

**Package insert**

**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**  
**2015-2016 Formula**  
**Initial U.S. Approval: 2007**

**RECENT MAJOR CHANGES**

Dosage and Administration (2) 08/2014

**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 <sup>a</sup>
9 years and older	One dose

<sup>a</sup>1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines. (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 (≥60%), redness (≥20%) and swelling (≥10%). The most common systemic adverse events were headache, myalgia (≥20%), irritability, malaise and fever (≥10%). (6.1)
- In adults 18 through 64 years of age, the most common injection-site adverse reactions when administered by needle and syringe were tenderness (≥60%), pain (≥40%), swelling (≥20%), and redness, itching (≥10%). The most common systemic adverse events were muscle aches (≥30%) and headache, malaise (≥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 (≥80%), swelling, pain, redness (≥60%), itching (≥20%) and bruising (≥10%). The most common systemic adverse events within this period were myalgia, malaise (≥30%), and headache (≥20%). (6.1)
- In adults 65 years of age and older, when administered by needle and syringe the most common injection-site adverse reactions were tenderness (≥30%) and pain (≥10%). No systemic adverse events occurred in ≥10% of subjects in this age group (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact bioCSL Inc. at 1-844-275-2461 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.**

**USE IN SPECIFIC POPULATIONS**

- Safety and effectiveness of AFLURIA have not been established in pregnant women or nursing mothers. (8.1, 8.3)
- Antibody responses were lower in geriatric subjects than in younger subjects. (8.5)
- 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)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2015

## Package insert

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### FULL PRESCRIBING INFORMATION: CONTENTS\*

- 1 INDICATIONS AND USAGE**
- 2 DOSAGE AND ADMINISTRATION**
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
  - 5.1 Fever and Febrile Seizures
  - 5.2 Guillain-Barré Syndrome
  - 5.3 Preventing and Managing Allergic Reactions
  - 5.4 Altered Immunocompetence
  - 5.5 Limitations of Vaccine Effectiveness
- 6 ADVERSE REACTIONS**
  - 6.1 Clinical Trials Experience
  - 6.2 Postmarketing Experience
  - 6.3 Adverse Reactions Associated With Influenza Vaccination
- 7 DRUG INTERACTIONS**
  - 7.1 Concurrent Use With Other Vaccines
  - 7.2 Concurrent Use With Immunosuppressive Therapies
- 8 USE IN SPECIFIC POPULATIONS**
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers
  - 8.4 Pediatric Use
  - 8.5 Geriatric Use
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
  - 12.1 Mechanism of Action
- 13 NONCLINICAL TOXICOLOGY**
  - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14 CLINICAL STUDIES**
  - 14.1 Efficacy Against Laboratory-Confirmed Influenza
  - 14.2 Immunogenicity in Children - Administration via Needle and Syringe
  - 14.3 Immunogenicity in Adults and Older Adults - Administration via Needle and Syringe
  - 14.4 Immunogenicity in Adults - Administration via PharmaJet Stratis Needle-Free Injection System
- 15 REFERENCES**
- 16 HOW SUPPLIED/STORAGE AND HANDLING**
  - 16.1 How Supplied
  - 16.2 Storage and Handling
- 17 PATIENT COUNSELING INFORMATION**

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

**Package insert**

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**FULL PRESCRIBING INFORMATION**

**1 INDICATIONS AND USAGE**

AFLURIA<sup>®</sup> is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B present in the vaccine. AFLURIA is approved for use in persons 5 years of age and older.

**2 DOSAGE AND ADMINISTRATION**

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

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

**Table 1: AFLURIA Schedule**

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

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

Shake thoroughly and inspect visually before use. 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.

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

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

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

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

**Package insert**

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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. 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 AFLURIA was 6% as compared to 4% in subjects who received the comparator. In all three

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161 pediatric studies, the rates of fever in subjects aged 5 through 8 years who received AFLURIA  
162 were lower after dose 2 than dose 1.

163  
164 Data in Tables 2 and 3 are presented for children 5 years and older.

165  
166 **Table 2: Proportion of Subjects 5 through 17 Years of Age with Solicited Local Adverse**  
167 **Reactions or Systemic Adverse Events within 7 Days after Administration of**  
168 **First or Second Dose of AFLURIA, Irrespective of Causality (Study 1)**  
169

	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	-	-

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

172 <sup>b</sup> N = number of subjects in the Safety Population for each treatment group.  
173

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174 **Table 3: Proportion of Subjects 5 through 17 Years of Age with Solicited Local Adverse**  
 175 **Reactions or Systemic Adverse Events Within 7 Days after Administration of**  
 176 **AFLURIA, Irrespective of Causality (Studies 2 and 3)**  
 177

	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

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

180 <sup>b</sup> N = number of subjects in the Safety Population for each treatment group. Denominators for Dose 1 were: N=82 for  
 181 Vomiting/Diarrhea, Irritability, Loss of appetite, N=513 for Malaise, Diarrhea, Nausea/Vomiting and N=593-595 for all  
 182 other parameters. Denominators for Dose 2 were: N=82 for Vomiting/Diarrhea, Irritability, Loss of appetite, N=344 for  
 183 Malaise, Diarrhea and Nausea/Vomiting and N=421-426 for all other parameters.

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

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

186

187 In Study 1, unsolicited adverse events that occurred in ≥ 5% of subjects who received  
 188 AFLURIA in ages 5 years through 8 years following the first or second dose included cough  
 189 (15%) and pyrexia (9%). Unsolicited adverse events that occurred in ≥ 5% of subjects who  
 190 received AFLURIA in ages 9 years through 17 years following the first dose included cough  
 191 (7%), oropharyngeal pain (7%), headache (7%) and nasal congestion (6%).  
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193 In Studies 2 and 3, unsolicited adverse events that occurred in  $\geq 5\%$  of subjects ages 5 years  
 194 through 8 years after the first or second dose included the following: upper respiratory tract  
 195 infection (13%), cough (10%), rhinorrhea (7%), headache (5%), nasopharyngitis (5%) and  
 196 pyrexia (5%). Unsolicited adverse events that occurred in  $\geq 5\%$  of subjects who received  
 197 AFLURIA in ages 9 years through 17 years following the first dose included upper respiratory  
 198 tract infection (9%) and headache (8%).

199  
200 **Adults**

201 In clinical studies comparing AFLURIA to placebo or another U.S.-licensed trivalent  
 202 inactivated influenza vaccine, a single dose of AFLURIA was administered to, and safety  
 203 information collected for, 11,104 subjects ages 18 through 64 years and 836 subjects ages 65  
 204 years and older. Clinical safety data for AFLURIA in adults are presented from three clinical  
 205 studies (Studies 4 through 6). In these studies, Afluria and comparator vaccine or placebo were  
 206 administered by needle and syringe.

207  
208 Study 4 included 1,357 subjects for safety analysis, ages 18 through 64 years, randomized to  
 209 receive AFLURIA (1,089 subjects) or placebo (268 subjects) (*see Clinical Studies [14]*).

210  
211 Study 5 included 15,020 subjects for safety analysis, ages 18 through 64 years, randomized to  
 212 receive AFLURIA (10,015 subjects) or placebo (5,005 subjects) (*see Clinical Studies [14]*).

213  
214 Study 6 included 1,266 subjects for safety analysis, ages 65 years and older, randomized to  
 215 receive AFLURIA (630 subjects) or another U.S.-licensed trivalent inactivated influenza  
 216 vaccine (manufactured by Sanofi Pasteur Inc.) as an active comparator (636 subjects) (*see*  
 217 *Clinical Studies [14]*).

218  
219 The safety assessment was identical for the three adult studies. Local (injection-site) adverse  
 220 reactions and systemic adverse events were solicited for 5 days post-vaccination (Table 4).  
 221 Unsolicited adverse events were collected for 21 days post-vaccination. All adverse events are  
 222 presented regardless of any treatment causality assigned by study investigators.

223  
224 Among adult studies 4 through 6, there were no vaccine-related deaths or vaccine-related  
 225 serious adverse events reported.

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227 **Table 4: Proportion of Subjects 18 Years of Age and Older with Solicited Local Adverse**  
 228 **Reactions or Systemic Adverse Events within 5 Days after Administration of**  
 229 **AFLURIA or Placebo, Irrespective of Causality (Studies 4, 5 and 6)**  
 230

	Percentage <sup>a</sup> 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 <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

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

233 <sup>b</sup> N = number of subjects in the Safety Population for each treatment group.  
 234

235 In Study 4, headache was the only unsolicited adverse event that occurred in ≥ 5% of subjects  
 236 who received AFLURIA or placebo (8% versus 6%, respectively).  
 237

238 In Study 5, headache was the only unsolicited adverse event that occurred in ≥ 5% of subjects  
 239 who received AFLURIA or placebo (12% versus 11%, respectively).  
 240

241 In Study 6, unsolicited adverse events that occurred in ≥ 5% of subjects who received  
 242 AFLURIA included headache (8%), nasal congestion (7%), cough (5%), rhinorrhea (5%), and  
 243 pharyngolaryngeal pain (5%).  
 244

245 Studies 1 to 6 were all conducted when AFLURIA was administered by needle and syringe.  
 246

247 Additionally, safety information has been collected in a clinical study of AFLURIA  
 248 administered using the PharmaJet Stratis Needle-Free Injection System (Study 7). Study 7  
 249 included 1,247 subjects for safety analysis, ages 18 through 64 years, randomized to receive  
 250 AFLURIA by either the PharmaJet Stratis Needle-Free Injection System (624 subjects) or

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251 needle and syringe (623 subjects). No deaths or vaccine-related serious adverse events were  
 252 reported in Study 7. Local (injection-site) adverse reactions and systemic adverse events were  
 253 solicited for 7 days post-vaccination (Table 5).  
 254

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

	Percentage <sup>a</sup> of Subjects Reporting Event	
	Study 7	
	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

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

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

265 <sup>c</sup> A total of 155 subjects (approximately randomly distributed between PharmaJet Stratis Needle-Free Injection System and  
 266 needle and syringe groups) received Diary Cards without itching listed as a solicited symptom.  
 267

268 In Study 7, no unsolicited adverse events occurred in  $\geq 5\%$  of subjects who received  
 269 AFLURIA administered via PharmaJet Stratis Needle-Free Injection System up to 28 days  
 270 post-vaccination.  
 271  
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273 **6.2 Postmarketing Experience**

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

281

282 **Blood and lymphatic system disorders**

283 Transient thrombocytopenia

284

285 **Immune system disorders**

286 Allergic reactions including anaphylactic shock and serum sickness

287

288 **Nervous system disorders**

289 Neuralgia, paresthesia, convulsions (including febrile seizures), encephalopathy, neuritis or  
290 neuropathy, transverse myelitis, and GBS

291

292 **Vascular disorders**

293 Vasculitis with transient renal involvement

294

295 **Skin and subcutaneous tissue disorders**

296 Pruritus, urticaria, and rash

297

298 **General disorders and administration site conditions**

299 Cellulitis and large injection site swelling

300

301 **6.3 Adverse Reactions Associated With Influenza Vaccination**

302 Anaphylaxis has been reported after administration of AFLURIA. Egg protein can induce  
303 immediate hypersensitivity reactions among persons who have severe egg allergy. Allergic  
304 reactions include hives, angioedema, asthma, and systemic anaphylaxis (*see [Contraindications](#)*  
305 *[4]*).

306

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

310

311 Microscopic polyangiitis (vasculitis) has been reported temporally associated with influenza  
312 vaccination.

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315 **7 DRUG INTERACTIONS**

316  
317 **7.1 Concurrent Use With Other Vaccines**

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

321  
322 AFLURIA should not be mixed with any other vaccine in the same syringe or vial.

323  
324 **7.2 Concurrent Use With Immunosuppressive Therapies**

325 The immunological response to AFLURIA may be diminished in individuals receiving  
326 corticosteroid or immunosuppressive therapies.

327  
328  
329 **8 USE IN SPECIFIC POPULATIONS**

330  
331 **8.1 Pregnancy**

332 Pregnancy Category B: A reproductive and developmental toxicity study has been performed  
333 in female rats at a dose approximately 265 times the human dose (on a mg/kg basis) and  
334 revealed no evidence of impaired female fertility or harm to the fetus due to AFLURIA. There  
335 are, however, no adequate and well-controlled studies in pregnant women. Because animal  
336 reproduction studies are not always predictive of human response, AFLURIA should be given  
337 to a pregnant woman only if clearly needed.

338  
339 In the reproductive and developmental toxicity study, the effect of AFLURIA on embryo-fetal  
340 and pre-weaning development was evaluated in pregnant rats. Animals were administered  
341 AFLURIA by intramuscular injection twice prior to gestation, once during the period of  
342 organogenesis (gestation day 6), and once later in pregnancy (gestation day 20), 0.5  
343 mL/rat/occasion (approximately a 265-fold excess relative to the projected human dose on a  
344 body weight basis). No adverse effects on mating, female fertility, pregnancy, parturition,  
345 lactation parameters, and embryo-fetal or pre-weaning development were observed. There  
346 were no vaccine-related fetal malformations or other evidence of teratogenesis.

347  
348 **8.3 Nursing Mothers**

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

352  
353 **8.4 Pediatric Use**

354 AFLURIA is not approved for use in children less than 5 years of age. In a clinical study in  
355 which children received AFLURIA or a US-licensed comparator vaccine (Study 1, *see Clinical*  
356 *Trials Experience, [6.1]*), the incidence of fever in children 6 months through 35 months of age

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357 following the first and second doses of AFLURIA were 37% and 15%, respectively, as  
 358 compared to 14% following each dose in the comparator group. Among children 3 years  
 359 through 4 years of age, the incidence of fever following the first and second doses of  
 360 AFLURIA were 32% and 14%, respectively, as compared to 11% and 16% in the comparator.  
 361 In an open-label study (Study 2), fever, irritability, loss of appetite, and vomiting/diarrhea  
 362 occurred more frequently in children 6 months through 35 months of age as compared to older  
 363 children. Across three pediatric studies of AFLURIA (Studies 1, 2, and 3), 1.2% of eligible  
 364 children (n=1,764) were discontinued from the second vaccination because of severe fever  
 365 ( $\geq 104^{\circ}\text{F}$ ) within 48 hours of the first vaccination. Across the three pediatric studies, two  
 366 children, a 7-month old and a 3-year old, experienced vaccine-related febrile seizures (rate of  
 367 0.07% across studies), one of which was serious.

368  
 369 Administration of CSL's 2010 Southern Hemisphere influenza vaccine was associated with  
 370 increased rates of fever and febrile seizures, predominantly in children below the age of 5 years  
 371 as compared to previous years, in postmarketing reports confirmed by postmarketing studies  
 372 (*see [Warnings and Precautions \[5.1\]](#)*).

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

377  
 378 **8.5 Geriatric Use**  
 379 In clinical studies, AFLURIA has been administered to, and safety information collected for,  
 380 836 subjects ages 65 years and older (*see [Clinical Trials Experience \[6.1\]](#)*). After  
 381 administration of AFLURIA, hemagglutination-inhibiting antibody responses in persons 65  
 382 years of age and older were lower as compared to younger adult subjects (*see [Clinical Studies](#)*  
 383 *[14]*).

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

388  
 389  
 390 **11 DESCRIPTION**

391  
 392 AFLURIA, Influenza Vaccine for intramuscular injection, is a sterile, clear, colorless to  
 393 slightly opalescent suspension with some sediment that resuspends upon shaking to form a  
 394 homogeneous suspension. AFLURIA is prepared from influenza virus propagated in the  
 395 allantoic fluid of embryonated chicken eggs. Following harvest, the virus is purified in a  
 396 sucrose density gradient using continuous flow zonal centrifugation. The purified virus is  
 397 inactivated with beta-propiolactone, and the virus particles are disrupted using sodium

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398 taurodeoxycholate to produce a “split virion”. The disrupted virus is further purified and  
399 suspended in a phosphate buffered isotonic solution.

400  
401 AFLURIA is standardized according to USPHS requirements for the 2015-2016 influenza  
402 season and is formulated to contain 45 mcg hemagglutinin (HA) per 0.5 mL dose in the  
403 recommended ratio of 15 mcg HA for each of the three influenza strains recommended for the  
404 2015-2016 Northern Hemisphere influenza season: A/California/7/2009 (H1N1), NYMC X-  
405 181, A/South Australia/55/2014 (H3N2), IVR-175, (an A/Switzerland/9715293/2013-like  
406 strain) and B/Phuket/3073/2013.

407  
408 Thimerosal, a mercury derivative, is not used in the manufacturing process for the single dose  
409 presentations; therefore these products contain no preservative. The multi-dose presentation  
410 contains thimerosal, added as a preservative; each 0.5 mL dose contains 24.5 mcg of mercury.

411  
412 A single 0.5 mL dose of AFLURIA contains sodium chloride (4.1 mg), monobasic sodium  
413 phosphate (80 mcg), dibasic sodium phosphate (300 mcg), monobasic potassium phosphate  
414 (20 mcg), potassium chloride (20 mcg), and calcium chloride (1.5 mcg). From the  
415 manufacturing process, each 0.5 mL dose may also contain residual amounts of sodium  
416 taurodeoxycholate ( $\leq 10$  ppm), ovalbumin ( $< 1$  mcg), neomycin sulfate ( $\leq 3$  nanograms [ng]),  
417 polymyxin B ( $\leq 0.5$  ng), and beta-propiolactone ( $\leq 2$  ng).

418  
419 The rubber tip cap and plunger used for the preservative-free, single-dose syringes and the  
420 rubber stoppers used for the multi-dose vial were not made with natural rubber latex.

421  
422

423 **12 CLINICAL PHARMACOLOGY**

424  
425 **12.1 Mechanism of Action**

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

433  
434 Antibody against one influenza virus type or subtype confers limited or no protection against  
435 another. Furthermore, antibody to one antigenic variant of influenza virus might not protect  
436 against a new antigenic variant of the same type or subtype. Frequent development of  
437 antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the  
438 reason for the usual change to one or more new strains in each year’s influenza vaccine.  
439 Therefore, inactivated influenza vaccines are standardized to contain the HA of three strains

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440 (i.e., typically two type A and one type B) representing the influenza viruses likely to be  
441 circulating in the US during the upcoming winter.

442  
443 Annual revaccination with the current vaccine is recommended because immunity declines  
444 during the year after vaccination and circulating strains of influenza virus change from year to  
445 year.<sup>1</sup>

446

447

448 **13 NONCLINICAL TOXICOLOGY**

449

450 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

454

455

456 **14 CLINICAL STUDIES**

457

458 **14.1 Efficacy Against Laboratory-Confirmed Influenza**

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

472

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

478

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479 **Table 6: Laboratory-Confirmed Influenza Infection Rate and Vaccine Efficacy in Adults**  
 480 **18 through 64 Years of Age (Study 5)**  
 481

	Subjects <sup>a</sup>	Laboratory-Confirmed Influenza Cases	Influenza Infection Rate	Vaccine Efficacy <sup>b</sup>	
	N			n/N %	%
<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		

482 Abbreviations: CI, confidence interval

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

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

486

487 **14.2 Immunogenicity in Children – Administration via Needle and Syringe**

488 Study 1 was a randomized, observer-blind, comparator-controlled study to evaluate the  
 489 immunological non-inferiority of AFLURIA to a U.S.-licensed trivalent inactivated influenza  
 490 vaccine (manufactured by Sanofi Pasteur, Inc.) in subjects 6 months through 17 years of age.  
 491 Study vaccines were administered by needle and syringe. Results are presented for children 5  
 492 through 17 years of age (Table 7). A total of 832 subjects (aged 5 through 17 years) were  
 493 enrolled. Subjects were randomized in a 1:1 ratio to receive AFLURIA (enrolled subjects:  
 494 417; evaluable subjects: 383) or the comparator vaccine (enrolled subjects: 415; evaluable  
 495 subjects: 383).

496

497 Children 6 months through 8 years of age with no history of influenza vaccination received 2  
 498 doses approximately 28 days apart. Children 6 months through 8 years of age with a history of  
 499 influenza vaccination and children 9 years of age and older received 1 dose. Children 6  
 500 months through 35 months of age received 0.25 mL of AFLURIA or comparator influenza  
 501 vaccine, and children 3 years of age and older received 0.5 mL of AFLURIA or comparator  
 502 influenza vaccine. Nearly equal proportions of subjects were male (49.9%) and female  
 503 (50.1%), and the majority were White (85.0%) or Black (10.3%).

504

505 Immunogenicity assessments were performed prior to vaccination and at 21 days after  
 506 vaccination. The co-primary endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted  
 507 for baseline HI titers) and the difference in seroconversion rates for each vaccine strain 21 days  
 508 after the final vaccination. Pre-specified non-inferiority criteria required that the upper bound  
 509 of the 2-sided 95% CI of the GMT ratio (Comparator/AFLURIA) did not exceed 1.5 and the  
 510 upper bound of the 2-sided 95% CI of the seroconversion rate difference (Comparator minus  
 511 AFLURIA) did not exceed 10.0% for each strain. As shown in Table 7, non-inferiority of

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

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

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

Abbreviations: CI, confidence interval; GMT, geometric mean titer.  
<sup>a</sup> GMT ratios are adjusted for baseline HI titers  
<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 increase in titer from  $< 1:10$  to  $\geq 1:40$ .  
<sup>c</sup> Note that the study was powered to assess the pre-specified non-inferiority criteria based on 1400 evaluable subjects.

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

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

Study 4 was a randomized, double-blinded, placebo-controlled, multi-center study in healthy subjects ages 18 through 64 years. A total of 1,357 subjects were vaccinated (1,089 subjects with AFLURIA and 268 with a placebo). Subjects who received AFLURIA were vaccinated using either the preservative-free or thimerosal-containing presentation. The evaluable

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545 population consisted of 1,341 subjects (1,077 in the AFLURIA group and 264 in the placebo  
546 group). The mean age of the entire evaluable population receiving AFLURIA was 38 years.  
547 62.5% of subjects were female, 81.3% were White, 12.1% were Black, and 6.2% were Asian.

548  
549 Serum HI antibody responses to AFLURIA met the pre-specified co-primary endpoint criteria  
550 for all three virus strains (Table 8). Similar responses were observed between genders. The  
551 study was not sufficiently diverse to assess immunogenicity by race or ethnicity.

552  
553 **Table 8: Serum Antibody Responses in Subjects 18 through 64 Years of Age Receiving**  
554 **AFLURIA (Study 4)**  
555

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)

556 <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  
557 bound of 95% CI for HI antibody titer  $\geq$  1:40 should be > 70% for the study population.

558 <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  
559 an increase in titer from < 1:10 to  $\geq$  1:40. Lower bound of 95% CI for seroconversion should be > 40% for the study  
560 population.

561  
562 Study 6 was a randomized, observer-blind, comparator-controlled study that enrolled 1,268  
563 subjects 65 years of age and older (Table 9). This study compared the immune response  
564 following administration of AFLURIA to that following a US-licensed trivalent inactivated  
565 influenza vaccine (manufactured by Sanofi Pasteur Inc.). Subjects were randomized in a 1:1  
566 ratio to receive a single vaccination of AFLURIA (enrolled subjects: 631; evaluable subjects:  
567 605) or the comparator vaccine (enrolled subjects: 637; evaluable subjects: 610).  
568 Immunogenicity assessments were performed prior to vaccination and at 21 days after  
569 vaccination. Most of the subjects in the per-protocol immunogenicity population were female  
570 (56.7%) and White (97.4%). 2.0% were Black and less than 1.0% were of other races or  
571 ethnicities.

572  
573 The co-primary endpoints were HI GMT ratios (adjusted for baseline HI titers) and the

Package insert

574 difference in seroconversion rates for each vaccine strain 21 days after vaccination. Pre-  
575 specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the  
576 GMT ratio (Comparator/AFLURIA) did not exceed 1.5 and the upper bound of the 2-sided  
577 95% CI of the seroconversion rate difference (Comparator minus AFLURIA) did not exceed  
578 10.0% for each strain. As shown in Table 9, non-inferiority of AFLURIA to the comparator  
579 vaccine was demonstrated in the per protocol population for influenza A subtypes A(H1N1)  
580 and A(H3N2), but not for influenza type B. For the B strain, non-inferiority was demonstrated  
581 for HI GMTs, but not for seroconversion rates. Post-hoc analyses of immunogenicity by  
582 gender did not demonstrate significant differences between males and females. The study was  
583 not sufficiently diverse to assess differences between races or ethnicities.

584  
585 **Table 9: Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of**  
586 **Non-Inferiority of AFLURIA to a U.S. Licensed Comparator, Adults 65 Years of**  
587 **Age and Older (Study 6)**  
588

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

589 Abbreviations: CI, confidence interval; GMT, geometric mean titer.  
590 <sup>a</sup> Post-vaccination GMTs were adjusted for baseline HI titers.  
591 <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  
592 an increase in titer from  $< 1:10$  to  $\geq 1:40$ .

593  
594 **14.4 Immunogenicity in Adults – Administration via PharmaJet Stratis Needle-**  
595 **Free Injection System**

596 Study 7 was a randomized, comparator-controlled non-inferiority study that enrolled 1,250  
597 subjects 18 through 64 years of age. This study compared the immune response following  
598 administration of AFLURIA when delivered IM using either the PharmaJet Stratis Needle-Free  
599 Injection System or needle and syringe. Immunogenicity assessments were performed prior to  
600 vaccination and at 28 days after vaccination in the immunogenicity population (1130 subjects,  
601 562 PharmaJet Stratis Needle-Free Injection System group, 568 needle and syringe group).  
602 The co-primary endpoints were HI GMT ratios for each vaccine strain and the absolute  
603 difference in seroconversion rates for each vaccine strain 28 days after vaccination. As shown  
604 in Table 10, non-inferiority of administration of AFLURIA by the PharmaJet Stratis Needle-  
605 Free Injection System compared to administration of AFLURIA by needle and syringe was  
606 demonstrated in the immunogenicity population for all strains. Post-hoc analyses of

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

**Table 10: Baseline and Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of Non-Inferiority of AFLURIA Administered by PharmaJet Stratis Needle-Free Injection System or Needle and Syringe, Adults 18 through 64 Years of Age (Study 7)**

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

Abbreviations: CI, confidence interval; GMT, geometric mean titer  
<sup>a</sup> GMT ratio is defined as post-vaccination GMT for Needle and Syringe/PharmaJet Stratis Needle-Free Injection System  
<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 increase in titer from  $< 1:10$  to  $\geq 1:40$ .  
<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 Stratis Needle-Free Injection System. GMT should not exceed 1.5. NI criteria for the seroconversion rate (SCR) difference: upper bound of 2-sided 95% CI on the difference between SCR Needle and Syringe – SCR PharmaJet Stratis Needle-Free Injection System should not exceed 10%.

15 REFERENCES

- Centers for Disease Control and Prevention. Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2010;59 (RR-8):1-62.
- Hannoun C, Megas F, Piercy J. Immunogenicity and Protective Efficacy of Influenza Vaccination. *Virus Res* 2004;103:133-138.

**Package insert**

635 3. Hobson D, Curry RL, Beare AS, et al. The Role of Serum Hemagglutination-  
636 Inhibiting Antibody in Protection against Challenge Infection with Influenza A2 and B  
637 Viruses. *J Hyg Camb* 1972;70:767-777.  
638

639

640 **16 HOW SUPPLIED/STORAGE AND HANDLING**

641

642 **16.1 How Supplied**

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

Presentation	Carton NDC Number	Components
Pre-Filled Syringe	33332-015-01	<ul style="list-style-type: none"> <li>Ten 0.5 mL single-dose syringes without needles [NDC 33332-015-02]</li> </ul>
Multi-Dose Vial	33332-115-10	<ul style="list-style-type: none"> <li>One 5 mL vial, which contains ten 0.5 mL doses [NDC 33332-115-11]</li> </ul>

644

645 **16.2 Storage and Handling**

- 646 • Store refrigerated at 2–8°C (36–46°F).
- 647 • Do not freeze. Discard if product has been frozen.
- 648 • Protect from light.
- 649 • Do not use AFLURIA beyond the expiration date printed on the label.
- 650 • Once the stopper of the multi-dose vial has been pierced the vial must be discarded  
651 within 28 days.

652

653

654 **17 PATIENT COUNSELING INFORMATION**

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

668

669

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670 Manufactured by:

671 **bioCSL Pty Ltd.**

672 Parkville, Victoria, 3052, Australia

673 US License No. 2002

674

675 Distributed by:

676 **bioCSL Inc.** 1020 First Avenue, King of Prussia, PA 19406, USA

677

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