

Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please send an e-mail to: [ocod@fda.hhs.gov](mailto:ocod@fda.hhs.gov) and include 508 Accommodation and the title of the document in the subject line of your e-mail.

## Package insert

### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**AFLURIA, Influenza Vaccine**  
**Suspension for Intramuscular Injection**  
**2022 Formula**  
**Initial U.S. Approval (AFLURIA): 2007**

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

- AFLURIA SOUTHERN HEMISPHERE 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 SOUTHERN HEMISPHERE 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 <sup>a</sup> , 0.25 mL each	If 2 doses, administer at least 1 month apart
36 months through 8 years	One or two doses <sup>a</sup> , 0.5mL each	If 2 doses, administer at least 1 month apart
9 years and older	One dose, 0.5mL	Not Applicable

<sup>a</sup> 1 or 2 doses depends on vaccination history. Two doses are recommended for children 6 months through 8 years who have not previously received  $\geq 2$  doses of trivalent or quadrivalent influenza vaccine  $\geq 4$  weeks apart or whose previous influenza vaccination history is unknown. (2)

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

- AFLURIA SOUTHERN HEMISPHERE is a suspension for injection supplied in 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 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 (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 ( $\geq 60\%$ ), redness ( $\geq 20\%$ ) and swelling ( $\geq 10\%$ ). The most common systemic adverse events were headache, myalgia ( $\geq 20\%$ ), irritability, malaise and fever ( $\geq 10\%$ ). (6.1)
- In adults 18 through 64 years of age, the most common injection-site adverse reactions were tenderness ( $\geq 60\%$ ), pain ( $\geq 40\%$ ), swelling ( $\geq 20\%$ ), and redness, itching ( $\geq 10\%$ ). The most common systemic adverse events were muscle aches ( $\geq 30\%$ ) and headache, malaise ( $\geq 20\%$ ). (6.1)
- In adults 65 years of age and older the most common injection-site adverse reactions were tenderness ( $\geq 30\%$ ) and pain ( $\geq 10\%$ ). No systemic adverse events occurred in  $\geq 10\%$  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 ( $\geq 20\%$ ). The most common systemic adverse events were irritability ( $\geq 30\%$ ), diarrhea and loss of appetite ( $\geq 20\%$ ). (6.1)
- In children 36 through 59 months of age, the most commonly reported injection site reactions were pain ( $\geq 30\%$ ) and redness ( $\geq 20\%$ ). The most commonly reported systemic adverse events were malaise and fatigue, and diarrhea ( $\geq 10\%$ ). (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 ( $\geq 80\%$ ), 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)

**To report SUSPECTED ADVERSE REACTIONS, contact Seqirus at 1-855-358-8966 or VAERS at 1-800-822-7967 or [www.vaers.hhs.gov](http://www.vaers.hhs.gov).**

#### -----USE IN SPECIFIC POPULATIONS-----

- The safety and effectiveness of AFLURIA 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 subjects. (8.5)

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 09/2021**

## Package insert

---

### FULL PRESCRIBING INFORMATION: CONTENTS\*

- |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li><b>1 INDICATIONS AND USAGE</b></li><li><b>2 DOSAGE AND ADMINISTRATION</b></li><li><b>3 DOSAGE FORMS AND STRENGTHS</b></li><li><b>4 CONTRAINDICATIONS</b></li><li><b>5 WARNINGS AND PRECAUTIONS</b><ul style="list-style-type: none"><li>5.1 Guillain-Barré Syndrome</li><li>5.2 Preventing and Managing Allergic Reactions</li><li>5.3 Altered Immunocompetence</li><li>5.4 Limitations of Vaccine Effectiveness</li></ul></li><li><b>6 ADVERSE REACTIONS</b><ul style="list-style-type: none"><li>6.1 Clinical Trials Experience</li><li><del>6.2 Postmarketing Experience</del><del>6.2 Postmarketing Experience</del></li><li>6.3 Adverse Reactions Associated With Influenza Vaccination</li></ul></li><li><b>7 DRUG INTERACTIONS</b><ul style="list-style-type: none"><li>7.1 Concurrent Use With Other Vaccines</li></ul></li><li><b>8 USE IN SPECIFIC POPULATIONS</b><ul style="list-style-type: none"><li>8.1 Pregnancy</li><li>8.2 Lactation</li><li>8.4 Pediatric Use</li><li>8.5 Geriatric Use</li></ul></li></ul> | <ul style="list-style-type: none"><li><b>11 DESCRIPTION</b></li><li><b>12 CLINICAL PHARMACOLOGY</b><ul style="list-style-type: none"><li>12.1 Mechanism of Action</li></ul></li><li><b>13 NONCLINICAL TOXICOLOGY</b><ul style="list-style-type: none"><li>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</li></ul></li><li><b>14 CLINICAL STUDIES</b><ul style="list-style-type: none"><li>14.1 Efficacy of AFLURIA Against Laboratory-Confirmed Influenza</li><li>14.2 Immunogenicity of AFLURIA in Children 5 through 17 Years Administered by Needle and Syringe</li><li><del>14.3 Immunogenicity of AFLURIA QUADRIVALENT in Children 6 months through 59 months of age Administered by Needle and Syringe</del><del>14.3 Immunogenicity of AFLURIA QUADRIVALENT in Children 6 months through 59 months of age Administered by Needle and Syringe</del></li><li>14.4 Immunogenicity of AFLURIA in Adults and Older Adults Administered by Needle and Syringe</li><li>14.5 Immunogenicity of AFLURIA in Adults Administered by PharmaJet Stratis Needle-Free Injection System</li></ul></li><li><b>15 REFERENCES</b></li><li><b>16 HOW SUPPLIED/STORAGE AND HANDLING</b><ul style="list-style-type: none"><li>16.1 How Supplied</li><li>16.2 Storage and Handling</li></ul></li><li><b>17 PATIENT COUNSELING INFORMATION</b></li></ul> |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

\* Sections or subsections omitted from the full prescribing information are not listed

**Package insert**

---

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

AFLURIA SOUTHERN HEMISPHERE (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 SOUTHERN HEMISPHERE 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<sup>®</sup> Stratis<sup>®</sup> Needle-Free Injection System (18 through 64 years of age).

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

**Table 1: AFLURIA SOUTHERN HEMISPHERE Dosage and Schedule**

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

<sup>a</sup> 1 or 2 doses depends on vaccination history. Two doses are recommended for children 6 months through 8 years who have not previously received  $\geq 2$  doses of trivalent or quadrivalent influenza vaccine  $\geq 4$  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.
- 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

**Package insert**

---

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

32 Between uses, return the multi-dose vial to the recommended storage conditions between 2-8°C  
33 (36–46°F). **Do not freeze.** Discard if the vaccine has been frozen.

34 **3 DOSAGE FORMS AND STRENGTHS**

35 AFLURIA SOUTHERN HEMISPHERE is a sterile suspension for intramuscular injection (*see*  
36 *Description [11]*).

37 AFLURIA SOUTHERN HEMISPHERE is supplied in:5 mL multi-dose vial (for persons 6  
38 months of age and older).

39 **4 CONTRAINDICATIONS**

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

43 **5 WARNINGS AND PRECAUTIONS**

44 **5.1 Guillain-Barré Syndrome**

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

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

52 **5.2 Preventing and Managing Allergic Reactions**

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

55 **5.3 Altered Immunocompetence**

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

58 **5.4 Limitations of Vaccine Effectiveness**

59 Vaccination with AFLURIA SOUTHERN HEMISPHERE may not protect all individuals.

**Package insert**

---

**60 6 ADVERSE REACTIONS**

61 The safety experience with AFLURIA and AFLURIA QUADRIVALENT is relevant to  
62 AFLURIA SOUTHERN HEMISPHERE because the vaccines are manufactured using the same  
63 process (see *Description [11]*). This section summarizes data obtained from clinical studies with  
64 AFLURIA and AFLURIA QUADRIVALENT.

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

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

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

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

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

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

**6.1 Clinical Trials Experience**

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

**94 Children – AFLURIA**

95 In clinical studies, AFLURIA has been administered to, and safety information collected for,  
96 3,009 children ages 6 months through 17 years. The exposure in children includes 1,601 aged 6

**Package insert**

---

97 months to less than 5 years, 756 children ages 5 years to less than 9 years and 652 children ages  
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.

Package insert

124 **Table 2: Proportion of Subjects 5 through 17 Years of Age with Solicited Local Adverse**  
 125 **Reactions or Systemic Adverse Events within 7 Days after Administration of**  
 126 **First or Second Dose of AFLURIA, Irrespective of Causality (Study 1)**  
 127

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

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

130 <sup>b</sup> N = number of subjects in the Safety Population for each treatment group.  
 131



Package insert

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

135

	Percentage <sup>a</sup> 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 <sup>b</sup>	Dose 2 N=82-426 <sup>b</sup>	Dose 1 N=397 <sup>b</sup>
<b>Local Adverse Reactions</b>			
Pain	61	56	68
Erythema	24	23	17
Swelling	17	17	13
<b>Systemic Adverse Events</b>			
Irritability <sup>d</sup>	18	16	-
Headache	16	10	27
Malaise or feeling generally unwell <sup>c</sup>	16	8	17
Any Fever	13	6	5
Fever ≥ 102.2°F	3	2	1
General Muscle Ache (Myalgia)	12	8	20
Nausea/Vomiting <sup>c</sup>	7	3	5
Vomiting/Diarrhea <sup>d</sup>	5	6	-
Loss of appetite <sup>d</sup>	5	4	-
Diarrhea <sup>c</sup>	4	2	5

136 <sup>a</sup> 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 <sup>b</sup> 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 <sup>c</sup> These preferred terms were used to describe Solicited Adverse Events in Study 2.

143 <sup>d</sup> These preferred terms were used to describe Solicited Adverse Events in Study 3.

144

145 In Study 1, unsolicited adverse events that occurred in ≥ 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 ≥ 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

**Package insert**

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  
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.

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) <sup>a</sup>**

	Percentage (%) <sup>b</sup> of Subjects in each Age Cohort Reporting an Event	
	6 through 35 months	36 through 59 months

**Package insert**

	AFLURIA Quadrivalent N= 668-669 <sup>c</sup>		Comparator N= 226-227 <sup>c</sup>		AFLURIA Quadrivalent N= 947-949 <sup>c</sup>		Comparator N= 317-318 <sup>c</sup>	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
<b>Local Adverse Reactions <sup>d</sup></b>								
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
<b>Systemic Adverse Events <sup>e</sup></b>								
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 <sup>f</sup>	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<sup>®</sup> Quadrivalent (Sanofi  
187 Pasteur)]

188 <sup>a</sup> NCT02914275

189 <sup>b</sup> 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 <sup>c</sup> 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 <sup>d</sup> 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,  
195 Grade 3 =  $\geq$  30mm diameter.

196 <sup>e</sup> 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 <sup>f</sup> Prophylactic antipyretics (acetaminophen or ibuprophen-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  
201 through 35 months (Afluria QIV 5.9%, Comparator QIV 9.0%); 36 through 59 months (Afluria QIV 3.7%, Comparator QIV  
202 2.5%).

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

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

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

**Package insert**

---

212 diarrhea (3.7%), otitis media (2.4%), vomiting (2.4%), nasal congestion (2.4%), nasopharyngitis  
213 (1.9%), irritability (1.7%), ear infection (1.6%), croup infectious (1.4%), teething (1.3%), rash  
214 (1.2%), influenza like illness (1.0%) and fatigue (1.0%), and were similar to comparator.

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

220

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

227

**228 Adults – AFLURIA**

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

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

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

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

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

245 The safety assessment was identical for the four adult studies. Local (injection-site) adverse  
246 reactions and systemic adverse events were solicited for 5 days post-vaccination (Table 5, studies  
247 5 through 7). Unsolicited adverse events were collected for 21 days post-vaccination. All  
248 adverse events are presented regardless of any treatment causality assigned by study  
249 investigators.

**Package insert**

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

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

	Percentage <sup>a</sup> 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 <sup>b</sup>	Placebo N=266 <sup>b</sup>	AFLURIA N=10,015 <sup>b</sup>	Placebo N=5005 <sup>b</sup>	AFLURIA N=630 <sup>b</sup>	Comparator N=636 <sup>b</sup>
<b>Local Adverse Reactions</b>						
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
<b>Systemic Adverse Events</b>						
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

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

258 <sup>b</sup> N = number of subjects in the Safety Population for each treatment group.

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

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

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

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

268 Additionally, safety information has been collected in a clinical study of AFLURIA administered

**Package insert**

269 using the PharmaJet Stratis Needle-Free Injection System (Study 9). Study 9 included 1,247  
270 subjects for safety analysis, ages 18 through 64 years, randomized to receive AFLURIA by either  
271 the PharmaJet Stratis Needle-Free Injection System (624 subjects) or needle and syringe (623  
272 subjects). No deaths or vaccine-related serious adverse events were reported in Study 7. Local  
273 (injection-site) adverse reactions and systemic adverse events were solicited for 7 days post-  
274 vaccination (Table 6).

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

279

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

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

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

285 <sup>c</sup> A total of 155 subjects (approximately randomly distributed between PharmaJet Stratis Needle-Free Injection System and  
286 needle and syringe groups) received Diary Cards without itching listed as a solicited symptom.

287

288 In Study 9, no unsolicited adverse events occurred in  $\geq 5\%$  of subjects who received AFLURIA

**Package insert**

---

289 administered by PharmaJet Stratis Needle-Free Injection System up to 28 days post-vaccination.

290 **6.2 Postmarketing Experience**

291 Because postmarketing reporting of adverse reactions is voluntary and from a population of  
292 uncertain size, it is not always possible to reliably estimate their frequency or establish a causal  
293 relationship to vaccine exposure. The adverse reactions described have been included in this  
294 section because they: 1) represent reactions that are known to occur following immunizations  
295 generally or influenza immunizations specifically; 2) are potentially serious; or 3) have been  
296 reported frequently. Currently, there are no post-marketing data available for AFLURIA  
297 SOUTHERN HEMISPHERE. These adverse reactions listed below reflect experience in both  
298 children and adults and include those identified during post-approval use of AFLURIA outside  
299 the U.S. since 1985.

300 **Blood and lymphatic system disorders**

301 Thrombocytopenia

302 **Immune system disorders**

303 Allergic or immediate hypersensitivity reactions including anaphylactic shock and serum  
304 sickness

305 **Nervous system disorders**

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

308 **Vascular disorders**

309 Vasculitis which may be associated with transient renal involvement

310 **Skin and subcutaneous tissue disorders**

311 Pruritus, urticaria, and rash

312 **General disorders and administration site conditions**

313 Cellulitis and large injection site swelling

314 Influenza-like illness

315 **6.3 Adverse Reactions Associated With Influenza Vaccination**

316 Anaphylaxis has been reported after administration of AFLURIA. Egg protein can induce  
317 immediate hypersensitivity reactions among persons who have severe egg allergy. Allergic  
318 reactions include hives, angioedema, asthma, and systemic anaphylaxis (*see [Contraindications](#)*  
319 *[4]*).

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

**Package insert**

---

323 Microscopic polyangiitis (vasculitis) has been reported temporally associated with influenza  
324 vaccination.

**325 7 DRUG INTERACTIONS****326 7.1 Concurrent Use With Other Vaccines**

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

331 AFLURIA SOUTHERN HEMISPHERE should not be mixed with any other vaccine in the same  
332 syringe or vial.

**333 8 USE IN SPECIFIC POPULATIONS**

334 Data in this section was obtained from studies with AFLURIA. The data is relevant to  
335 AFLURIA SOUTHERN HEMISPHERE, because both vaccines are manufactured using the  
336 same process (see [Description \[11\]](#)).

**337 8.1 Pregnancy****338 Risk Summary**

339 All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general  
340 population, the estimated background risk of major birth defects and miscarriage in clinically  
341 recognized pregnancies is 2% to 4% and 15% to 20%, respectively. There are insufficient data  
342 for AFLURIA in pregnant women to inform vaccine-associated risks in pregnancy.

343 A developmental toxicity study has been performed in female rats administered AFLURIA  
344 prior to mating and during gestation. A single human dose (0.5 mL, divided) was injected on  
345 each occasion. This study revealed no evidence of harm to the fetus due to AFLURIA (see [8.1](#)  
346 [Pregnancy -Data](#)).

**347 Clinical Considerations****348 *Disease-associated Maternal and/or Embryo-Fetal Risk***

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

**352 Data****353 *Animal Data***

354 In a developmental toxicity study, female rats were administered a single human dose [0.5 mL  
355 (divided)] of AFLURIA by intramuscular injection 21 days and 7 days prior to mating, and on  
356 gestation day 6. Some rats were administered an additional dose on gestation day 20. No



**Package insert**

---

357 vaccine-related fetal malformations or variations and no adverse effects on pre-weaning  
358 development were observed in the study.

359 **8.2 Lactation**

360 Risk Summary

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

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

369 **8.4 Pediatric Use**

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

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

375 **8.5 Geriatric Use**

376 In clinical studies, AFLURIA has been administered to, and safety information collected for,  
377 836 subjects ages 65 years and older (*see Clinical Trials Experience [6.1]*). After administration  
378 of AFLURIA, hemagglutination-inhibiting antibody responses in persons 65 years of age and  
379 older were lower as compared to younger adult subjects (*see Clinical Studies [14]*).

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

383 **11 DESCRIPTION**

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

## Package insert

---

392 AFLURIA SOUTHERN HEMISPHERE is standardized according to USPHS requirements for  
393 the 2022 Southern Hemisphere influenza season and is formulated to contain 45 mcg  
394 hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 mcg HA for each of the  
395 three influenza strains recommended for the 2022 Southern Hemisphere influenza season:  
396 A/Victoria/2570/2019 IVR-215 (an A/Victoria/2570/2019 (H1N1)pdm09-like virus),  
397 A/Darwin/6/2021 IVR-227 (an A/Darwin/9/2021 (H3N2)-like virus) and  
398 B/Austria/1359417/2021 BVR-26 (a B/Austria/1359417/2021-like virus). A 0.25 mL dose  
399 contains 7.5 mcg HA of each of the same three influenza strains.

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

402 A single 0.5 mL dose of AFLURIA SOUTHERN HEMISPHERE contains sodium chloride  
403 (4.1 mg), monobasic sodium phosphate (80 mcg), dibasic sodium phosphate (300 mcg),  
404 monobasic potassium phosphate (20 mcg), potassium chloride (20 mcg), and calcium chloride  
405 (0.5 mcg). From the manufacturing process, each 0.5 mL dose may also contain residual  
406 amounts of sodium taurodeoxycholate ( $\leq 10$  ppm), ovalbumin ( $< 1$  mcg), sucrose ( $< 10$  mcg),  
407 neomycin sulfate ( $\leq 61.5$  nanograms [ng]), polymyxin B ( $\leq 10.5$  ng), beta-propiolactone ( $\leq 2$  ng)  
408 and hydrocortisone ( $\leq 0.56$  ng). A single 0.25 mL dose of AFLURIA SOUTHERN  
409 HEMISPHERE contains half of these quantities.

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

## 411 12 CLINICAL PHARMACOLOGY

### 412 12.1 Mechanism of Action

413 Influenza illness and its complications follow infection with influenza viruses. Global  
414 surveillance of influenza identifies yearly antigenic variants. For example, since 1977 antigenic  
415 variants of influenza A (H1N1 and H3N2) and influenza B viruses have been in global  
416 circulation. Specific levels of hemagglutination inhibition (HI) antibody titers post-vaccination  
417 with inactivated influenza vaccine have not been correlated with protection from influenza virus.  
418 In some human studies, antibody titers of 1:40 or greater have been associated with protection  
419 from influenza illness in up to 50% of subjects.<sup>2,3</sup>

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

**Package insert**

---

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

**431 13 NONCLINICAL TOXICOLOGY****432 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

**436 14 CLINICAL STUDIES**

437 This section summarizes data obtained from clinical studies with AFLURIA and AFLURIA  
438 QUADRIVALENT. Data from AFLURIA and AFLURIA QUADRIVALENT are relevant to  
439 AFLURIA SOUTHERN HEMISPHERE because the vaccines are manufactured using the same  
440 process (see *Description [11]*).

**441 14.1 Efficacy of AFLURIA Against Laboratory-Confirmed Influenza**

442 In Study 6, the efficacy of AFLURIA was demonstrated in a randomized, observer-blind,  
443 placebo-controlled study conducted in 15,044 subjects. Healthy subjects 18 through 64 years of  
444 age were randomized in a 2:1 ratio to receive a single dose of AFLURIA (enrolled subjects:  
445 10,033; evaluable subjects: 9,889) or placebo (enrolled subjects: 5,011; evaluable subjects:  
446 4,960). The mean age of all randomized subjects was 35.5 years. 54.4% were female and 90.2%  
447 were White. Laboratory-confirmed influenza was assessed by active and passive surveillance of  
448 influenza-like illness (ILI) beginning 2 weeks post-vaccination until the end of the influenza  
449 season, approximately 6 months post-vaccination. ILI was defined as at least one respiratory  
450 symptom (e.g., cough, sore throat, nasal congestion) and at least one systemic symptom (e.g.,  
451 oral temperature of 100.0°F or higher, feverishness, chills, body aches). Nasal and throat swabs  
452 were collected from subjects who presented with an ILI for laboratory confirmation by viral  
453 culture and real-time reverse transcription polymerase chain reaction. Influenza virus strain was  
454 further characterized using gene sequencing and pyrosequencing.

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

**Package insert**

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

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

461 Abbreviations: CI, confidence interval

462 <sup>a</sup> The Per Protocol Population was identical to the Evaluable Population in this study.

463 <sup>b</sup> Vaccine efficacy = 1 minus the ratio of AFLURIA/placebo infection rates. The objective of the study was to demonstrate that  
464 the lower limit of the CI for vaccine efficacy was greater than 40%.

465  
466 **14.2 Immunogenicity of AFLURIA in Children 5 through 17 Years Administered**  
467 **by Needle and Syringe**

468 Study 1 was a randomized, observer-blind, comparator-controlled study to evaluate the  
469 immunological non-inferiority of AFLURIA to a U.S.-licensed trivalent inactivated influenza  
470 vaccine (manufactured by Sanofi Pasteur, Inc.) in subjects 6 months through 17 years of age.  
471 Study vaccines were administered by needle and syringe. Results are presented for children 5  
472 through 17 years of age (Table 8). A total of 832 subjects (aged 5 through 17 years) were  
473 enrolled. Subjects were randomized in a 1:1 ratio to receive AFLURIA (enrolled subjects: 417;  
474 evaluable subjects: 383) or the comparator vaccine (enrolled subjects: 415; evaluable subjects:  
475 383).

476  
477 Children 6 months through 8 years of age with no history of influenza vaccination received 2  
478 doses approximately 28 days apart. Children 6 months through 8 years of age with a history of  
479 influenza vaccination and children 9 years of age and older received 1 dose. Children 6 months  
480 through 35 months of age received 0.25 mL of AFLURIA or comparator influenza vaccine, and  
481 children 3 years of age and older received 0.5 mL of AFLURIA or comparator influenza vaccine.  
482 Nearly equal proportions of subjects were male (49.9%) and female (50.1%), and the majority  
483 were White (85.0%) or Black (10.3%).

484  
485 Immunogenicity assessments were performed prior to vaccination and at 30 days after  
486 vaccination. The co-primary endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted  
487 for baseline HI titers) and the difference in seroconversion rates for each vaccine strain 21 days  
488 after the final vaccination. Pre-specified non-inferiority criteria required that the upper bound

**Package insert**

489 of the 2-sided 95% CI of the GMT ratio (Comparator/AFLURIA) did not exceed 1.5 and the  
 490 upper bound of the 2-sided 95% CI of the seroconversion rate difference (Comparator minus  
 491 AFLURIA) did not exceed 10.0% for each strain. As shown in Table 8, non-inferiority of  
 492 AFLURIA to the comparator vaccine was demonstrated in the per protocol population for  
 493 influenza A subtypes A(H1N1) and A(H3N2), but not for influenza type B. For influenza type  
 494 B, non-inferiority was demonstrated for HI GMTs, but not for seroconversion rates. Note that  
 495 the study was powered to assess the pre-specified non-inferiority criteria based on 1400  
 496 evaluable subjects. Analysis of the 761 subjects aged 5 through 17 years reduced the power of  
 497 the study and widened the confidence intervals. In the pre-specified analysis, AFLURIA was  
 498 not inferior to the comparator vaccine for all three virus strains. Post-hoc analyses of  
 499 immunogenicity by gender did not demonstrate significant differences between males and  
 500 females. The study was not sufficiently diverse to assess differences between races or ethnicities.  
 501

502 **Table 8: Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of**  
 503 **Non-Inferiority of AFLURIA to a U.S.-Licensed Comparator, Subjects 5**  
 504 **through 17 Years of Age (Study 1)**  
 505

Strain	Post-vaccination GMT		GMT Ratio <sup>a</sup>	Seroconversion % <sup>b</sup>		Difference	Met both pre-defined non-inferiority criteria? <sup>c</sup>
	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

506 Abbreviations: CI, confidence interval; GMT, geometric mean titer.  
 507 <sup>a</sup> GMT ratios are adjusted for baseline HI titers  
 508 <sup>b</sup> Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer  $\geq$  1:10 or  
 509 an increase in titer from  $<$  1:10 to  $\geq$  1:40.  
 510 <sup>c</sup> Note that the study was powered to assess the pre-specified non-inferiority criteria based on 1400 evaluable subjects.  
 511

512 **14.3 Immunogenicity of AFLURIA QUADRIVALENT in Children 6 months**  
 513 **through 59 months of age Administered by Needle and Syringe**

514 Data have also been collected in a clinical study of AFLURIA QUADRIVALENT, which is  
 515 relevant to AFLURIA and AFLURIA SOUTHERN HEMISPHERE because the vaccines are  
 516 manufactured using the same process and have overlapping compositions (Study 4).

517 Study 4 was a randomized, observer-blind, comparator-controlled trial conducted in the U.S. in  
 518 children 6 months through 59 months of age. A total of 2247 subjects were randomized 3:1 to

**Package insert**

---

519 receive AFLURIA QUADRIVALENT (N=1684) or a U.S.-licensed comparator quadrivalent  
520 influenza vaccine (N=563). Children 6 months through 35 months received one or two 0.25  
521 mL doses and children 36 months through 59 months received one or two 0.5 mL doses.  
522 Subjects were eligible to receive a second dose at least 28 days after the first dose depending  
523 on their influenza vaccination history, consistent with the 2016-2017 recommendations of the  
524 Advisory Committee on Immunization Practices (ACIP) for Prevention and Control of Seasonal  
525 Influenza with Vaccines. Approximately 40% of subjects in each treatment group received two  
526 vaccine doses.

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

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

Package insert

545 **Table 9: Post-Vaccination HI Antibody GMTs, SCRs, and Analyses of Non-Inferiority**  
 546 **of AFLURIA QUADRIVALENT Relative to a U.S.-Licensed Comparator**  
 547 **Quadrivalent Influenza Vaccine for each Strain 28 Days after Last**  
 548 **Vaccination Among a Pediatric Population 6 through 59 Months of Age (Per**  
 549 **Protocol Population) (Study 4)<sup>a, b</sup>**

Strain	Post-vaccination GMT		GMT Ratio <sup>c</sup>	Seroconversion % <sup>d</sup>		SCR Difference <sup>e</sup>	Met both pre-defined non-inferiority criteria? <sup>f</sup>
	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 <sup>g</sup> )	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 <sup>g</sup> )	500.5 (n=484)	1.27 (1.15, 1.42)	82.3 (80.2, 84.2) (n=1455 <sup>i</sup> )	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 <sup>g</sup> )	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 <sup>g</sup> )	52.9 (n=483 <sup>h</sup> )	0.97 (0.86, 1.09)	60.2 (57.6, 62.7) (n=1456)	61.1 (56.6, 65.4) (n=483 <sup>h</sup> )	0.9 (-4.2, 6.1)	Yes

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

552 <sup>a</sup> NCT02914275

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

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

561 <sup>d</sup> Seroconversion rate was defined as the percentage of subjects with either a prevaccination HI titer < 1:10 and a  
 562 postvaccination HI titer ≥ 1:40 or a prevaccination HI titer ≥ 1:10 and a 4-fold increase in postvaccination HI titer.

563 <sup>e</sup> Seroconversion rate difference = Comparator SCR percentage minus AFLURIA QUADRIVALENT SCR percentage.

564 <sup>f</sup> Noninferiority (NI) criterion for the GMT ratio: upper bound of two-sided 95% CI on the GMT ratio of Comparator /  
 565 AFLURIA QUADRIVALENT should not exceed 1.5. NI criterion for the SCR difference: upper bound of two-sided 95%  
 566 CI on the difference between SCR Comparator– AFLURIA QUADRIVALENT should not exceed 10%.

567 <sup>g</sup> Subject 8400402-0073 was excluded from the Per-Protocol Population for the adjusted GMT analysis for the GMT ratio  
 568 because the subject did not have information on all covariates (unknown prevaccination history).

569 <sup>h</sup> Subject 8400427-0070 had missing B/Victoria Antigen pre-vaccination titer.

570 <sup>i</sup> Subject 8400402-0074 had missing A/H3N2 post-vaccination titer.

571 **14.4 Immunogenicity of AFLURIA in Adults and Older Adults Administered by**  
 572 **Needle and Syringe**

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

**Package insert**

578 Study 5 was a randomized, double-blinded, placebo-controlled, multi-center study in healthy  
579 subjects ages 18 through 64 years. A total of 1,357 subjects were vaccinated [1,089 subjects  
580 with AFLURIA and 268 with a placebo]. Subjects who received AFLURIA were vaccinated  
581 using either the preservative-free or thimerosal-containing presentation. The evaluable  
582 population consisted of 1,341 subjects [1,077 in the AFLURIA group and 264 in the placebo  
583 group]. The mean age of the entire evaluable population receiving AFLURIA was 38 years.  
584 62.5% of subjects were female, 81.3% were White, 12.1% were Black, and 6.2% were Asian.

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

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

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

590 <sup>a</sup> 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  
591 of 95% CI for HI antibody titer  $\geq$  1:40 should be > 70% for the study population.

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

594 Study 7 was a randomized, observer-blind, comparator-controlled study that enrolled 1,268  
595 subjects 65 years of age and older (Table 11). This study compared the immune response  
596 following administration of AFLURIA to that following a U.S.-licensed trivalent inactivated  
597 influenza vaccine (manufactured by Sanofi Pasteur Inc.). Subjects were randomized in a 1:1  
598 ratio to receive a single vaccination of AFLURIA (enrolled subjects: 631; evaluable subjects:  
599 605) or the comparator vaccine (enrolled subjects: 637; evaluable subjects: 610).  
600 Immunogenicity assessments were performed prior to vaccination and at 21 days after  
601 vaccination. Most of the subjects in the per-protocol immunogenicity population were female  
602 (56.7%) and White (97.4%). 2.0% were Black and less than 1.0% were of other races or



**Package insert**

603 ethnicities.

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

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

Strain	Post-vaccination GMT		GMT Ratio <sup>a</sup>	Seroconversion % <sup>b</sup>		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

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

619 <sup>a</sup> Post-vaccination GMTs were adjusted for baseline HI titers.

620 <sup>b</sup> Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer  $\geq 1:10$  or  
621 an increase in titer from  $< 1:10$  to  $\geq 1:40$ .

622 **14.5 Immunogenicity of AFLURIA in Adults Administered by PharmaJet Stratis**  
623 **Needle-Free Injection System**

624 Study 9 was a randomized, comparator-controlled non-inferiority study that enrolled 1,250  
625 subjects 18 through 64 years of age. This study compared the immune response following  
626 administration of AFLURIA when delivered IM using either the PharmaJet Stratis Needle-Free  
627 Injection System or needle and syringe. Immunogenicity assessments were performed prior to  
628 vaccination and at 28 days after vaccination in the immunogenicity population (1,130 subjects,  
629 562 PharmaJet Stratis Needle-Free Injection System group, 568 needle and syringe group). The  
630 co-primary endpoints were HI GMT ratios for each vaccine strain and the absolute difference in  
631 seroconversion rates for each vaccine strain 28 days after vaccination. As shown in Table 12,  
632 non-inferiority of administration of AFLURIA by the PharmaJet Stratis Needle-Free Injection

**Package insert**

633 System compared to administration of AFLURIA by needle and syringe was demonstrated in  
 634 the immunogenicity population for all strains. Post-hoc analyses of immunogenicity by age  
 635 showed that younger subjects (18 through 49 years) elicited higher immunological responses  
 636 than older subjects (50 through 64 years). Post-hoc analyses of immunogenicity according to  
 637 gender and body mass index did not reveal significant influences of these variables on immune  
 638 responses. The study population was not sufficiently diverse to assess immunogenicity by race  
 639 or ethnicity.

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

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

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

645 <sup>a</sup> GMT ratio is defined as post-vaccination GMT for Needle and Syringe/PharmaJet Stratis Needle-Free Injection System

646 <sup>b</sup> Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer  $\geq 1:10$  or  
 647 an increase in titer from  $< 1:10$  to  $\geq 1:40$ .

648 <sup>c</sup> Non-inferiority (NI) criteria for the GMT ratio: upper bound of 2-sided 95% CI on the ratio of Needle and Syringe/PharmaJet  
 649 Stratis Needle-Free Injection System. GMT should not exceed 1.5. NI criteria for the seroconversion rate (SCR) difference:  
 650 upper bound of 2-sided 95% CI on the difference between SCR Needle and Syringe – SCR PharmaJet Stratis Needle-Free  
 651 Injection System should not exceed 10%.

652 **15 REFERENCES**

- 653 1. Centers for Disease Control and Prevention Advisory Committee on Immunization  
 654 Practices (ACIP). *Vaccine Recommendations and Guidelines of the ACIP*. Available  
 655 from: <https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html>  
 656 2. Hannoun C, Megas F, Piercy J. Immunogenicity and Protective Efficacy of Influenza  
 657 Vaccination. *Virus Res* 2004;103:133-138.

**Package insert**

---

- 658 3. Hobson D, Curry RL, Beare AS, et al. The Role of Serum Hemagglutination-Inhibiting  
659 Antibody in Protection against Challenge Infection with Influenza A2 and B Viruses.  
660 *J Hyg Camb* 1972;70:767-777.

661 **16 HOW SUPPLIED/STORAGE AND HANDLING**

662 **16.1 How Supplied**

663 Multi-dose vial product presentation includes a package insert and the following component:

Presentation	Carton NDC Number	Component
Multi-Dose Vial	33332-751-10	<ul style="list-style-type: none"><li>One 5 mL vial [NDC 33332-751-11]</li></ul>

664 **16.2 Storage and Handling**

- 665
  - 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 SOUTHERN HEMISPHERE beyond the expiration date printed  
668 on the label.
  - Once the stopper of the multi-dose vial has been pierced the vial must be discarded within  
670 28 days.
  - The number of needle punctures should not exceed 20 per multi-dose vial.

673 **17 PATIENT COUNSELING INFORMATION**

- 674
  - Inform the vaccine recipient or guardian of the potential benefits and risks of  
675 immunization with AFLURIA SOUTHERN HEMISPHERE.
  - Inform the vaccine recipient or guardian that AFLURIA SOUTHERN HEMISPHERE  
676 is an inactivated vaccine that cannot cause influenza but stimulates the immune system  
677 to produce antibodies that protect against influenza, and that the full effect of the vaccine  
678 is generally achieved approximately 3 weeks after vaccination.
  - Instruct the vaccine recipient or guardian to report any severe or unusual adverse  
680 reactions to their healthcare provider.
  - Provide the vaccine recipient or guardian with Vaccine Information Statements which  
682 are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to  
683 immunization. These materials are available free of charge at the Centers for Disease  
684 Control and Prevention (CDC) website ([www.cdc.gov/vaccines](http://www.cdc.gov/vaccines)).
  - Instruct the vaccine recipient or guardian that annual revaccination is recommended.

687 Manufactured by:

688 **Seqirus Pty Ltd.** Parkville, Victoria, 3052, Australia

689 U.S. License No. 2044



**Package insert**

---

690 Distributed by:  
691 **Seqirus USA Inc.** 25 Deforest Avenue, Summit, NJ 07901, USA 1-855-358-8966  
692 AFLURIA is a registered trademark of Seqirus UK Limited or its affiliates.  
693 PharmaJet® and STRATIS® are registered trademarks of PharmaJet, Inc.  
694