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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

INDICATIONS AND USAGE

- AFLURIA QUADRIVALENT SOUTHERN HEMISPHERE 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 SOUTHERN HEMISPHERE 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. Two doses are recommended for children 6 months through 8 years who have not previously received ≥2 doses of trivalent or quadrivalent influenza vaccine ≥4 weeks apart or whose previous influenza vaccination history is unknown. (2)

DOSAGE FORMS AND STRENGTHS

AFLURIA QUADRIVALENT SOUTHERN HEMISPHERE is a suspension for injection supplied in a 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 SOUTHERN HEMISPHERE 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 SOUTHERN HEMISPHERE 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)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: MM/YYYY

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1 FULL PRESCRIBING INFORMATION**1 INDICATIONS AND USAGE**

AFLURIA QUADRIVALENT SOUTHERN HEMISPHERE 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 SOUTHERN HEMISPHERE 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 SOUTHERN HEMISPHERE are presented in Table 1.

Table 1: AFLURIA QUADRIVALENT SOUTHERN HEMISPHERE 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. Two doses are recommended for children 6 months through 8 years who have not previously received ≥ 2 doses of trivalent or quadrivalent influenza vaccine ≥ 4 weeks apart or whose previous influenza vaccination history is unknown.

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 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.

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- 30 • PharmaJet Stratis Needle-Free Injection System: For instructions on withdrawal of a 0.5 mL
31 dose and use of the PharmaJet Stratis Needle-Free Injection System, refer to the Instructions
32 For Use for the PharmaJet Stratis Needle-Free Injection System.
33

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

38 **3 DOSAGE FORMS AND STRENGTHS**

39 AFLURIA QUADRIVALENT SOUTHERN HEMISPHERE is a sterile suspension for
40 intramuscular injection (see [Description \[11\]](#)).
41

42 AFLURIA QUADRIVALENT SOUTHERN HEMISPHERE is supplied in 5 mL multi-dose vial
43 (for persons 6 months of age and older).

44 **4 CONTRAINDICATIONS**

45 AFLURIA QUADRIVALENT SOUTHERN HEMISPHERE is contraindicated in individuals
46 with known severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine
47 including egg protein, or to a 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 SOUTHERN HEMISPHERE
52 should be based on careful 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.

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60 **5.3 Altered Immunocompetence**

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

64 **5.4 Limitations of Vaccine Effectiveness**

65 Vaccination with AFLURIA QUADRIVALENT SOUTHERN HEMISPHERE may not protect
66 all individuals.

67 **6 ADVERSE REACTIONS**

68 The safety experience with AFLURIA QUADRIVALENT and AFLURIA (trivalent
69 formulation) is relevant to AFLURIA QUADRIVALENT SOUTHERN HEMISPHERE because
70 the vaccines are manufactured using the same process (*see Description [11]*). This section
71 summarizes data obtained from clinical studies with AFLURIA QUADRIVALENT and
72 AFLURIA (trivalent formulation).

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

77 In adults 65 years of age and older, the most commonly reported injection-site adverse reaction
78 observed in clinical studies with AFLURIA QUADRIVALENT administered by needle and
79 syringe was pain ($\geq 20\%$). The most common systemic adverse event observed was myalgia (\geq
80 10%).

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

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

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

93 In children 6 months through 35 months of age, the most frequently reported injection site
94 reactions in the clinical study with AFLURIA QUADRIVALENT administered by needle and

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95 syringe were pain and redness ($\geq 20\%$). The most common systemic adverse events were
96 irritability ($\geq 30\%$), diarrhea and loss of appetite ($\geq 20\%$).

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

100

101 **6.1 Clinical Trials Experience**

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

105 *Adults*

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

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

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125 **Table 2: Proportion of Subjects Per Age Cohort with Any Solicited Local Adverse**
126 **Reactions or Systemic Adverse Events within 7 Days after Administration of**
127 **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

128 Abbreviations: Gr 3, Grade 3.

129 ^a NCT02214225

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

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

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

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

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

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

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145 In the 180 days following vaccination, 2.3%, 1.6%, and 1.5% of all subjects who received
146 AFLURIA QUADRIVALENT, TIV-1, and TIV-2, respectively, experienced SAEs, including
147 six deaths, five in the AFLURIA QUADRIVALENT group and one in the TIV-2 group. The
148 majority of SAEs occurred after Study Day 28 and in subjects ≥ 65 years of age who had co-
149 morbid illnesses. No SAEs or deaths appeared related to the study vaccines.

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

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157 **Table 3: Proportion of Subjects 18 through 64 Years of Age with Solicited Local**
 158 **Adverse Reactions or Systemic Adverse Events within 7 Days after**
 159 **Administration of AFLURIA (trivalent formulation) by PharmaJet Stratis**
 160 **Needle-Free Injection 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

161 ^a NCT01688921

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

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

167 ^d Local adverse reactions: Grade 3 is pain, tenderness or itching that prevents daily activity; Swelling, redness or bruising: any =
 168 ≥ 25mm diameter, Grade 3 = > 100mm diameter.

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

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

173 In adults 18 through 64 years who received AFLURIA (trivalent formulation) administered by
 174 PharmaJet Stratis Needle-Free Injection System, commonly reported unsolicited adverse events
 175 were headache (4.2%), injection site hematoma (1.8%), injection site erythema (1.1%), myalgia
 176 (1.0%) and nausea (1.0%).

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

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

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

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199 **Table 4: Proportion of Subjects Per Age Cohort with Any Solicited Local Adverse**
200 **Reactions or Systemic Adverse Events within 7 Days after Administration of**
201 **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

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

204 ^aNCT02545543

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

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

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

211 ^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
212 that which prevents daily activity or requires significant medical intervention.
213

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

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

220 The most commonly reported unsolicited adverse events in the 28 days following the first or
221 second dose of AFLURIA QUADRIVALENT in subjects 5 through 8 years of age were cough

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222 (2.4%), pyrexia (1.8%), rhinorrhea (1.2%), and headache (1.0%), and were similar to the
223 comparator.

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

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

233 *Children 6 Months Through 59 Months of Age*

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

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

Package insert

255 **Table 5: Proportion of Subjects Per Age Cohort with Any Solicited Local Adverse**
256 **Reactions or Systemic Adverse Events within 7 Days after Administration of**
257 **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

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

260 ^a NCT02914275

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

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

265 ^d Local adverse reactions: Grade 3 pain is that which prevents daily activity (36 through 59 month subjects); or cried when limb
266 was moved or spontaneously painful (6 through 35 month subjects); Swelling/Lump and redness: any = ≥ 0mm diameter, Grade
267 3 = ≥ 30mm diameter.

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

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

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

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

Package insert

280 The most commonly reported unsolicited adverse events in the 28 days following the first or
281 second dose of AFLURIA QUADRIVALENT in subjects 6 through 35 months of age were
282 rhinorrhea (11.2%), cough (10.4%), pyrexia (6.3%), upper respiratory tract infection (4.8%),
283 diarrhea (3.7%), otitis media (2.4%), vomiting (2.4%), nasal congestion (2.4%), nasopharyngitis
284 (1.9%), irritability (1.7%), ear infection (1.6%), croup infectious (1.4%), teething (1.3%), rash
285 (1.2%), influenza like illness (1.0%) and fatigue (1.0%), and were similar to comparator.

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

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

297

298 6.2 Postmarketing Experience

299 Because postmarketing reporting of adverse events is voluntary and from a population of
300 uncertain size, it is not always possible to reliably estimate their frequency or establish a causal
301 relationship to vaccine exposure. The adverse events described have been included in this
302 section because they: 1) represent reactions that are known to occur following immunizations
303 generally or influenza immunizations specifically; 2) are potentially serious; or 3) have been
304 reported frequently. Currently, there are no post-marketing data available for AFLURIA
305 QUADRIVALENT SOUTHERN HEMISPHERE and there are limited postmarketing data
306 available for AFLURIA QUADRIVALENT. The adverse events listed below reflect experience
307 in both children and adults and include those identified during post-approval use of AFLURIA
308 (trivalent formulation) outside the U.S. since 1985.

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

310 Blood and lymphatic system disorders

311 Thrombocytopenia

312 Immune system disorders

313 Allergic or immediate hypersensitivity reactions including anaphylactic shock and serum
314 sickness

315 Nervous system disorders

Package insert

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

318 **Vascular disorders**

319 Vasculitis which may be associated with transient renal involvement

320 **Skin and subcutaneous tissue disorders**

321 Pruritus, urticaria, and rash

322 **General disorders and administration site conditions**

323 Cellulitis and large injection site swelling

324 Influenza-like illness

325 **7 DRUG INTERACTIONS**

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

328 **8 USE IN SPECIFIC POPULATIONS**

329 Data in this section were obtained from studies with AFLURIA (trivalent formulation). The data
330 are relevant to AFLURIA QUADRIVALENT SOUTHERN HEMISPHERE, because both
331 vaccines are manufactured using the same process (see [Description \[11\]](#)).

332 **8.1 Pregnancy**

333 Risk summary

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

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

349 Clinical Considerations

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

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

Data*Animal Data*

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

8.2 Lactation**Risk Summary**

363 It is not known whether AFLURIA QUADRIVALENT SOUTHERN HEMISPHERE is
364 excreted in human milk. Data are not available to assess the effects of AFLURIA
365 QUADRIVALENT SOUTHERN HEMISPHERE on the breastfed infant or on milk
366 production/excretion.

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

8.4 Pediatric Use

373 The safety and effectiveness of AFLURIA QUADRIVALENT SOUTHERN HEMISPHERE in
374 persons less than 6 months of age have not been established.

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

8.5 Geriatric Use

380 In clinical studies, AFLURIA QUADRIVALENT has been administered to, and safety
381 information collected for, 867 subjects aged 65 years and older (*see Adverse Reactions [6]*). The
382 65 years and older age group included 539 subjects 65 through 74 years and 328 subjects 75
383 years and older. After administration of AFLURIA QUADRIVALENT, hemagglutination-
384 inhibiting antibody responses were non-inferior to comparator trivalent influenza (TIV-1 and
385 TIV-2) in persons 65 years of age and older, but were lower than younger adult subjects (*see
386 Clinical Studies [14]*).

Package insert

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

391 **11 DESCRIPTION**

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

401 AFLURIA QUADRIVALENT SOUTHERN HEMISPHERE is standardized according to
402 USPHS requirements for the 2021 Southern Hemisphere influenza season and is formulated to
403 contain 60 mcg hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 mcg HA
404 for each of the four influenza strains recommended for the 2021 Southern Hemisphere influenza
405 season:

406 A/Victoria/2570/2019 IVR-215 (an A/Victoria/2570/2019 (H1N1)pdm09-like virus), A/Hong
407 Kong/2671/2019 IVR-208 (an A/Hong Kong/2671/2019 (H3N2)-like virus),
408 B/Victoria/705/2018 BVR-11 (a B/Washington/02/2019-like virus) and B/Phuket/3073/2013
409 BVR-1B (a B/Phuket/3073/2013-like virus). A 0.25 mL dose contains 7.5 mcg HA of each of
410 the same four influenza strains.

411 The multi-dose presentation contains thimerosal added as a preservative; each 0.5 mL dose
412 contains 24.5 mcg of mercury and each 0.25 mL dose contains 12.25 mcg of mercury.

413 A single 0.5 mL dose of AFLURIA QUADRIVALENT SOUTHERN HEMISPHERE contains
414 sodium chloride (4.1 mg), monobasic sodium phosphate (80 mcg), dibasic sodium phosphate
415 (300 mcg), monobasic potassium phosphate (20 mcg), potassium chloride (20 mcg), and calcium
416 chloride (0.5 mcg). From the manufacturing process, each 0.5 mL dose may also contain
417 residual amounts of sodium taurodeoxycholate (≤ 10 ppm), ovalbumin (< 1 mcg), sucrose (< 10
418 mcg), neomycin sulfate (≤ 81.8 nanograms [ng]), polymyxin B (≤ 14 ng), beta-propiolactone
419 (≤ 1.5 ng) and hydrocortisone (≤ 0.56 ng). A single 0.25 mL dose of AFLURIA
420 QUADRIVALENT SOUTHERN HEMISPHERE contains half of these quantities.

421 The rubber stoppers used for the multi-dose vial were not made with natural rubber latex.

Package insert

422 **12 CLINICAL PHARMACOLOGY**423 **12.1 Mechanism of Action**

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

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

440 Annual revaccination with the current vaccine is recommended because immunity declines
441 during the year after vaccination and circulating strains of influenza virus change from year to
442 year.

443 **13 NONCLINICAL TOXICOLOGY**444 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

449 **14 CLINICAL STUDIES**

450 This section summarizes data obtained from clinical studies with AFLURIA QUADRIVALENT
451 and AFLURIA (trivalent formulation). Data from AFLURIA QUADRIVALENT and
452 AFLURIA (trivalent formulation) are relevant to AFLURIA QUADRIVALENT SOUTHERN
453 HEMISPHERE because the vaccines are manufactured using the same process (see [Description
454 \[11\]](#)).

455

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14.1 Efficacy Against Laboratory-Confirmed Influenza

456
457 The efficacy of AFLURIA (trivalent formulation) is relevant to AFLURIA QUADRIVALENT
458 because both vaccines are manufactured using the same process and have overlapping
459 compositions (*see Description [11]*).

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

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

Package insert

479 **Table 6: AFLURIA (trivalent formulation): Laboratory-Confirmed Influenza Infection**
480 **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 %
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		

481 Abbreviations: CI, confidence interval.

482 ^aNCT00562484

483 ^bThe Per Protocol Population was identical to the Evaluable Population in this study.

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

486 **14.2 Immunogenicity of AFLURIA QUADRIVALENT in Adults and Older Adults**
487 **Administered by Needle and Syringe**

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

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

502 Serum HI antibody responses to AFLURIA QUADRIVALENT were non-inferior to both TIVs
503 for all influenza strains for subjects 18 years of age and older. Additionally, non-inferiority was
504 demonstrated for both endpoints in both age sub-groups, adults aged 18 through 64 years and 65
505 years and older, for all strains (Table 7). Superiority of the immune response to each of the
506 influenza B strains contained in AFLURIA QUADRIVALENT was shown relative to the
507 antibody response after vaccination with TIV formulations not containing that B lineage strain



Package insert

508 for subjects 18 years of age and older. Superiority against the alternate B strain was also
509 demonstrated for each of the influenza B strains in both age sub-groups; 18 through 64 years and
510 65 years and older. Post-hoc analyses of immunogenicity endpoints by gender did not
511 demonstrate meaningful differences between males and females. The study population was not
512 sufficiently diverse to assess differences between races or ethnicities.

Package insert

513 **Table 7: Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of**
514 **Non-Inferiority of AFLURIA QUADRIVALENT Relative to Trivalent**
515 **Influenza 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

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

517 ^a NCT02214225

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

520 ^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
521 increase in titer from $< 1:10$ to $\geq 1:40$.

522 ^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
523 Yamagata) or TIV-2 (B Victoria)/AFLURIA Quadrivalent should not exceed 1.5. NI criterion for the SCR difference: upper
524 bound of 2-sided 95% CI on the difference between SCR Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria) minus
525 AFLURIA Quadrivalent should not exceed 10%.

526 ^e Pooled TIV/AFLURIA Quadrivalent

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

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

Package insert

529 ^h Pooled TIV – AFLURIA Quadrivalent
 530 ⁱ TIV-1 (B Yamagata) - AFLURIA Quadrivalent
 531 ^j TIV-2 (B Victoria) - AFLURIA Quadrivalent

532 **14.3 Immunogenicity of AFLURIA (trivalent formulation) Administered by**
 533 **PharmaJet Stratis Needle-Free Injection System**

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

550 **Table 8: Baseline and Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and**
 551 **Analyses of Non-Inferiority of AFLURIA (trivalent formulation) Administered**
 552 **by PharmaJet Stratis Needle-Free Injection System or Needle and Syringe,**
 553 **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

554 Abbreviations: CI, confidence interval; GMT, geometric mean titer.
 555 ^a NCT01688921

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- 556 ^b GMT ratio is defined as post-vaccination GMT for Needle and Syringe/PharmaJet Stratis Needle-Free Injection System.
557 ^c Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer $\geq 1:10$ or
558 an increase in titer from $< 1:10$ to $\geq 1:40$.
559 ^d Non-inferiority (NI) criterion for the GMT ratio: upper bound of 2-sided 95% CI on the GMT ratio of Needle and
560 Syringe/PharmaJet Stratis Needle-Free Injection System should not exceed 1.5. NI criterion for the seroconversion rate
561 (SCR) difference: upper bound of 2-sided 95% CI on the difference between SCR Needle and Syringe – SCR PharmaJet
562 Stratis Needle-Free Injection System should not exceed 10%.

563 **14.4 Immunogenicity of AFLURIA QUADRIVALENT in Children 5 through 17** 564 **Years Administered by Needle and Syringe**

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

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

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

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592 **Table 9: Post-Vaccination HI Antibody GMTs, SCRs, and Analyses of Non-Inferiority of**
 593 **AFLURIA QUADRIVALENT Relative to a U.S.-Licensed Comparator**
 594 **Quadrivalent Influenza Vaccine for each Strain 28 Days after Last Vaccination**
 595 **Among a Pediatric Population 5 through 17 Years of Age (Per Protocol**
 596 **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

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

599 ^a NCT02545543

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

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

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

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

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

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

615 **14.5 Immunogenicity of AFLURIA QUADRIVALENT in Children 6 Months**
 616 **through 59 Months Administered by Needle and Syringe**

617 Study 4 was a randomized, observer-blind, comparator-controlled trial conducted in the U.S. in
 618 children 6 months through 59 months of age. A total of 2247 subjects were randomized 3:1 to
 619 receive AFLURIA QUADRIVALENT (N=1684) or a U.S.-licensed comparator quadrivalent
 620 influenza vaccine (N=563). Children 6 months through 35 months received one or two 0.25
 621 mL doses and children 36 months through 59 months received one or two 0.5 mL doses.
 622 Subjects were eligible to receive a second dose at least 28 days after the first dose depending

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623 on their influenza vaccination history, consistent with the 2016-2017 recommendations of the
624 Advisory Committee on Immunization Practices (ACIP) for Prevention and Control of Seasonal
625 Influenza with Vaccines. Approximately 40% of subjects in each treatment group received two
626 vaccine doses.

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

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

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645 **Table 10: Post-Vaccination HI Antibody GMTs, SCRs, and Analyses of Non-Inferiority**
 646 **of AFLURIA QUADRIVALENT Relative to a U.S.-Licensed Comparator**
 647 **Quadrivalent Influenza Vaccine for each Strain 28 Days after Last**
 648 **Vaccination Among a Pediatric Population 6 through 59 Months of Age (Per**
 649 **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

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

652 ^a NCT02914275

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

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

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

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

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

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

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

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

671 **15 REFERENCES**

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681 16 HOW SUPPLIED/STORAGE AND HANDLING

682 16.1 How Supplied

683 Each product presentation includes a package insert and the following component:

Presentation	Carton NDC Number	Components
Multi-Dose Vial	33332-211-10	<ul style="list-style-type: none">One 5 mL vial [NDC 33332-211-11]

684 16.2 Storage and Handling

- 685 • Store refrigerated at 2–8°C (36–46°F).
- 686 • Do not freeze. Discard if product has been frozen.
- 687 • Protect from light.
- 688 • Do not use AFLURIA QUADRIVALENT SOUTHERN HEMISPHERE beyond the
689 expiration date printed on the label.
- 690 • Between uses, return the multi-dose vial to the recommended storage conditions.
- 691 • Once the stopper of the multi-dose vial has been pierced the vial must be discarded within
692 28 days.
- 693 • The number of needle punctures should not exceed 20 per multi-dose vial.

694 17 PATIENT COUNSELING INFORMATION

- 695 • Inform the vaccine recipient or guardian of the potential benefits and risks of
696 immunization with AFLURIA QUADRIVALENT SOUTHERN HEMISPHERE.
- 697 • Inform the vaccine recipient or guardian that AFLURIA QUADRIVALENT
698 SOUTHERN HEMISPHERE is an inactivated vaccine that cannot cause influenza but
699 stimulates the immune system to produce antibodies that protect against influenza, and
700 that the full effect of the vaccine is generally achieved approximately 3 weeks after
701 vaccination.
- 702 • Instruct the vaccine recipient or guardian to report any severe or unusual adverse
703 reactions to their healthcare provider.
- 704 • Provide the vaccine recipient Vaccine Information Statements prior to immunization.
705 These materials are available free of charge at the Centers for Disease Control and
706 Prevention (CDC) website (www.cdc.gov/vaccines).
- 707 • Instruct the vaccine recipient that annual revaccination is recommended.



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710 U.S. License No. 2044

711 Distributed by:
712 **Seqirus USA Inc.** 25 Deforest Avenue, Summit, NJ 07901, USA
713 1-855-358-8966

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