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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
2017-2018 Formula
Initial U.S. Approval: 2007

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 5 years of age and older. (1)

DOSAGE AND ADMINISTRATION

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

Age	Schedule
5 years through 8 years	One dose or two doses at least 1 month apart ^a
9 years and older	One dose

^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 two presentations:

- 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

- Administration of CSL's 2010 Southern Hemisphere influenza vaccine was associated with increased rates of fever and febrile seizures in children predominantly below the age of 5 years as compared to previous years. Febrile events were also observed in children 5 through 8 years of age. (5.1)
- 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. (5.2)
- Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. (5.3)
- Immunocompromised persons may have a diminished immune response to AFLURIA. (5.4)

ADVERSE REACTIONS

- In children 5 through 17 years of age, the most common injection-site adverse reactions when 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 ($\geq 10\%$). (6.1)
- In adults 18 through 64 years of age, the most common injection-site adverse reactions when administered by needle and syringe 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 18 through 64 years of age, the most common injection-site adverse reactions when 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)
- In adults 65 years of age and older, when administered by needle and syringe 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)

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

- AFLURIA is not approved for use in children less than 5 years of age because of increased rates of fever and febrile seizures. One comparator-controlled trial demonstrated higher rates of fever in recipients of AFLURIA as compared to a trivalent inactivated influenza vaccine control. (8.4)
- Antibody responses were lower in geriatric subjects than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 03/2017

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1 **FULL PRESCRIBING INFORMATION**

2
3
4 **1 INDICATIONS AND USAGE**

5
6 AFLURIA[®] is an inactivated influenza vaccine indicated for active immunization against
7 influenza disease caused by influenza virus subtypes A and type B present in the vaccine.
8 AFLURIA is approved for use in persons 5 years of age and older.
9

10
11 **2 DOSAGE AND ADMINISTRATION**

12
13 For intramuscular (IM) injection only, by needle and syringe (5 years of age and older) or by
14 PharmaJet[®] Stratis[®] Needle-Free Injection System (18 through 64 years of age). A single dose
15 is 0.5 mL.
16

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

18 **Table 1: AFLURIA Schedule**

Age	Schedule
5 years through 8 years	One dose or two doses at least 1 month apart ^a
9 years and older	One dose

19 ^a 1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations
20 on prevention and control of influenza with vaccines.
21

22 Shake thoroughly and inspect visually before use. Parenteral drug products should be
23 inspected visually for particulate matter and discoloration prior to administration, whenever
24 suspension and container permit. If either of these conditions exists, the vaccine should not be
25 administered.
26

27 May be administered by needle and syringe (5 years of age and older) or PharmaJet Stratis
28 Needle-Free Injection System (18 through 64 years of age only).
29

30 When using the single-dose pre-filled syringe, shake the syringe thoroughly and administer the
31 dose immediately.
32

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

- 35 • Needle and Syringe: Draw up the exact dose using a separate sterile needle and syringe for
36 each individual patient. It is recommended that small syringes (0.5 mL or 1 mL) be used to
37 minimize any product loss.

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

41

42 The preferred site for intramuscular injection is the deltoid muscle of the upper arm.

43

44 Between uses, return the multi-dose vial to the recommended storage conditions between
45 2-8°C (36-46°F). **Do not freeze.** Discard if the vaccine has been frozen.

46

47

48 **3 DOSAGE FORMS AND STRENGTHS**

49

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

51

52 AFLURIA is supplied in two presentations:

53

- 54 • 0.5 mL pre-filled syringe (single dose).
- 55 • 5 mL multi-dose vial (ten 0.5 mL doses).

56

57

58 **4 CONTRAINDICATIONS**

59

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

63

64

65 **5 WARNINGS AND PRECAUTIONS**

66

67 **5.1 Fever and Febrile Seizures**

68 Administration of CSL's 2010 Southern Hemisphere influenza vaccine was associated with
69 postmarketing reports of increased rates of fever and febrile seizures in children predominantly
70 below the age of 5 years as compared to previous years; these increased rates were confirmed
71 by postmarketing studies. Febrile events were also observed in children 5 through 8 years of
72 age.

73

74 **5.2 Guillain-Barré Syndrome**

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

78

79 The 1976 swine influenza vaccine was associated with an increased frequency of GBS.

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80 Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza
81 viruses is unclear. If influenza vaccine does pose a risk, it is probably slightly more than one
82 additional case per 1 million persons vaccinated.

83

84 **5.3 Preventing and Managing Allergic Reactions**

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

87

88 **5.4 Altered Immunocompetence**

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

91

92 **5.5 Limitations of Vaccine Effectiveness**

93 Vaccination with AFLURIA may not protect all individuals.

94

95

96 **6 ADVERSE REACTIONS**

97

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

102

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

108

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

114

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

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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

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

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

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

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

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

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

In this section, safety data from the pediatric studies are limited to children 5 years of age and older. AFLURIA is not approved for use in children less than 5 years of age. See [Warnings and Precautions \[5.1\]](#) and [Use in Specific Populations \[8.4\]](#) for risks of AFLURIA in children less than 5 years of age.

In the comparator-controlled trial (Study 1), the rate of fever after the first dose of AFLURIA in subjects aged 5 through 8 years was 16% as compared to 8% in subjects who received the comparator. The rate of fever in subjects aged 9 through 17 years following a single dose of

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162 AFLURIA was 6% as compared to 4% in subjects who received the comparator. In all three
163 pediatric studies, the rates of fever in subjects aged 5 through 8 years who received AFLURIA
164 were lower after dose 2 than dose 1.

165

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

167

168 **Table 2: Proportion of Subjects 5 through 17 Years of Age with Solicited Local Adverse**
169 **Reactions or Systemic Adverse Events within 7 Days after Administration of**
170 **First or Second Dose of AFLURIA, Irrespective of Causality (Study 1)**
171

	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 $\geq 102.2^{\circ}\text{F}$	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 $\geq 102.2^{\circ}\text{F}$	0	0	-	-

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

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

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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)

	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

^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. Denominators for Dose 1 were: N=82 for Vomiting/Diarrhea, Irritability, Loss of appetite, N=513 for Malaise, Diarrhea, Nausea/Vomiting and N=593-595 for all other parameters. Denominators for Dose 2 were: N=82 for Vomiting/Diarrhea, Irritability, Loss of appetite, N=344 for Malaise, Diarrhea and Nausea/Vomiting and N=421-426 for all other parameters.

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

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

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

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195 In Studies 2 and 3, unsolicited adverse events that occurred in $\geq 5\%$ of subjects ages 5 years
196 through 8 years after the first or second dose included the following: upper respiratory tract
197 infection (13%), cough (10%), rhinorrhea (7%), headache (5%), nasopharyngitis (5%) and
198 pyrexia (5%). Unsolicited adverse events that occurred in $\geq 5\%$ of subjects who received
199 AFLURIA in ages 9 years through 17 years following the first dose included upper respiratory
200 tract infection (9%) and headache (8%).

201

202 *Adults*

203 In clinical studies comparing AFLURIA to placebo or a comparator trivalent inactivated
204 influenza vaccine, a single dose of AFLURIA was administered to, and safety information
205 collected for, 11,104 subjects ages 18 through 64 years and 836 subjects ages 65 years and
206 older. Clinical safety data for AFLURIA in adults are presented from three clinical studies
207 (Studies 4 through 6) conducted in the US and one clinical study (Study 7) conducted in the
208 UK

209

210 Study 4 included 1,357 subjects for safety analysis, ages 18 through 64 years, randomized to
211 receive AFLURIA (1,089 subjects) or placebo (268 subjects) (*see Clinical Studies [14]*).

212

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

215

216 Study 6 included 1,266 subjects for safety analysis, ages 65 years and older, randomized to
217 receive AFLURIA (630 subjects) or another U.S.-licensed trivalent inactivated influenza
218 vaccine (manufactured by Sanofi Pasteur Inc.) as an active comparator (636 subjects) (*see*
219 *Clinical Studies [14]*). Study 7 included 275 subjects for safety analysis, ages 65 years and
220 older, randomized to receive AFLURIA (206 subjects) or a UK-licensed trivalent inactivated
221 influenza vaccine (manufactured by GSK) as an active comparator (69 subjects).

222

223 The safety assessment was identical for the four adult studies. Local (injection-site) adverse
224 reactions and systemic adverse events were solicited for 5 days post-vaccination (Table 4,
225 studies 4 through 6). Unsolicited adverse events were collected for 21 days post-vaccination.
226 All adverse events are presented regardless of any treatment causality assigned by study
227 investigators.

228

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

231

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232 **Table 4: Proportion of Subjects 18 Years of Age and Older with Solicited Local Adverse**
 233 **Reactions or Systemic Adverse Events within 5 Days after Administration of**
 234 **AFLURIA or Placebo, Irrespective of Causality (Studies 4, 5 and 6)**
 235

	Percentage ^a of Subjects in each Age Group Reporting Event					
	Study 4 Subjects 18 through 64 years		Study 5 Subjects 18 through 64 years		Study 6 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

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

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

239
 240 In Study 4, headache was the only unsolicited adverse event that occurred in ≥ 5% of subjects
 241 who received AFLURIA or placebo (8% versus 6%, respectively).
 242

243 In Study 5, unsolicited adverse events that occurred in ≥ 5% of subjects who received
 244 AFLURIA or placebo included headache (AFLURIA 12%, placebo 11%) and oropharyngeal
 245 pain (AFLURIA 5%, placebo 5%).
 246

247 In Study 6, headache was the only unsolicited adverse event that occurred in ≥ 5% of subjects
 248 who received AFLURIA (5%).
 249

250 Studies 1 to 7 were all conducted when AFLURIA was administered by needle and syringe.

251
 252 Additionally, safety information has been collected in a clinical study of AFLURIA
 253 administered using the PharmaJet Stratis Needle-Free Injection System (Study 8). Study 8
 254 included 1,247 subjects for safety analysis, ages 18 through 64 years, randomized to receive

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255 AFLURIA by either the PharmaJet Stratis Needle-Free Injection System (624 subjects) or
256 needle and syringe (623 subjects). No deaths or vaccine-related serious adverse events were
257 reported in Study 8. Local (injection-site) adverse reactions and systemic adverse events were
258 solicited for 7 days post-vaccination (Table 5).

259
260 **Table 5: Proportion of Subjects 18 through 64 Years of Age with Solicited Local Adverse**
261 **Reactions or Systemic Adverse Events within 7 Days after Administration of**
262 **AFLURIA by PharmaJet Stratis Needle-Free Injection System or Needle and**
263 **Syringe Irrespective of Causality (Study 8).**

	Percentage ^a of Subjects Reporting Event	
	Study 8	
	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

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

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

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

272
273 In Study 8, no unsolicited adverse events occurred in $\geq 5\%$ of subjects who received
274 AFLURIA administered via PharmaJet Stratis Needle-Free Injection System up to 28 days
275 post-vaccination.

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277

278 6.2 Postmarketing Experience

279 Because postmarketing reporting of adverse reactions is voluntary and from a population of
280 uncertain size, it is not always possible to reliably estimate their frequency or establish a causal
281 relationship to vaccine exposure. The adverse reactions described have been included in this
282 section because they: 1) represent reactions that are known to occur following immunizations
283 generally or influenza immunizations specifically; 2) are potentially serious; or 3) have been
284 reported frequently. These adverse reactions reflect experience in both children and adults and
285 include those identified during post-approval use of AFLURIA outside the US since 1985.

286

287 Blood and lymphatic system disorders

288 Thrombocytopenia

289

290 Immune system disorders

291 Allergic or immediate hypersensitivity reactions including anaphylactic shock and serum
292 sickness

293

294 Nervous system disorders

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

297

298 Vascular disorders

299 Vasculitis which may be associated with transient renal involvement

300

301 Skin and subcutaneous tissue disorders

302 Pruritus, urticaria, and rash

303

304 General disorders and administration site conditions

305 Cellulitis and large injection site swelling

306 Influenza-like illness

307

308 6.3 Adverse Reactions Associated With Influenza Vaccination

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

313

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

317

318 Microscopic polyangiitis (vasculitis) has been reported temporally associated with influenza

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319 vaccination.

320

321

322 **7 DRUG INTERACTIONS**

323

324 **7.1 CONCURRENT USE WITH OTHER VACCINES**

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

328

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

330

331

332 **8 USE IN SPECIFIC POPULATIONS**

333

334 **8.1 Pregnancy**

335

336

337 Pregnancy Category B:

338

339 A reproductive and developmental toxicity study has been performed in female rats at a dose
340 approximately 265 times the human dose (on a mg/kg basis) and revealed no evidence of
341 impaired female fertility or harm to the fetus due to AFLURIA. There are, however, no
342 adequate and well controlled studies in pregnant women. Because animal reproduction studies
343 are not always predictive of human response, AFLURIA should be given to a pregnant woman
344 only if clearly needed.

345 In the reproductive and developmental toxicity study, the effect of AFLURIA on embryo-fetal
346 and pre-weaning development was evaluated in pregnant rats. Animals were administered
347 AFLURIA by intramuscular injection twice prior to gestation, once during the period of
348 organogenesis (gestation day 6), and once later in pregnancy (gestation day 20), 0.5
349 mL/rat/occasion (approximately a 265-fold excess relative to the projected human dose on a
350 body weight basis). No adverse effects on mating, female fertility, pregnancy, parturition,
351 lactation parameters, and embryo-fetal or pre-weaning development were observed. There
352 were no vaccine-related fetal malformations or other evidence of teratogenesis.

353

354

355 **8.3 Nursing Mothers**

356 AFLURIA has not been evaluated in nursing mothers. It is not known whether AFLURIA is
357 excreted in human milk. Because many drugs are excreted in human milk, caution should be
358 exercised when AFLURIA is administered to a nursing woman.

359

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360

361 8.4 Pediatric Use

362 AFLURIA is not approved for use in children less than 5 years of age. In a clinical study in
363 which children received AFLURIA or a US-licensed comparator vaccine (Study 1, *see Clinical*
364 *Trials Experience, [6.1]*), the incidence of fever in children 6 months through 35 months of age
365 following the first and second doses of AFLURIA were 37% and 15%, respectively, as
366 compared to 14% following each dose in the comparator group. Among children 3 years
367 through 4 years of age, the incidence of fever following the first and second doses of
368 AFLURIA were 32% and 14%, respectively, as compared to 11% and 16% in the comparator.
369 In an open-label study (Study 2), fever, irritability, loss of appetite, and vomiting/diarrhea
370 occurred more frequently in children 6 months through 35 months of age as compared to older
371 children. Across three pediatric studies of AFLURIA (Studies 1, 2, and 3), 1.2% of eligible
372 children (n=1,764) were discontinued from the second vaccination because of severe fever
373 ($\geq 104^{\circ}\text{F}$) within 48 hours of the first vaccination. Across the three pediatric studies, two
374 children, a 7-month old and a 3-year old, experienced vaccine-related febrile seizures (rate of
375 0.07% across studies), one of which was serious.

376

377 Administration of CSL's 2010 Southern Hemisphere influenza vaccine was associated with
378 increased rates of fever and febrile seizures, predominantly in children below the age of 5 years
379 as compared to previous years, in postmarketing reports confirmed by postmarketing studies
380 (*see Warnings and Precautions [5.1]*).

381

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

385

386 8.5 Geriatric Use

387 In clinical studies, AFLURIA has been administered to, and safety information collected for,
388 836 subjects ages 65 years and older (*see Clinical Trials Experience [6.1]*). After
389 administration of AFLURIA, hemagglutination-inhibiting antibody responses in persons 65
390 years of age and older were lower as compared to younger adult subjects (*see Clinical Studies*
391 *[14]*).

392

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

396

397

398 11 DESCRIPTION

399

400 AFLURIA, Influenza Vaccine for intramuscular injection, is a sterile, clear, colorless to
401 slightly opalescent suspension with some sediment that resuspends upon shaking to form a

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402 homogeneous suspension. AFLURIA is prepared from influenza virus propagated in the
403 allantoic fluid of embryonated chicken eggs. Following harvest, the virus is purified in a
404 sucrose density gradient using continuous flow zonal centrifugation. The purified virus is
405 inactivated with beta-propiolactone, and the virus particles are disrupted using sodium
406 taurodeoxycholate to produce a “split virion”. The disrupted virus is further purified and
407 suspended in a phosphate buffered isotonic solution.

408
409 AFLURIA is standardized according to USPHS requirements for the 2017-2018 influenza
410 season and is formulated to contain 45 mcg hemagglutinin (HA) per 0.5 mL dose in the
411 recommended ratio of 15 mcg HA for each of the three influenza strains recommended for the
412 2017-2018 Northern Hemisphere influenza season: A/Singapore/GP1908/2015 (H1N1), IVR-
413 180A, A/Hong Kong/4801/2014 (H3N2), NYMC X-263B, and B/Brisbane/46/2015.

414
415 Thimerosal, a mercury derivative, is not used in the manufacturing process for the single dose
416 presentations; therefore these products contain no preservative. The multi-dose presentation
417 contains thimerosal, added as a preservative; each 0.5 mL dose contains 24.5 mcg of mercury.

418
419 A single 0.5 mL dose of AFLURIA contains sodium chloride (4.1 mg), monobasic sodium
420 phosphate (80 mcg), dibasic sodium phosphate (300 mcg), monobasic potassium phosphate
421 (20 mcg), potassium chloride (20 mcg), and calcium chloride (0.5 mcg). From the
422 manufacturing process, each 0.5 mL dose may also contain residual amounts of sodium
423 taurodeoxycholate (≤ 10 ppm), ovalbumin (< 1 mcg), sucrose (< 10 mcg), neomycin sulfate
424 (≤ 61.5 nanograms [ng]), polymyxin B (≤ 10.5 ng), and beta-propiolactone (≤ 2 ng).

425
426 The rubber tip cap and plunger used for the preservative-free, single-dose syringes and the
427 rubber stoppers used for the multi-dose vial were not made with natural rubber latex.

428 429 430 **12 CLINICAL PHARMACOLOGY**

431 432 **12.1 Mechanism of Action**

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

440
441 Antibody against one influenza virus type or subtype confers limited or no protection against
442 another. Furthermore, antibody to one antigenic variant of influenza virus might not protect
443 against a new antigenic variant of the same type or subtype. Frequent development of

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444 antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the
445 reason for the usual change to one or more new strains in each year's influenza vaccine.
446 Therefore, inactivated influenza vaccines are standardized to contain the HA of three strains
447 (i.e., typically two type A and one type B) representing the influenza viruses likely to be
448 circulating in the US during the upcoming winter.

449
450 Annual revaccination with the current vaccine is recommended because immunity declines
451 during the year after vaccination and circulating strains of influenza virus change from year to
452 year.¹

453
454
13 NONCLINICAL TOXICOLOGY

455
456
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

457 AFLURIA has not been evaluated for carcinogenic or mutagenic potential, or male infertility
458 in animals. A reproductive study of female rats vaccinated with AFLURIA revealed no
459 impairment of fertility (see [Pregnancy, 8.1](#)).

460
461
462
14 CLINICAL STUDIES

463
464
14.1 Efficacy Against Laboratory-Confirmed Influenza

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

478
479
480 Attack rates and vaccine efficacy, defined as the relative reduction in the influenza infection
481 rate for AFLURIA compared to placebo, were calculated using the per protocol population.
482 Vaccine efficacy against laboratory-confirmed influenza infection due to influenza A or B
483 virus strains contained in the vaccine was 60% with a lower limit of the 95% CI of 41% ([Table](#)
484 [6](#)).

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486 **Table 6: Laboratory-Confirmed Influenza Infection Rate and Vaccine Efficacy in Adults**
 487 **18 through 64 Years of Age (Study 5)**
 488

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

489 Abbreviations: CI, confidence interval

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

491 ^b Vaccine efficacy = 1 minus the ratio of AFLURIA/placebo infection rates. The objective of the study was to demonstrate that
 492 the lower limit of the CI for vaccine efficacy was greater than 40%.
 493

494 **14.2 Immunogenicity in Children – Administration via Needle and Syringe**

495 Study 1 was a randomized, observer-blind, comparator-controlled study to evaluate the
 496 immunological non-inferiority of AFLURIA to a U.S.-licensed trivalent inactivated influenza
 497 vaccine (manufactured by Sanofi Pasteur, Inc.) in subjects 6 months through 17 years of age.
 498 Study vaccines were administered by needle and syringe. Results are presented for children 5
 499 through 17 years of age (Table 7). A total of 832 subjects (aged 5 through 17 years) were
 500 enrolled. Subjects were randomized in a 1:1 ratio to receive AFLURIA (enrolled subjects:
 501 417; evaluable subjects: 383) or the comparator vaccine (enrolled subjects: 415; evaluable
 502 subjects: 383).
 503

504 Children 6 months through 8 years of age with no history of influenza vaccination received 2
 505 doses approximately 28 days apart. Children 6 months through 8 years of age with a history of
 506 influenza vaccination and children 9 years of age and older received 1 dose. Children 6
 507 months through 35 months of age received 0.25 mL of AFLURIA or comparator influenza
 508 vaccine, and children 3 years of age and older received 0.5 mL of AFLURIA or comparator
 509 influenza vaccine. Nearly equal proportions of subjects were male (49.9%) and female
 510 (50.1%), and the majority were White (85.0%) or Black (10.3%).
 511

512 Immunogenicity assessments were performed prior to vaccination and at 21 days after
 513 vaccination. The co-primary endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted
 514 for baseline HI titers) and the difference in seroconversion rates for each vaccine strain 21 days
 515 after the final vaccination. Pre-specified non-inferiority criteria required that the upper bound
 516 of the 2-sided 95% CI of the GMT ratio (Comparator/AFLURIA) did not exceed 1.5 and the
 517 upper bound of the 2-sided 95% CI of the seroconversion rate difference (Comparator minus

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518 AFLURIA) did not exceed 10.0% for each strain. As shown in Table 7, non-inferiority of
 519 AFLURIA to the comparator vaccine was demonstrated in the per protocol population for
 520 influenza A subtypes A(H1N1) and A(H3N2), but not for influenza type B. For influenza type
 521 B, non-inferiority was demonstrated for HI GMTs, but not for seroconversion rates. Note that
 522 the study was powered to assess the pre-specified non-inferiority criteria based on 1400
 523 evaluable subjects. Analysis of the 761 subjects aged 5 through 17 years reduced the power of
 524 the study and widened the confidence intervals. In the pre-specified analysis, AFLURIA was
 525 not inferior to the comparator vaccine for all three virus strains. Post-hoc analyses of
 526 immunogenicity by gender did not demonstrate significant differences between males and
 527 females. The study was not sufficiently diverse to assess differences between races or
 528 ethnicities.

530 **Table 7: Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of**
 531 **Non-Inferiority of AFLURIA to a U.S.-Licensed Comparator, Subjects 5**
 532 **through 17 Years of Age (Study 1)**
 533

Strain	Post-vaccination GMT		GMT Ratio ^a	Seroconversion % ^b		Difference	Met both 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

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

539
 540 **14.3 Immunogenicity in Adults and Older Adults – Administration via Needle**
 541 **and Syringe**

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

547
 548 Study 4 was a randomized, double-blinded, placebo-controlled, multi-center study in healthy
 549 subjects ages 18 through 64 years. A total of 1,357 subjects were vaccinated (1,089 subjects
 550 with AFLURIA and 268 with a placebo). Subjects who received AFLURIA were vaccinated

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551 using either the preservative-free or thimerosal-containing presentation. The evaluable
552 population consisted of 1,341 subjects (1,077 in the AFLURIA group and 264 in the placebo
553 group). The mean age of the entire evaluable population receiving AFLURIA was 38 years.
554 62.5% of subjects were female, 81.3% were White, 12.1% were Black, and 6.2% were Asian.

555
556 Serum HI antibody responses to AFLURIA met the pre-specified co-primary endpoint criteria
557 for all three virus strains (Table 8). Similar responses were observed between genders. The
558 study was not sufficiently diverse to assess immunogenicity by race or ethnicity.

559
560 **Table 8: Serum Antibody Responses in Subjects 18 through 64 Years of Age Receiving**
561 **AFLURIA (Study 4)**
562

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)

563 ^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
564 bound of 95% CI for HI antibody titer \geq 1:40 should be > 70% for the study population.

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

568
569 Study 6 was a randomized, observer-blind, comparator-controlled study that enrolled 1,268
570 subjects 65 years of age and older (Table 9). This study compared the immune response
571 following administration of AFLURIA to that following a US-licensed trivalent inactivated
572 influenza vaccine (manufactured by Sanofi Pasteur Inc.). Subjects were randomized in a 1:1
573 ratio to receive a single vaccination of AFLURIA (enrolled subjects: 631; evaluable subjects:
574 605) or the comparator vaccine (enrolled subjects: 637; evaluable subjects: 610).
575 Immunogenicity assessments were performed prior to vaccination and at 21 days after
576 vaccination. Most of the subjects in the per-protocol immunogenicity population were female
577 (56.7%) and White (97.4%). 2.0% were Black and less than 1.0% were of other races or
578 ethnicities.

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579
580 The co-primary endpoints were HI GMT ratios (adjusted for baseline HI titers) and the
581 difference in seroconversion rates for each vaccine strain 21 days after vaccination. Pre-
582 specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the
583 GMT ratio (Comparator/AFLURIA) did not exceed 1.5 and the upper bound of the 2-sided
584 95% CI of the seroconversion rate difference (Comparator minus AFLURIA) did not exceed
585 10.0% for each strain. As shown in Table 9, non-inferiority of AFLURIA to the comparator
586 vaccine was demonstrated in the per protocol population for influenza A subtypes A(H1N1)
587 and A(H3N2), but not for influenza type B. For the B strain, non-inferiority was demonstrated
588 for HI GMTs, but not for seroconversion rates. Post-hoc analyses of immunogenicity by
589 gender did not demonstrate significant differences between males and females. The study was
590 not sufficiently diverse to assess differences between races or ethnicities.

591
592 **Table 9: Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of**
593 **Non-Inferiority of AFLURIA to a U.S. Licensed Comparator, Adults 65 Years of**
594 **Age and Older (Study 6)**
595

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

596 Abbreviations: CI, confidence interval; GMT, geometric mean titer.
597 ^a Post-vaccination GMTs were adjusted for baseline HI titers.
598 ^b Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer $\geq 1:10$ or
599 an increase in titer from $< 1:10$ to $\geq 1:40$.

600
601 **14.4 Immunogenicity in Adults – Administration via PharmaJet Stratis Needle-**
602 **Free Injection System**

603 Study 8 was a randomized, comparator-controlled non-inferiority study that enrolled 1,250
604 subjects 18 through 64 years of age. This study compared the immune response following
605 administration of AFLURIA when delivered IM using either the PharmaJet Stratis Needle-Free
606 Injection System or needle and syringe. Immunogenicity assessments were performed prior to
607 vaccination and at 28 days after vaccination in the immunogenicity population (1,130 subjects,
608 562 PharmaJet Stratis Needle-Free Injection System group, 568 needle and syringe group).
609 The co-primary endpoints were HI GMT ratios for each vaccine strain and the absolute
610 difference in seroconversion rates for each vaccine strain 28 days after vaccination. As shown

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611 in Table 10, non-inferiority of administration of AFLURIA by the PharmaJet Stratis Needle-
612 Free Injection System compared to administration of AFLURIA by needle and syringe was
613 demonstrated in the immunogenicity population for all strains. Post-hoc analyses of
614 immunogenicity by age showed that younger subjects (18 through 49 years) elicited higher
615 immunological responses than older subjects (50 through 64 years). Post-hoc analyses of
616 immunogenicity according to gender and body mass index did not reveal significant influences
617 of these variables on immune responses. The study population was not sufficiently diverse to
618 assess immunogenicity by race or ethnicity.

619

620 **Table 10: Baseline and Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and**
621 **Analyses of Non-Inferiority of AFLURIA Administered by PharmaJet Stratis**
622 **Needle-Free Injection System or Needle and Syringe, Adults 18 through 64**
623 **Years of Age (Study 8)**

624

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

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

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

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

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

633

634

635 **15 REFERENCES**

636

- 637 1. Centers for Disease Control and Prevention. Prevention and Control of Influenza:
638 Recommendations of the Advisory Committee on Immunization Practices (ACIP).
639 *MMWR Recomm Rep* 2010;59 (RR-8):1-62.

Package insert

- 640 2. Hannoun C, Megas F, Piercy J. Immunogenicity and Protective Efficacy of Influenza
641 Vaccination. *Virus Res* 2004;103:133-138.
642 3. Hobson D, Curry RL, Beare AS, et al. The Role of Serum Hemagglutination-
643 Inhibiting Antibody in Protection against Challenge Infection with Influenza A2 and B
644 Viruses. *J Hyg Camb* 1972;70:767-777.
645

646
647 **16 HOW SUPPLIED/STORAGE AND HANDLING**

648
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	33332-017-01	<ul style="list-style-type: none"> Ten 0.5 mL single-dose syringes fitted with a Luer-Lok™ attachment without needles [NDC 33332-017-02]
Multi-Dose Vial	33332-117-10	<ul style="list-style-type: none"> One 5 mL vial, which contains ten 0.5 mL doses [NDC 33332-117-11]

651
652 **16.2 Storage and Handling**

- 653
 - Store refrigerated at 2–8°C (36–46°F).
654
 - Do not freeze. Discard if product has been frozen.
655
 - Protect from light.
656
 - Do not use AFLURIA beyond the expiration date printed on the label.
657
 - Once the stopper of the multi-dose vial has been pierced the vial must be discarded
658 within 28 days.
659

660
661 **17 PATIENT COUNSELING INFORMATION**

- 662
 - Inform the vaccine recipient or guardian of the potential benefits and risks of
663 immunization with AFLURIA.
664
 - Inform the vaccine recipient or guardian that AFLURIA is an inactivated vaccine that
665 cannot cause influenza but stimulates the immune system to produce antibodies that
666 protect against influenza, and that the full effect of the vaccine is generally achieved
667 approximately 3 weeks after vaccination.
668
 - Instruct the vaccine recipient or guardian to report any severe or unusual adverse
669 reactions to their healthcare provider.
670
 - Provide the vaccine recipient or guardian with Vaccine Information Statements which
671 are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to
672 immunization. These materials are available free of charge at the Centers for Disease
673 Control and Prevention (CDC) website (www.cdc.gov/vaccines).
674
 - Instruct the vaccine recipient or guardian that annual revaccination is recommended.



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675

676

677 Manufactured by:

678 **Seqirus Pty Ltd**

679 Parkville, Victoria, 3052, Australia

680 US License No. 2044

681

682 Distributed by:

683 **Seqirus USA Inc.** 25 Deforest Avenue, Summit, NJ 07901, USA 1-855-358-8966

684

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688