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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

AFLURIA, Influenza Vaccine
Suspension for Intramuscular Injection
2018-2019 Formula
Initial U.S. Approval: 2007

-----RECENT MAJOR CHANGES-----

Indications and Usage (1) XX/2018
Dosage and Administration (2) XX/2018

-----INDICATIONS AND USAGE-----

- AFLURIA is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B present in the vaccine. (1)
- AFLURIA is approved for use in persons 6 months of age and older. (1)

-----DOSAGE AND ADMINISTRATION-----

For intramuscular (IM) 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 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 , 0.5mL 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. (2)

-----DOSAGE FORMS AND STRENGTHS-----

AFLURIA 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 (ten 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 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 (trivalent formulation) administered by needle and syringe in children and adults:

- In children 5 through 17 years of age, the most common injection-site adverse reactions were pain (≥ 60%), redness (≥ 20%) and swelling (≥ 10%). The most common systemic adverse events were headache, myalgia (≥ 20%), irritability, malaise and fever (≥ 10%). (6.1)
- In adults 18 through 64 years of age, the most common injection-site adverse reactions were tenderness (≥ 60%), pain (≥ 40%), swelling (≥ 20%), and redness (≥ 10%). The most common systemic adverse events were muscle aches (≥ 30%) and headache, malaise (≥ 20%). (6.1)
- In adults 65 years of age and older the most common injection-site adverse reactions were tenderness (≥ 30%) and pain (≥ 10%). No systemic adverse events occurred in ≥ 10% of subjects in this age group (6.1)

AFLURIA QUADRIVALENT (Influenza Vaccine), a four-strain version of AFLURIA administered by needle and syringe in children:

- 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 administered by the PharmaJet Stratis Needle-Free Injection System:

- In adults 18 through 64 years of age, the most common injection-site adverse reactions when AFLURIA was administered by the PharmaJet® Stratis® Needle-Free Injection System up to 7 days post-vaccination were tenderness (≥ 80%), swelling, pain, redness (≥ 60%), itching (≥ 20%) and bruising (≥ 10%). The most common systemic adverse events within this period were myalgia, malaise (≥ 30%), and headache (≥ 20%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Seqirus 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 in persons less than 6 months of age have not been established. (8.4)
- Antibody responses were lower in geriatric subjects than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2018

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

AFLURIA[®] (Influenza Vaccine) is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B present in the vaccine. AFLURIA is approved for use in persons 6 months of age and older.

2 DOSAGE AND ADMINISTRATION

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

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

Table 1: AFLURIA 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 dose 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

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

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

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

When using the multi-dose vial, shake the vial thoroughly before withdrawing each dose, and administer the dose immediately.

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

The preferred sites for intramuscular injection are the anterolateral aspect of the thigh in infants 6 months through 11 months of age, the anterolateral aspect of the thigh (or the deltoid muscle

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

31 Between uses, return the multi-dose vial to the recommended storage conditions between 2-8°C
32 (36–46°F). **Do not freeze.** Discard if the vaccine has been frozen.

33 **3 DOSAGE FORMS AND STRENGTHS**

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

35 AFLURIA is supplied in three presentations:

- 36 • 0.25 mL pre-filled syringe (single dose, for persons 6 months through 35 months of
37 age)
- 38 • 0.5 mL pre-filled syringe (single dose, for persons 36 months of age and older).
- 39 • 5 mL multi-dose vial (for persons 6 months of age and older).

40 **4 CONTRAINDICATIONS**

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

44 **5 WARNINGS AND PRECAUTIONS**

45 **5.1 Guillain-Barré Syndrome**

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

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

53 **5.2 Preventing and Managing Allergic Reactions**

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

56 **5.3 Altered Immunocompetence**

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

59 **5.4 Limitations of Vaccine Effectiveness**

60 Vaccination with AFLURIA may not protect all individuals.

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6 ADVERSE REACTIONS

In children 5 through 17 years of age, the most common injection site reactions observed in clinical studies with AFLURIA administered by needle and syringe were pain ($\geq 60\%$), redness ($\geq 20\%$) and swelling ($\geq 10\%$). The most common systemic adverse events were headache, myalgia ($\geq 20\%$), irritability, malaise and fever ($\geq 10\%$).

The safety experience with AFLURIA QUADRIVALENT (influenza vaccine), a four strain version of AFLURIA is relevant because both vaccines are manufactured using the same process and have overlapping compositions (see [Description \[11\]](#)).

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

In children 36 through 59 months of age, the most frequently reported injection site reactions in a clinical study with AFLURIA QUADRIVALENT administered by needle and syringe were pain ($\geq 30\%$) and redness ($\geq 20\%$). The most commonly reported systemic adverse events were malaise and fatigue, and diarrhea ($\geq 10\%$).

In adults 18 through 64 years of age, the most common injection-site adverse reactions observed in clinical studies with AFLURIA administered by needle and syringe were tenderness ($\geq 60\%$), pain ($\geq 40\%$), swelling ($\geq 20\%$), redness and itching ($\geq 10\%$). The most common systemic adverse events observed were muscle aches ($\geq 30\%$), headache and malaise ($\geq 20\%$).

In adults 65 years of age and older, the most common injection-site adverse reactions observed in clinical studies with AFLURIA administered by needle and syringe were tenderness ($\geq 30\%$) and pain ($\geq 10\%$). No systemic adverse reactions occurred in $\geq 10\%$ of subjects in this age group.

In adults 18 through 64 years of age, using the PharmaJet Stratis Needle-Free Injection System, the most common injection-site adverse reactions observed in a clinical study with AFLURIA up to 7 days post-vaccination were tenderness ($\geq 80\%$), swelling, pain, redness ($\geq 60\%$), itching ($\geq 20\%$) and bruising ($\geq 10\%$). The most common systemic adverse events within this period were myalgia, malaise ($\geq 30\%$) and headache ($\geq 20\%$).

6.1 Clinical Trials Experience

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

Children – AFLURIA

In clinical studies, AFLURIA has been administered to, and safety information collected for, 3,009 children ages 6 months through 17 years. The exposure in children includes 1,601 aged 6 months to less than 5 years, 756 children ages 5 years to less than 9 years and 652 children ages

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98 9 years through 17 years. Clinical safety data for AFLURIA in children are presented from three
99 clinical studies (Studies 1, 2 and 3). Data from a comparator-controlled trial (Study 1) are
100 presented, followed by pooled data from two open label studies (Studies 2 and 3). Subjects 6
101 months through 8 years of age received one or two vaccinations, administered by needle and
102 syringe, as determined by previous vaccination history (for further details on clinical study design,
103 dosing and demographics *see Clinical Studies [14]*).

104 Study 1 included 1,468 subjects for safety analysis, ages 6 months through 17 years, randomized
105 to receive AFLURIA (735 subjects) or another U.S.-licensed trivalent inactivated influenza
106 vaccine (manufactured by Sanofi Pasteur, Inc.) (733 subjects).

107 Study 2 included 1,976 subjects for safety analysis, ages 6 months through 17 years. All subjects
108 received AFLURIA.

109 Study 3 included 298 subjects for safety analysis, ages 6 months through 8 years. All subjects
110 received AFLURIA.

111 The safety assessment was similar for the three pediatric studies. Local (injection site) adverse
112 reactions and systemic adverse events were solicited for 7 days post-vaccination (Tables 2 and
113 3). Unsolicited adverse events were collected for 30 days post-vaccination. All adverse events
114 are presented regardless of any treatment causality assigned by study investigators.

115 Among the pediatric studies, there were no vaccine-related deaths or vaccine-related serious
116 adverse events reported in children 5 years of age and older.

117 In the comparator-controlled trial (Study 1), the rate of fever after the first dose of AFLURIA in
118 subjects aged 5 through 8 years was 16% as compared to 8% in subjects who received the
119 comparator. The rate of fever in subjects aged 9 through 17 years following a single dose of
120 AFLURIA was 6% as compared to 4% in subjects who received the comparator. In all three
121 pediatric studies, the rates of fever in subjects aged 5 through 8 years who received AFLURIA
122 were lower after dose 2 than dose 1.

123 Data in Tables 2 and 3 are presented for children 5 years and older.

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Table 2: Proportion of Subjects 5 through 17 Years of Age with Solicited Local Adverse Reactions or Systemic Adverse Events within 7 Days after Administration of First or Second Dose of AFLURIA, Irrespective of Causality (Study 1)

	Percentage ^a of Subjects in each Age Group Reporting Event			
	Subjects 5 through 8 years		Subjects 9 through 17 years	
	AFLURIA N=161 ^b	Comparator N=165 ^b	AFLURIA N=254 ^b	Comparator N=250 ^b
After the First Dose				
Local Adverse Reactions				
Pain	63	60	66	60
Redness	23	27	17	17
Induration	17	17	15	16
Systemic Adverse Events				
Myalgia	34	30	40	37
Malaise	24	13	22	20
Headache	21	19	27	26
Any Fever	16	8	6	4
Fever ≥102.2°F	5	1	3	1
Nausea/Vomiting	12	8	9	10
Diarrhea	7	7	8	10
	AFLURIA N=39 ^b	Comparator N=53 ^b		
After the Second Dose				
Local Adverse Reactions				
Pain	36	38	-	-
Redness	10	19	-	-
Induration	8	17	-	-
Systemic Adverse Events				
Diarrhea	13	6	-	-
Headache	13	13	-	-
Myalgia	13	17	-	-
Malaise	5	8	-	-
Nausea/Vomiting	3	8	-	-
Any Fever	0	2	-	-
Fever ≥102.2°F	0	0	-	-

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

Table 3: Proportion of Subjects 5 through 17 Years of Age with Solicited Local Adverse Reactions or Systemic Adverse Events Within 7 Days after Administration of AFLURIA, Irrespective of Causality (Studies 2 and 3)

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	Percentage ^a of Subjects in each Age Group Reporting Event		
	Studies 2 and 3 Subjects 5 through 8 years		Study 2 Subjects 9 through 17 years
	Dose 1 N=82-595 ^b	Dose 2 N=82-426 ^b	Dose 1 N=397 ^b
Local Adverse Reactions			
Pain	61	56	68
Erythema	24	23	17
Swelling	17	17	13
Systemic Adverse Events			
Irritability ^d	18	16	-
Headache	16	10	27
Malaise or feeling generally unwell ^c	16	8	17
Any Fever	13	6	5
Fever $\geq 102.2^{\circ}\text{F}$	3	2	1
General Muscle Ache (Myalgia)	12	8	20
Nausea/Vomiting ^c	7	3	5
Vomiting/Diarrhea ^d	5	6	-
Loss of appetite ^d	5	4	-
Diarrhea ^c	4	2	5

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

138 ^b N = number of subjects in the Safety Population for each treatment group. Denominators for Dose 1 were: N=82 for
139 Vomiting/Diarrhea, Irritability, Loss of appetite, N=513 for Malaise, Diarrhea, Nausea/Vomiting and N=593-595 for all other
140 parameters. Denominators for Dose 2 were: N=82 for Vomiting/Diarrhea, Irritability, Loss of appetite, N=344 for Malaise,
141 Diarrhea and Nausea/Vomiting and N=421-426 for all other parameters.

142 ^c These preferred terms were used to describe Solicited Adverse Events in Study 2.

143 ^d These preferred terms were used to describe Solicited Adverse Events in Study 3.

144

145 In Study 1, unsolicited adverse events that occurred in $\geq 5\%$ of subjects 5 through 8 years
146 following the first or second dose of AFLURIA included cough (15%) and pyrexia (9%).
147 Unsolicited adverse events that occurred in $\geq 5\%$ of subjects 9 through 17 years following a
148 single dose of AFLURIA included cough (7%), oropharyngeal pain (7%), headache (7%) and
149 nasal congestion (6%).

150

151 In Studies 2 and 3, unsolicited adverse events that occurred in $\geq 5\%$ of subjects ages 5 years
152 through 8 years after the first or second dose of AFLURIA included the following: upper
153 respiratory tract infection (13%), cough (10%), rhinorrhea (7%), headache (5%), nasopharyngitis
154 (5%) and pyrexia (5%). Unsolicited adverse events that occurred in $\geq 5\%$ of subjects 9 through

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155 17 years following a single dose of AFLURIA included upper respiratory tract infection (9%)
156 and headache (8%).
157

158 ***Children 6 Months Through 59 Months of Age – AFLURIA QUADRIVALENT***

159 The safety experience with AFLURIA QUADRIVALENT (influenza vaccine), a four strain
160 version of AFLURIA is relevant because both vaccines are manufactured using the same process
161 and have overlapping compositions (see [Description \[11\]](#)). The safety of AFLURIA in children
162 6 through 59 months is based on a clinical trial conducted with AFLURIA QUADRIVALENT,
163 Study 4, a randomized, observer-blind, comparator-controlled trial conducted in the U.S. in 2247
164 subjects aged 6 through 59 months. Subjects were stratified into one of two age cohorts of 6
165 through 35 months or 36 through 59 months (41.6% and 58.4% of the study population,
166 respectively). The mean age of the population was 36.6 months, 51.6% were male, and racial
167 groups consisted of 71.0% White, 21.5% Black, 1.1% Asian, 0.7% Native Hawaiian/Pacific
168 Islander, and 0.3% American Indian/Native American; 26.4% of subjects were Hispanic/Latino.
169 The mean ages of subjects 6 through 35 months and 36 through 59 months were 21.7 months
170 and 47.1 months, respectively. Subjects in the safety population (N=2232) received either
171 AFLURIA QUADRIVALENT (N=1673) or a U.S.-licensed comparator quadrivalent influenza
172 vaccine (N=559). Study subjects were scheduled to receive either a single vaccination or two
173 vaccinations 28 days apart based on their previous vaccination history. In this study, AFLURIA
174 QUADRIVALENT and comparator vaccine were administered by needle and syringe (see
175 [Clinical Studies \[14\]](#)).

176 Local (injection site) adverse reactions and systemic adverse events were solicited for 7 days
177 post-vaccination. Cellulitis-like reactions (defined as concurrent Grade 3 pain, redness, and
178 swelling/lump) at the injection site were monitored for 28 days post-vaccination. Subjects were
179 instructed to report and return to clinic within 24 hours in the event of a cellulitis-like reaction.
180 Unsolicited adverse events were collected for 28 days post-vaccination, and SAEs for 6 months
181 following the last vaccination. All solicited local adverse reactions and systemic adverse events
182 following any vaccination (first or second dose) are presented in Table 4.

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183 **Table 4: Proportion of Subjects Per Age Cohort with Any Solicited Local Adverse**
184 **Reactions or Systemic Adverse Events within 7 Days after Administration of**
185 **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

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

188 ^a NCT02914275

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

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

193 ^d Local adverse reactions: Grade 3 pain is that which prevents daily activity (36 through 59 month subjects); or cried when limb
194 was moved or spontaneously painful (6 through 35 month subjects); Swelling/Lump and redness: any = \geq 0mm diameter, Grade
195 3 = \geq 30mm diameter.

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

199 ^f Prophylactic antipyretics (acetaminophen or ibuprofen-containing medications) were not permitted. Antipyretics used to treat
200 fever were permitted. The frequencies of antipyretic use in the seven days following any vaccination were as follows: 6 through
201 35 months (Afluria QIV 5.9%, Comparator QIV 9.0%); 36 through 59 months (Afluria QIV 3.7%, Comparator QIV 2.5%).

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

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

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208 The most commonly reported unsolicited adverse events in the 28 days following the first or
209 second dose of AFLURIA QUADRIVALENT in subjects 6 through 35 months of age were
210 rhinorrhea (11.2%), cough (10.4%), pyrexia (6.3%), upper respiratory tract infection (4.8%),
211 diarrhea (3.7%), otitis media (2.4%), vomiting (2.4%), nasal congestion (2.4%), nasopharyngitis
212 (1.9%), irritability (1.7%), ear infection (1.6%), croup infectious (1.4%), teething (1.3%), rash
213 (1.2%), influenza like illness (1.0%) and fatigue (1.0%), and were similar to comparator.

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

219
220 No deaths were reported in Study 4. In the 180 days following vaccinations, AFLURIA
221 QUADRIVALENT and comparator vaccine recipients experienced similar rates of serious
222 adverse events (SAEs), none of which were related to study vaccines. No vaccine-related febrile
223 seizures occurred in Study 4. Unrelated SAEs of febrile seizures occurred in two AFLURIA
224 QUADRIVALENT recipients (6 through 35 months age group) at 43 and 104 days post-
225 vaccinations.

226

Adults – AFLURIA

227
228 In clinical studies comparing AFLURIA to placebo or a comparator trivalent inactivated
229 influenza vaccine, a single dose of AFLURIA was administered to, and safety information
230 collected for, 11,104 subjects ages 18 through 64 years and 836 subjects ages 65 years and older.
231 Clinical safety data for AFLURIA in adults are presented from three clinical studies (Studies 5
232 through 7) conducted in the U.S. and one clinical study (Study 8) conducted in the UK.

233 Study 5 included 1,357 subjects for safety analysis, ages 18 through 64 years, randomized to
234 receive AFLURIA (1,089 subjects) or placebo (268 subjects) (*see Clinical Studies [14]*).

235 Study 6 included 15,020 subjects for safety analysis, ages 18 through 64 years, randomized to
236 receive AFLURIA (10,015 subjects) or placebo (5,005 subjects) (*see Clinical Studies [14]*).

237 Study 7 included 1,266 subjects for safety analysis, ages 65 years and older, randomized to
238 receive AFLURIA (630 subjects) or another U.S.-licensed trivalent inactivated influenza vaccine
239 (manufactured by Sanofi Pasteur Inc.) as an active comparator (636 subjects) (*see Clinical
240 Studies [14]*).

241 Study 8 included 275 subjects for safety analysis, ages 65 years and older, randomized to receive
242 AFLURIA (206 subjects) or a UK-licensed trivalent inactivated influenza vaccine (manufactured
243 by GSK) as an active comparator (69 subjects).

244 The safety assessment was identical for the four adult studies. Local (injection-site) adverse
245 reactions and systemic adverse events were solicited for 5 days post-vaccination (Table 5, studies



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246 5 through 7). Unsolicited adverse events were collected for 21 days post-vaccination. All
247 adverse events are presented regardless of any treatment causality assigned by study
248 investigators.

249 Among adult studies, there were no vaccine-related deaths or vaccine-related serious adverse
250 events reported.

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251 **Table 5: Proportion of Subjects 18 Years of Age and Older with Solicited Local Adverse**
252 **Reactions or Systemic Adverse Events within 5 Days after Administration of**
253 **AFLURIA or Placebo, Irrespective of Causality (Studies 5, 6 and 7)**

	Percentage ^a of Subjects in each Age Group Reporting Event					
	Study 5 Subjects 18 through 64 years		Study 6 Subjects 18 through 64 years		Study 7 Subjects ≥ 65 years	
	AFLURIA N=1087-1088 ^b	Placebo N=266 ^b	AFLURIA N=10,015 ^b	Placebo N=5005 ^b	AFLURIA N=630 ^b	Comparator N=636 ^b
Local Adverse Reactions						
Tenderness (Pain on touching)	60	18	69	17	36	31
Pain (without touching)	40	9	48	11	15	14
Redness	16	8	4	<1	3	1
Swelling	9	1	4	<1	7	8
Bruising	5	1	1	1	<1	1
Systemic Adverse Events						
Headache	26	26	25	23	9	11
Malaise	19	19	29	26	7	6
Muscle aches	13	9	21	12	9	8
Nausea	6	9	7	6	2	1
Chills/Shivering	3	2	5	4	2	2
Fever	1	1	3	2	<1	1

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

256 ^b N = number of subjects in the Safety Population for each treatment group.

257 In Study 5, headache was the only unsolicited adverse event that occurred in ≥ 5% of subjects
258 who received AFLURIA or placebo (8% versus 6%, respectively).

259 In Study 6, unsolicited adverse events that occurred in ≥ 5% of subjects who received AFLURIA
260 or placebo included headache (AFLURIA 12%, placebo 11%) and oropharyngeal pain
261 (AFLURIA 5%, placebo 5%).

262 In Study 7, headache was the only unsolicited adverse event that occurred in ≥ 5% of subjects
263 who received AFLURIA (5%).

264 Studies 1 to 8 were all conducted when AFLURIA and AFLURIA QUADRIVALENT were
265 administered by needle and syringe.

266 Additionally, safety information has been collected in a clinical study of AFLURIA administered
267 using the PharmaJet Stratis Needle-Free Injection System (Study 9). Study 9 included 1,247
268 subjects for safety analysis, ages 18 through 64 years, randomized to receive AFLURIA by either
269 the PharmaJet Stratis Needle-Free Injection System (624 subjects) or needle and syringe (623
270 subjects). No deaths or vaccine-related serious adverse events were reported in Study 7. Local

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271 (injection-site) adverse reactions and systemic adverse events were solicited for 7 days post-
272 vaccination (Table 6).

273 **Table 6: Proportion of Subjects 18 through 64 Years of Age with Solicited Local Adverse**
274 **Reactions or Systemic Adverse Events within 7 Days after Administration of**
275 **AFLURIA by PharmaJet Stratis Needle-Free Injection System or Needle and**
276 **Syringe Irrespective of Causality (Study 9).**
277

	Percentage ^a of Subjects Reporting Event	
	Study 9	
	Subjects 18 through 64 years	
	AFLURIA	
	PharmaJet Stratis Needle-Free Injection System N=540-616 ^b	Needle and Syringe N=599-606 ^b
Local Adverse Reactions		
Tenderness	89	78
Swelling	65	20
Pain	64	49
Redness	60	19
Itching ^c	28	10
Bruising	18	5
Systemic Adverse Events		
Myalgia	36	36
Malaise	31	28
Headache	25	22
Chills	7	7
Nausea	7	7
Vomiting	1	2
Fever	0	0

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

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

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

285

286 In Study 9, no unsolicited adverse events occurred in $\geq 5\%$ of subjects who received AFLURIA
287 administered by PharmaJet Stratis Needle-Free Injection System up to 28 days post-vaccination.

288 **6.2 Postmarketing Experience**

289 Because postmarketing reporting of adverse reactions is voluntary and from a population of
290 uncertain size, it is not always possible to reliably estimate their frequency or establish a causal

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291 relationship to vaccine exposure. The adverse reactions described have been included in this
292 section because they: 1) represent reactions that are known to occur following immunizations
293 generally or influenza immunizations specifically; 2) are potentially serious; or 3) have been
294 reported frequently. These adverse reactions reflect experience in both children and adults and
295 include those identified during post-approval use of AFLURIA outside the U.S. since 1985.

296 **Blood and lymphatic system disorders**

297 Thrombocytopenia

298 **Immune system disorders**

299 Allergic or immediate hypersensitivity reactions including anaphylactic shock and serum
300 sickness

301 **Nervous system disorders**

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

304 **Vascular disorders**

305 Vasculitis which may be associated with transient renal involvement

306 **Skin and subcutaneous tissue disorders**

307 Pruritus, urticaria, and rash

308 **General disorders and administration site conditions**

309 Cellulitis and large injection site swelling

310 Influenza-like illness

311 **6.3 Adverse Reactions Associated With Influenza Vaccination**

312 Anaphylaxis has been reported after administration of AFLURIA. Egg protein can induce
313 immediate hypersensitivity reactions among persons who have severe egg allergy. Allergic
314 reactions include hives, angioedema, asthma, and systemic anaphylaxis (*see [Contraindications](#)*
315 *[4]*).

316 Neurological disorders temporally associated with influenza vaccination, such as
317 encephalopathy, optic neuritis/neuropathy, partial facial paralysis, and brachial plexus
318 neuropathy, have been reported.

319 Microscopic polyangiitis (vasculitis) has been reported temporally associated with influenza
320 vaccination.

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321 **7 DRUG INTERACTIONS**

322 **7.1 Concurrent Use With Other Vaccines**

323 There are no data to assess the concomitant administration of AFLURIA with other vaccines. If
324 AFLURIA is given at the same time as another injectable vaccine(s), the vaccine(s) should be
325 administered in separate syringes and a separate arm should be used.

326 AFLURIA should not be mixed with any other vaccine in the same syringe or vial.

327 **8 USE IN SPECIFIC POPULATIONS**

328 **8.1 Pregnancy**

329 Risk Summary

330 All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general
331 population, the estimated background risk of major birth defects and miscarriage in clinically
332 recognized pregnancies is 2% to 4% and 15% to 20%, respectively. There are insufficient data
333 for AFLURIA in pregnant women to inform vaccine-associated risks in pregnancy.
334 A developmental toxicity study has been performed in female rats administered AFLURIA prior
335 to mating and during gestation. A single human dose (0.5 mL, divided) was injected on each
336 occasion. This study revealed no evidence of harm to the fetus due to AFLURIA (*see [8.1](#)*
337 *[Pregnancy -Data](#)*).

338 Clinical Considerations

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

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

343 Data

344 *Animal Data*

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

350 **8.2 Lactation**

351 Risk Summary

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

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

358 **8.4 Pediatric Use**

359 The safety and effectiveness of AFLURIA in persons less than 6 months of age have not been
360 established.

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

364 **8.5 Geriatric Use**

365 In clinical studies, AFLURIA has been administered to, and safety information collected for,
366 836 subjects ages 65 years and older (*see Clinical Trials Experience [6.1]*). After administration
367 of AFLURIA, hemagglutination-inhibiting antibody responses in persons 65 years of age and
368 older were lower as compared to younger adult subjects (*see Clinical Studies [14]*).

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

372 **11 DESCRIPTION**

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

381 AFLURIA is standardized according to USPHS requirements for the 2018-2019 influenza
382 season and is formulated to contain 45 mcg hemagglutinin (HA) per 0.5 mL dose in the
383 recommended ratio of 15 mcg HA for each of the three influenza strains recommended for the
384 2018-2019 Northern Hemisphere influenza season: A/Singapore/GP1908/2015 IVR 180A
385 (H1N1) (an A/Michigan/45/2015 – like virus), A/Singapore/INFIMH-16-0019/2016 IVR-186
386 (H3N2) (an A/Singapore/INFIMH-16-0019/2016 – like virus) and B/Maryland/15/2016 (a
387 B/Colorado/06/2017 – like virus). A 0.25 mL dose contains 7.5 mcg HA of each of the same
388 three influenza strains.

389 Thimerosal, a mercury derivative, is not used in the manufacturing process for the single dose
390 presentations; therefore these products contain no preservative. The multi-dose presentation

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391 contains thimerosal, added as a preservative; each 0.5 mL dose contains 24.5 mcg of mercury
392 and each 0.25 mL dose contains 12.25 mcg of mercury.

393 A single 0.5 mL dose of AFLURIA contains sodium chloride (4.1 mg), monobasic sodium
394 phosphate (80 mcg), dibasic sodium phosphate (300 mcg), monobasic potassium phosphate
395 (20 mcg), potassium chloride (20 mcg), and calcium chloride (0.5 mcg). From the
396 manufacturing process, each 0.5 mL dose may also contain residual amounts of sodium
397 taurodeoxycholate (≤ 10 ppm), ovalbumin (< 1 mcg), sucrose (< 10 mcg), neomycin sulfate
398 (≤ 61.5 nanograms [ng]), polymyxin B (≤ 10.5 ng), and beta-propiolactone (≤ 2 ng). A single
399 0.25 mL dose of AFLURIA contains half of these quantities.

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

402 12 CLINICAL PHARMACOLOGY**403 12.1 Mechanism of Action**

404 Influenza illness and its complications follow infection with influenza viruses. Global
405 surveillance of influenza identifies yearly antigenic variants. For example, since 1977 antigenic
406 variants of influenza A (H1N1 and H3N2) and influenza B viruses have been in global
407 circulation. Specific levels of hemagglutination inhibition (HI) antibody titers post-vaccination
408 with inactivated influenza vaccine have not been correlated with protection from influenza virus.
409 In some human studies, antibody titers of 1:40 or greater have been associated with protection
410 from influenza illness in up to 50% of subjects.^{2,3}

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

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

422 13 NONCLINICAL TOXICOLOGY**423 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

424 AFLURIA has not been evaluated for carcinogenic or mutagenic potential, or male infertility in
425 animals. A reproductive study of female rats vaccinated with AFLURIA revealed no impairment
426 of fertility (see Pregnancy, 8.1).

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427 **14 CLINICAL STUDIES**

428 **14.1 Efficacy of AFLURIA Against Laboratory-Confirmed Influenza**

429 In Study 6, the efficacy of AFLURIA was demonstrated in a randomized, observer-blind,
430 placebo-controlled study conducted in 15,044 subjects. Healthy subjects 18 through 64 years of
431 age were randomized in a 2:1 ratio to receive a single dose of AFLURIA (enrolled subjects:
432 10,033; evaluable subjects: 9,889) or placebo (enrolled subjects: 5,011; evaluable subjects:
433 4,960). The mean age of all randomized subjects was 35.5 years. 54.4% were female and 90.2%
434 were White. Laboratory-confirmed influenza was assessed by active and passive surveillance of
435 influenza-like illness (ILI) beginning 2 weeks post-vaccination until the end of the influenza
436 season, approximately 6 months post-vaccination. ILI was defined as at least one respiratory
437 symptom (e.g., cough, sore throat, nasal congestion) and at least one systemic symptom (e.g.,
438 oral temperature of 100.0°F or higher, feverishness, chills, body aches). Nasal and throat swabs
439 were collected from subjects who presented with an ILI for laboratory confirmation by viral
440 culture and real-time reverse transcription polymerase chain reaction. Influenza virus strain was
441 further characterized using gene sequencing and pyrosequencing.

442 Attack rates and vaccine efficacy, defined as the relative reduction in the influenza infection rate
443 for AFLURIA compared to placebo, were calculated using the per protocol population. Vaccine
444 efficacy against laboratory-confirmed influenza infection due to influenza A or B virus strains
445 contained in the vaccine was 60% with a lower limit of the 95% CI of 41% (Table 7).

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446 **Table 7: Laboratory-Confirmed Influenza Infection Rate and Vaccine Efficacy in Adults**
447 **18 through 64 Years of Age (Study 6)**

	Subjects ^a	Laboratory-Confirmed Influenza Cases	Influenza Infection Rate	Vaccine Efficacy ^b	
	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		

448 Abbreviations: CI, confidence interval

449 ^a The Per Protocol Population was identical to the Evaluable Population in this study.

450 ^b Vaccine efficacy = 1 minus the ratio of AFLURIA/placebo infection rates. The objective of the study was to demonstrate that
451 the lower limit of the CI for vaccine efficacy was greater than 40%.

452
453 **14.2 Immunogenicity of AFLURIA in Children 5 through 17 Years Administered**
454 **by Needle and Syringe**

455 Study 1 was a randomized, observer-blind, comparator-controlled study to evaluate the
456 immunological non-inferiority of AFLURIA to a U.S.-licensed trivalent inactivated influenza
457 vaccine (manufactured by Sanofi Pasteur, Inc.) in subjects 6 months through 17 years of age.
458 Study vaccines were administered by needle and syringe. Results are presented for children 5
459 through 17 years of age (Table 8). A total of 832 subjects (aged 5 through 17 years) were
460 enrolled. Subjects were randomized in a 1:1 ratio to receive AFLURIA (enrolled subjects: 417;
461 evaluable subjects: 383) or the comparator vaccine (enrolled subjects: 415; evaluable subjects:
462 383).

463
464 Children 6 months through 8 years of age with no history of influenza vaccination received 2
465 doses approximately 28 days apart. Children 6 months through 8 years of age with a history of
466 influenza vaccination and children 9 years of age and older received 1 dose. Children 6 months
467 through 35 months of age received 0.25 mL of AFLURIA or comparator influenza vaccine, and
468 children 3 years of age and older received 0.5 mL of AFLURIA or comparator influenza vaccine.
469 Nearly equal proportions of subjects were male (49.9%) and female (50.1%), and the majority
470 were White (85.0%) or Black (10.3%).

471
472 Immunogenicity assessments were performed prior to vaccination and at 30 days after
473 vaccination. The co-primary endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted
474 for baseline HI titers) and the difference in seroconversion rates for each vaccine strain 21 days
475 after the final vaccination. Pre-specified non-inferiority criteria required that the upper bound

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476 of the 2-sided 95% CI of the GMT ratio (Comparator/AFLURIA) did not exceed 1.5 and the
 477 upper bound of the 2-sided 95% CI of the seroconversion rate difference (Comparator minus
 478 AFLURIA) did not exceed 10.0% for each strain. As shown in Table 8, non-inferiority of
 479 AFLURIA to the comparator vaccine was demonstrated in the per protocol population for
 480 influenza A subtypes A(H1N1) and A(H3N2), but not for influenza type B. For influenza type
 481 B, non-inferiority was demonstrated for HI GMTs, but not for seroconversion rates. Note that
 482 the study was powered to assess the pre-specified non-inferiority criteria based on 1400
 483 evaluable subjects. Analysis of the 761 subjects aged 5 through 17 years reduced the power of
 484 the study and widened the confidence intervals. In the pre-specified analysis, AFLURIA was
 485 not inferior to the comparator vaccine for all three virus strains. Post-hoc analyses of
 486 immunogenicity by gender did not demonstrate significant differences between males and
 487 females. The study was not sufficiently diverse to assess differences between races or ethnicities.
 488

489 **Table 8: Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of**
 490 **Non-Inferiority of AFLURIA to a U.S.-Licensed Comparator, Subjects 5**
 491 **through 17 Years of Age (Study 1)**
 492

Strain	Post-vaccination GMT		GMT Ratio ^a	Seroconversion % ^b		Difference	Met both pre-defined non-inferiority criteria? ^c
	Comparator N=381	AFLURIA N=380	Comparator over AFLURIA (95% CI)	Comparator N=381	AFLURIA N=380	Comparator minus AFLURIA (95% CI)	
A(H1N1)	526.2	507.4	1.03 (0.88, 1.21)	62.7	62.6	0.1 (-6.8, 7.0)	Yes
A(H3N2)	1060.0	961.3	1.07 (0.94, 1.23)	72.2	69.7	2.4 (-4.0, 8.9)	Yes
B	123.3	110.1	1.10 (0.94, 1.29)	75.1	70.0	5.1 (-1.3, 11.4)	No

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

494 ^a GMT ratios are adjusted for baseline HI titers

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

497 ^c Note that the study was powered to assess the pre-specified non-inferiority criteria based on 1400 evaluable subjects.
 498

499 **14.3 Immunogenicity of AFLURIA QUADRIVALENT in Children 6 months**
 500 **through 59 months of age Administered by Needle and Syringe**

501 Data have also been collected in a clinical study of AFLURIA QUADRIVALENT, which is
 502 relevant to AFLURIA because both vaccines are manufactured using the same process and have
 503 overlapping compositions (Study 4).

504 Study 4 was a randomized, observer-blind, comparator-controlled trial conducted in the U.S. in
 505 children 6 months through 59 months of age. A total of 2247 subjects were randomized 3:1 to
 506 receive AFLURIA QUADRIVALENT (N=1684) or a U.S.-licensed comparator quadrivalent

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507 influenza vaccine (N=563). Children 6 months through 35 months received one or two 0.25
508 mL doses and children 36 months through 59 months received one or two 0.5 mL doses.
509 Subjects were eligible to receive a second dose at least 28 days after the first dose depending
510 on their influenza vaccination history, consistent with the 2016-2017 recommendations of the
511 Advisory Committee on Immunization Practices (ACIP) for Prevention and Control of Seasonal
512 Influenza with Vaccines. Approximately 40% of subjects in each treatment group received two
513 vaccine doses.

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

517 The primary objective was to demonstrate that vaccination with AFLURIA QUADRIVALENT
518 elicits an immune response that is not inferior to that of a comparator vaccine containing the
519 same recommended virus strains. The Per Protocol Population (AFLURIA QUADRIVALENT
520 n=1456, Comparator QIV n=484) was used for the primary endpoint analyses. The co-primary
521 endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted for baseline HI titers and other
522 covariates) and seroconversion rates for each vaccine strain, 28 days after the last vaccination.
523 Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the
524 GMT ratio (Comparator QIV/AFLURIA QUADRIVALENT) did not exceed 1.5 and the upper
525 bound of the 2-sided 95% CI of the seroconversion rate difference (Comparator QIV minus
526 AFLURIA QUADRIVALENT) did not exceed 10.0% for each strain. Serum HI antibody
527 responses to AFLURIA QUADRIVALENT were non-inferior for both GMT ratio and
528 seroconversion rates relative to the comparator vaccine for all influenza strains (Table 9).
529 Analyses of immunogenicity endpoints by gender did not demonstrate meaningful differences
530 between males and females. The study population was not sufficiently diverse to assess
531 differences among races or ethnicities.

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532 **Table 9: Post-Vaccination HI Antibody GMTs, SCR, and Analyses of Non-Inferiority**
 533 **of AFLURIA QUADRIVALENT Relative to a U.S.-Licensed Comparator**
 534 **Quadrivalent Influenza Vaccine for each Strain 28 Days after Last Vaccination**
 535 **Among a Pediatric Population 6 through 59 Months of Age (Per Protocol**
 536 **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

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

539 ^a NCT02914275

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

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

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

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

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

554 ^g Subject 8400402-0073 was excluded from the Per-Protocol Population for the adjusted GMT analysis for the GMT ratio

555 because the subject did not have information on all covariates (unknown prevaccination history).

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

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

558 **14.4 Immunogenicity of AFLURIA in Adults and Older Adults Administered by**
 559 **Needle and Syringe**

560 Two randomized, controlled clinical studies of AFLURIA evaluated the immune responses by
 561 measuring HI antibody titers to each virus strain in the vaccine in adults as compared to placebo
 562 (adults 18 through 64 years) or another U.S.-licensed trivalent influenza vaccine (adults ≥ 65
 563 years). In these studies, post-vaccination immunogenicity was evaluated on sera obtained 21
 564 days after administration of a single dose of AFLURIA.

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565 Study 5 was a randomized, double-blinded, placebo-controlled, multi-center study in healthy
566 subjects ages 18 through 64 years. A total of 1,357 subjects were vaccinated [1,089 subjects
567 with AFLURIA and 268 with a placebo]. Subjects who received AFLURIA were vaccinated
568 using either the preservative-free or thimerosal-containing presentation. The evaluable
569 population consisted of 1,341 subjects [1,077 in the AFLURIA group and 264 in the placebo
570 group]. The mean age of the entire evaluable population receiving AFLURIA was 38 years.
571 62.5% of subjects were female, 81.3% were White, 12.1% were Black, and 6.2% were Asian.

572 Serum HI antibody responses to AFLURIA met the pre-specified co-primary endpoint criteria
573 for all three virus strains (Table 10). Similar responses were observed between genders. The
574 study was not sufficiently diverse to assess immunogenicity by race or ethnicity.

575 **Table 10: Serum Antibody Responses in Subjects 18 through 64 Years of Age Receiving**
576 **AFLURIA (Study 5)**

Strain Variable	AFLURIA N=1077 value (95% CI)	Placebo N=264 value (95% CI)
A(H1N1)		
HI Titer \geq 1:40 ^a	97.8% (96.7, 98.6)	74.6% (68.9, 79.8)
Seroconversion Rate (%) ^b	48.7% (45.6, 51.7)	2.3% (0.8, 4.9)
A(H3N2)		
HI Titer \geq 1:40 ^a	99.9% (99.5, 100.0)	72.0% (66.1, 77.3)
Seroconversion Rate (%) ^b	71.5% (68.7, 74.2)	0.0% (N/A)
B		
HI Titer \geq 1:40 ^a	94.2% (92.7, 95.6)	47.0% (40.8, 53.2)
Seroconversion Rate (%) ^b	69.7% (66.9, 72.5)	0.4% (< 0.1, 2.1)

577 ^a HI titer \geq 1:40 is defined as the proportion of subjects with a minimum post-vaccination HI antibody titer of 1:40. Lower bound
578 of 95% CI for HI antibody titer \geq 1:40 should be > 70% for the study population.

579 ^b Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer \geq 1:10 or an
580 increase in titer from < 1:10 to \geq 1:40. Lower bound of 95% CI for seroconversion should be > 40% for the study population.

581 Study 7 was a randomized, observer-blind, comparator-controlled study that enrolled 1,268
582 subjects 65 years of age and older (Table 11). This study compared the immune response
583 following administration of AFLURIA to that following a U.S.-licensed trivalent inactivated
584 influenza vaccine (manufactured by Sanofi Pasteur Inc.). Subjects were randomized in a 1:1
585 ratio to receive a single vaccination of AFLURIA (enrolled subjects: 631; evaluable subjects:
586 605) or the comparator vaccine (enrolled subjects: 637; evaluable subjects: 610).
587 Immunogenicity assessments were performed prior to vaccination and at 21 days after
588 vaccination. Most of the subjects in the per-protocol immunogenicity population were female
589 (56.7%) and White (97.4%). 2.0% were Black and less than 1.0% were of other races or
590 ethnicities.

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591 The co-primary endpoints were HI GMT ratios (adjusted for baseline HI titers) and the difference
 592 in seroconversion rates for each vaccine strain 21 days after vaccination. Pre-specified non-
 593 inferiority criteria required that the upper bound of the 2-sided 95% CI of the GMT ratio
 594 (Comparator/AFLURIA) did not exceed 1.5 and the upper bound of the 2-sided 95% CI of the
 595 seroconversion rate difference (Comparator minus AFLURIA) did not exceed 10.0% for each
 596 strain. As shown in Table 11, non-inferiority of AFLURIA to the comparator vaccine was
 597 demonstrated in the per protocol population for influenza A subtypes A(H1N1) and A(H3N2),
 598 but not for influenza type B. For the B strain, non-inferiority was demonstrated for HI GMTs,
 599 but not for seroconversion rates. Post-hoc analyses of immunogenicity by gender did not
 600 demonstrate significant differences between males and females. The study was not sufficiently
 601 diverse to assess differences between races or ethnicities.

602 **Table 11: Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of**
 603 **Non-Inferiority of AFLURIA to a U.S. Licensed Comparator, Adults 65 Years**
 604 **of Age and Older (Study 7)**

Strain	Post-vaccination GMT		GMT Ratio ^a	Seroconversion % ^b		Difference	Met both pre-defined non-inferiority criteria?
	Comparator N=610	AFLURIA N=605	Comparator over AFLURIA (95% CI)	Comparator N=610	AFLURIA N=605	Comparator minus AFLURIA (95% CI)	
A(H1N1)	59.2	59.4	1.04 (0.92, 1.18)	43.0	38.8	4.1 (-1.4, 9.6)	Yes
A(H3N2)	337.7	376.8	0.95 (0.83, 1.08)	68.7	69.4	-0.7 (-5.9, 4.5)	Yes
B	33.4	30.4	1.12 (1.01, 1.25)	34.4	29.3	5.2 (-0.1, 10.4)	No

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

606 ^a Post-vaccination GMTs were adjusted for baseline HI titers.

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

609 **14.5 Immunogenicity of AFLURIA in Adults Administered by PharmaJet Stratis**
 610 **Needle-Free Injection System**

611 Study 9 was a randomized, comparator-controlled non-inferiority study that enrolled 1,250
 612 subjects 18 through 64 years of age. This study compared the immune response following
 613 administration of AFLURIA when delivered IM using either the PharmaJet Stratis Needle-Free
 614 Injection System or needle and syringe. Immunogenicity assessments were performed prior to
 615 vaccination and at 28 days after vaccination in the immunogenicity population (1,130 subjects,
 616 562 PharmaJet Stratis Needle-Free Injection System group, 568 needle and syringe group). The
 617 co-primary endpoints were HI GMT ratios for each vaccine strain and the absolute difference in
 618 seroconversion rates for each vaccine strain 28 days after vaccination. As shown in Table 12,
 619 non-inferiority of administration of AFLURIA by the PharmaJet Stratis Needle-Free Injection
 620 System compared to administration of AFLURIA by needle and syringe was demonstrated in

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621 the immunogenicity population for all strains. Post-hoc analyses of immunogenicity by age
622 showed that younger subjects (18 through 49 years) elicited higher immunological responses
623 than older subjects (50 through 64 years). Post-hoc analyses of immunogenicity according to
624 gender and body mass index did not reveal significant influences of these variables on immune
625 responses. The study population was not sufficiently diverse to assess immunogenicity by race
626 or ethnicity.

627 **Table 12: Baseline and Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and**
628 **Analyses of Non-Inferiority of AFLURIA Administered by PharmaJet Stratis**
629 **Needle-Free Injection System or Needle and Syringe, Adults 18 through 64**
630 **Years of Age (Study 9)**

Strain	Baseline GMT		Post-vaccination GMT		GMT Ratio ^a	Seroconversion % ^b		Difference	Met both pre-defined non-inferiority criteria? ^c
	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

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

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

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

635 ^c Non-inferiority (NI) criteria for the GMT ratio: upper bound of 2-sided 95% CI on the ratio of Needle and Syringe/PharmaJet
636 Stratis Needle-Free Injection System. GMT should not exceed 1.5. NI criteria for the seroconversion rate (SCR) difference:
637 upper bound of 2-sided 95% CI on the difference between SCR Needle and Syringe – SCR PharmaJet Stratis Needle-Free
638 Injection System should not exceed 10%.

639 **15 REFERENCES**

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646 Antibody in Protection against Challenge Infection with Influenza A2 and B Viruses.
647 *J Hyg Camb* 1972;70:767-777.

648 **16 HOW SUPPLIED/STORAGE AND HANDLING**

649 **16.1 How Supplied**

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

Presentation	Carton NDC Number	Components
Pre-Filled Syringe	33332-518-20	<ul style="list-style-type: none">Ten 0.25 mL single-dose syringes fitted with a Luer-Lok™ attachment without needles [NDC 33332-518-21]
Pre-Filled Syringe	33332-018-01	<ul style="list-style-type: none">Ten 0.5 mL single-dose syringes fitted with a Luer-Lok™ attachment without needles [NDC 33332-018-02]
Multi-Dose Vial	33332-118-10	<ul style="list-style-type: none">One 5 mL vial, which contains ten 0.5 mL doses [NDC 33332-118-11]

651 **16.2 Storage and Handling**

- 652
 - Store refrigerated at 2–8°C (36–46°F).
 - Do not freeze. Discard if product has been frozen.
 - Protect from light.
 - Do not use AFLURIA beyond the expiration date printed on the label.
 - Once the stopper of the multi-dose vial has been pierced the vial must be discarded within

656 28 days.

657

658 **17 PATIENT COUNSELING INFORMATION**

- 659
 - Inform the vaccine recipient or guardian of the potential benefits and risks of
 - 660 immunization with AFLURIA.
 - 661 • Inform the vaccine recipient or guardian that AFLURIA is an inactivated vaccine that
 - 662 cannot cause influenza but stimulates the immune system to produce antibodies that
 - 663 protect against influenza, and that the full effect of the vaccine is generally achieved
 - 664 approximately 3 weeks after vaccination.
 - 665 • Instruct the vaccine recipient or guardian to report any severe or unusual adverse
 - 666 reactions to their healthcare provider.
 - 667 • Provide the vaccine recipient or guardian with Vaccine Information Statements which
 - 668 are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to
 - 669 immunization. These materials are available free of charge at the Centers for Disease
 - 670 Control and Prevention (CDC) website (www.cdc.gov/vaccines).
 - 671 • Instruct the vaccine recipient or guardian that annual revaccination is recommended.



Package insert

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675 Distributed by:
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