1709) or a U.S.-licensed comparator
556 quadrivalent influenza vaccine (N=569). Subjects 5 through 8 years of age were eligible to
557 receive a second dose at least 28 days after the first dose depending on their influenza vaccination
558 history, consistent with the 2015-2016 recommendations of the Advisory Committee on
559 Immunization Practices (ACIP) for Prevention and Control of Seasonal Influenza with Vaccines.
560 Approximately 25% of subjects in each treatment group in the 5 through 8 years of age sub-
561 group received two vaccine doses.

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

565 The primary objective was to demonstrate that vaccination with AFLURIA QUADRIVALENT
566 elicits an immune response that is not inferior to that of a comparator vaccine containing the
567 same recommended virus strains. The Per Protocol Population (AFLURIA QUADRIVALENT
568 n=1605, Comparator n=528) was used for the primary endpoint analyses. The co-primary
569 endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted for baseline HI titers and other
570 covariates) and seroconversion rates for each vaccine strain, 28 days after the last vaccination.
571 Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the
572 GMT ratio (Comparator/AFLURIA QUADRIVALENT) did not exceed 1.5 and the upper bound
573 of the 2-sided 95% CI of the seroconversion rate difference (Comparator minus AFLURIA
574 QUADRIVALENT) did not exceed 10.0% for each strain. Serum HI antibody responses to
575 AFLURIA QUADRIVALENT were non-inferior for both GMT ratio and seroconversion rates
576 relative to the comparator vaccine for all influenza strains (Table 9). Analyses of
577 immunogenicity endpoints by gender did not demonstrate meaningful differences between males
578 and females. The study population was not sufficiently diverse to assess differences among races
579 or ethnicities.

Package insert

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

Strain	Post-vaccination GMT		GMT Ratio ^c	Seroconversion % ^d		SCR Difference ^e	Met both pre-defined non-inferiority criteria? ^f
	AFLURIA Quadrivalent N=1605	Comparator N=528	Comparator over AFLURIA Quadrivalent (95% CI)	AFLURIA Quadrivalent N=1605 (95% CI)	Comparator N=528 (95% CI)	Comparator minus AFLURIA Quadrivalent (95% CI)	
A(H1N1)	952.6 (n=1604 ^g)	958.8	1.01 (0.93, 1.09)	66.4 (64.0, 68.7)	63.3 (59.0, 67.4)	-3.1 (-8.0, 1.8)	Yes
A(H3N2)	886.4 (n=1604 ^g)	930.6	1.05 (0.96, 1.15)	82.9 (81.0, 84.7)	83.3 (79.9, 86.4)	0.4 (-4.5, 5.3)	Yes
B/Phuket/3073/2013 (B Yamagata)	60.9 (n=1604 ^g)	54.3	0.89 (0.81, 0.98)	58.5 (56.0, 60.9)	55.1 (50.8, 59.4)	-3.4 (-8.3, 1.5)	Yes
B/Brisbane/60/2008 (B Victoria)	145.0 (n=1604 ^g)	133.4	0.92 (0.83, 1.02)	72.1 (69.8, 74.3)	70.1 (66.0, 74.0)	-2.0 (-6.9, 2.9)	Yes

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

587 ^a NCT02545543

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

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

595 ^d Seroconversion rate was defined as the percentage of subjects with either a prevaccination HI titer < 1:10 and a
596 postvaccination HI titer ≥ 1:40 or a prevaccination HI titer ≥ 1:10 and a 4-fold increase in postvaccination HI titer.

597 ^e Seroconversion rate difference = Comparator SCR percentage minus AFLURIA QUADRIVALENT SCR percentage.

598 ^f Non-inferiority (NI) criterion for the GMT ratio: upper bound of two-sided 95% CI on the GMT ratio of Comparator
599 /AFLURIA QUADRIVALENT should not exceed 1.5. NI criterion for the SCR difference: upper bound of two-sided 95%
600 CI on the difference between SCR Comparator – AFLURIA QUADRIVALENT should not exceed 10%.

601 ^g Subject 8400394-0046 was excluded from the Per-Protocol Population for the adjusted GMT analysis for the GMT ratio since
602 the subject did not have information on all covariates (unknown prevaccination history).

603 **14.5 Immunogenicity of AFLURIA QUADRIVALENT in Children 6 Months**
604 **through 59 Months Administered by Needle and Syringe**

605 Study 4 was a randomized, observer-blind, comparator-controlled trial conducted in the U.S. in
606 children 6 months through 59 months of age. A total of 2247 subjects were randomized 3:1 to
607 receive AFLURIA QUADRIVALENT (N=1684) or a U.S.-licensed comparator quadrivalent
608 influenza vaccine (N=563). Children 6 months through 35 months received one or two 0.25
609 mL doses and children 36 months through 59 months received one or two 0.5 mL doses.
610 Subjects were eligible to receive a second dose at least 28 days after the first dose depending
611 on their influenza vaccination history, consistent with the 2016-2017 recommendations of the
612 Advisory Committee on Immunization Practices (ACIP) for Prevention and Control of Seasonal

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613 Influenza with Vaccines. Approximately 40% of subjects in each treatment group received two
614 vaccine doses.

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

618 The primary objective was to demonstrate that vaccination with AFLURIA QUADRIVALENT
619 elicits an immune response that is not inferior to that of a comparator vaccine containing the
620 same recommended virus strains. The Per Protocol Population (AFLURIA QUADRIVALENT
621 n=1456, Comparator QIV n=484) was used for the primary endpoint analyses. The co-primary
622 endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted for baseline HI titers and other
623 covariates) and seroconversion rates for each vaccine strain, 28 days after the last vaccination.
624 Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the
625 GMT ratio (Comparator QIV/AFLURIA QUADRIVALENT) did not exceed 1.5 and the upper
626 bound of the 2-sided 95% CI of the seroconversion rate difference (Comparator QIV minus
627 AFLURIA QUADRIVALENT) did not exceed 10.0% for each strain. Serum HI antibody
628 responses to AFLURIA QUADRIVALENT were non-inferior for both GMT ratio and
629 seroconversion rates relative to the comparator vaccine for all influenza strains (Table 10).
630 Analyses of immunogenicity endpoints by gender did not demonstrate meaningful differences
631 between males and females. The study population was not sufficiently diverse to assess
632 differences among races or ethnicities.

Package insert

633 **Table 10: Post-Vaccination HI Antibody GMTs, SCRs, and Analyses of Non-Inferiority**
 634 **of AFLURIA QUADRIVALENT Relative to a U.S.-Licensed Comparator**
 635 **Quadrivalent Influenza Vaccine for each Strain 28 Days after Last**
 636 **Vaccination Among a Pediatric Population 6 through 59 Months of Age (Per**
 637 **Protocol Population) (Study 4)^{a, b}**

Strain	Post-vaccination GMT		GMT Ratio ^c	Seroconversion % ^d		SCR Difference ^e	Met both pre-defined non-inferiority criteria? ^f
	AFLURIA Quadrivalent N=1456	Comparator N=484	Comparator over AFLURIA Quadrivalent (95% CI)	AFLURIA Quadrivalent N=1456 (95% CI)	Comparator N=484 (95% CI)	Comparator minus AFLURIA Quadrivalent (95% CI)	
A(H1N1)	353.5 (n=1455 ^g)	281.0 (n=484)	0.79 (0.72, 0.88)	79.1 (76.9, 81.1) (n=1456)	68.8 (64.5, 72.9) (n=484)	-10.3 (-15.4, -5.1)	Yes
A(H3N2)	393.0 (n=1454 ^g)	500.5 (n=484)	1.27 (1.15, 1.42)	82.3 (80.2, 84.2) (n=1455 ^h)	84.9 (81.4, 88.0) (n=484)	2.6 (-2.5, 7.8)	Yes
B/Phuket/3073/2013 (B Yamagata)	23.7 (n=1455 ^g)	26.5 (n=484)	1.12 (1.01, 1.24)	38.9 (36.4, 41.4) (n=1456)	41.9 (37.5, 46.5) (n=484)	3.1 (-2.1, 8.2)	Yes
B/Brisbane/60/2008 (B Victoria)	54.6 (n=1455 ^g)	52.9 (n=483 ^h)	0.97 (0.86, 1.09)	60.2 (57.6, 62.7) (n=1456)	61.1 (56.6, 65.4) (n=483 ^h)	0.9 (-4.2, 6.1)	Yes

638 Abbreviations: CI, confidence interval; Comparator, Comparator quadrivalent influenza vaccine (Fluzone Quadrivalent
 639 [Sanofi Aventis]); GMT (adjusted), geometric mean titer; SCR, seroconversion rate.

640 ^a NCT02914275

641 ^b The Per-Protocol Population comprised all subjects (6 through 35 months of age receiving one or two 0.25 mL doses and 36
 642 through 59 months of age receiving one or two 0.5 mL doses) in the Evaluable Population who did not have any protocol
 643 deviations that were medically assessed as potentially impacting on immunogenicity results.

644 ^c GMT Ratio = Comparator / AFLURIA QUADRIVALENT. Adjusted analysis model: Log-transformed Post-Vaccination HI
 645 Titer=Vaccine + Age Cohort [6 through 35 months or 36 through 59 months] + Gender + Vaccination History [y/n] + Log-
 646 transformed Pre-Vaccination HI Titer + Site + Number of Doses (1 vs 2) + Age Cohort*Vaccine. The Age Cohort*Vaccine
 647 interaction term was excluded from the model fit for the strains A(H1N1), A(H3N2) and B/Yamagata as the interaction result
 648 was non-significant (p>0.05). Least square means were back transformed.

649 ^d Seroconversion rate was defined as the percentage of subjects with either a prevaccination HI titer < 1:10 and a
 650 postvaccination HI titer ≥ 1:40 or a prevaccination HI titer ≥ 1:10 and a 4-fold increase in postvaccination HI titer.

651 ^e Seroconversion rate difference = Comparator SCR percentage minus AFLURIA QUADRIVALENT SCR percentage.

652 ^f Noninferiority (NI) criterion for the GMT ratio: upper bound of two-sided 95% CI on the GMT ratio of Comparator /
 653 AFLURIA QUADRIVALENT should not exceed 1.5. NI criterion for the SCR difference: upper bound of two-sided 95% CI
 654 on the difference between SCR Comparator – AFLURIA QUADRIVALENT should not exceed 10%.

655 ^g Subject 8400402-0073 was excluded from the Per-Protocol Population for the adjusted GMT analysis for the GMT ratio
 656 because the subject did not have information on all covariates (unknown prevaccination history).

657 ^h Subject 8400427-0070 had missing B/Victoria Antigen pre-vaccination titer.

658 ⁱ Subject 8400402-0074 had missing A/H3N2 post-vaccination titer.

659 **15 REFERENCES**

- 660 1. Centers for Disease Control and Prevention. Prevention and Control of Influenza:
 661 Recommendations of the Advisory Committee on Immunization Practices (ACIP).
 662 *MMWR Recomm Rep* 2010;59 (RR-8):1-62.
 663 2. Hannoun C, Megas F, Piercy J. Immunogenicity and Protective Efficacy of Influenza
 664 Vaccination. *Virus Res* 2004;103:133-138.
 665 3. Hobson D, Curry RL, Beare AS, et al. The Role of Serum Hemagglutination-Inhibiting
 666 Antibody in Protection against Challenge Infection with Influenza A2 and B Viruses.
 667 *J Hyg Camb* 1972;70:767-777.

Package insert668 **16 HOW SUPPLIED/STORAGE AND HANDLING**669 **16.1 How Supplied**

670 Each product presentation includes a package insert and the following components:

Presentation	Carton NDC Number	Components
Pre-Filled Syringe	33332-220-20	<ul style="list-style-type: none">Ten 0.25 mL single-dose syringes fitted with a Luer-Lok™ attachment without needles [NDC 33332-220-21]
Pre-Filled Syringe	33332-320-01	<ul style="list-style-type: none">Ten 0.5 mL single-dose syringes fitted with a Luer-Lok™ attachment without needles [NDC 33332-320-02]
Multi-Dose Vial	33332-420-10	<ul style="list-style-type: none">One 5 mL vial [NDC 33332-420-11]

671 **16.2 Storage and Handling**

- 672 • Store refrigerated at 2–8°C (36–46°F).
- 673 • Do not freeze. Discard if product has been frozen.
- 674 • Protect from light.
- 675 • Do not use AFLURIA QUADRIVALENT beyond the expiration date printed on the
- 676 label.
- 677 • Between uses, return the multi-dose vial to the recommended storage conditions.
- 678 • Once the stopper of the multi-dose vial has been pierced the vial must be discarded within
- 679 28 days.
- 680 • The number of needle punctures should not exceed 20 per multi-dose vial.

681 **17 PATIENT COUNSELING INFORMATION**

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



Package insert

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

701 Distributed by:
702 **Seqirus USA Inc.** 25 Deforest Avenue, Summit, NJ 07901, USA
703 1-855-358-8966

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