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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Influenza A (H1N1) 2009 Monovalent Vaccine safely and effectively. See full prescribing information for Influenza A (H1N1) 2009 Monovalent Vaccine.

Influenza A (H1N1) 2009 Monovalent Vaccine
Manufactured by CSL Limited
Suspension for Intramuscular Injection
Initial U.S. Approval: 2007

RECENT MAJOR CHANGES

Indications and Usage (1)	11/2009
Dosage and Administration (2.2)	11/2009

INDICATIONS AND USAGE

- Influenza A (H1N1) 2009 Monovalent Vaccine is an inactivated influenza virus vaccine indicated for active immunization of persons ages 6 months and older against influenza disease caused by pandemic (H1N1) 2009 virus. (1)
- This indication is based on the immune response elicited by the seasonal trivalent Influenza Virus Vaccine manufactured by CSL (AFLURIA). CSL's Influenza A (H1N1) 2009 Monovalent Vaccine and AFLURIA are manufactured by the same process. There have been no controlled clinical studies demonstrating a decrease in influenza disease after vaccination with AFLURIA. (14)

DOSAGE AND ADMINISTRATION

Based on currently available information, the vaccination regimen is as follows:

Children

- **6 months through 35 months of age** (0.25 mL dose, intramuscular injection):
Two 0.25 mL doses approximately 4 weeks apart. (2.2)
- **36 months through 9 years of age** (0.5 mL dose, intramuscular injection):
Two 0.5 mL doses approximately 4 weeks apart. (2.2)
- **10 years of age and older**
A single 0.5 mL dose for intramuscular injection. (2.2)

Adults

- **18 years of age and older:**
A single 0.5 mL dose for intramuscular injection. (2.2)

DOSAGE FORMS AND STRENGTHS

Influenza A (H1N1) 2009 Monovalent Vaccine, a sterile suspension for intramuscular injection, is supplied in three presentations:

- 0.25 mL single-dose, pre-filled syringe, no preservative. (3)
- 0.5 mL single-dose, pre-filled syringe, no preservative. (3)
- 5 mL multi-dose vial containing ten doses. Thimerosal, a mercury derivative, is added as a preservative; each 0.5 mL dose contains 24.5 micrograms (mcg) of mercury. (3,11)

CONTRAINDICATIONS

- Hypersensitivity to eggs, neomycin, or polymyxin, or life-threatening reaction to previous influenza vaccination. (4, 11)

WARNINGS AND PRECAUTIONS

- If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give Influenza A (H1N1) 2009 Monovalent Vaccine should be based on careful consideration of the potential benefits and risks. (5.1)
- Immunocompromised persons may have a diminished immune response to Influenza A (H1N1) 2009 Monovalent Vaccine. (5.2)

ADVERSE REACTIONS

Adverse reactions information is based on studies conducted with seasonal trivalent Influenza Virus Vaccine manufactured by CSL (AFLURIA).

- In adults, the most common ($\geq 10\%$) local (injection-site) adverse reactions were tenderness, pain, redness, and swelling. The most common ($\geq 10\%$) systemic adverse reactions were headache, malaise, and muscle aches. (6)
- In children, the most common ($\geq 10\%$) local (injection-site) adverse reactions were pain, redness, and swelling. The most common ($\geq 10\%$) systemic adverse reactions were irritability, rhinitis, fever, cough, loss of appetite, vomiting/diarrhea, headache, muscle aches and sore throat. (6)

To report SUSPECTED ADVERSE REACTIONS, contact CSL Biotherapies at 1-888-435-8633 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

DRUG INTERACTIONS

- Do not mix with any other vaccine in the same syringe or vial. (7.1)
- Immunosuppressive therapies may diminish the immune response to Influenza A (H1N1) 2009 Monovalent Vaccine. (7.2)

USE IN SPECIFIC POPULATIONS

Information is based on studies conducted with seasonal trivalent Influenza Virus Vaccine manufactured by CSL (AFLURIA).

- Safety and effectiveness of Influenza A (H1N1) 2009 Monovalent Vaccine have not been established in pregnant women or nursing mothers and in the pediatric population below 6 months of age. (8.1, 8.3, 8.4)
- Antibody responses were lower in geriatric subjects than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2009

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

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1 FULL PRESCRIBING INFORMATION

4 **1 INDICATIONS AND USAGE**

6 Influenza A (H1N1) 2009 Monovalent Vaccine is an inactivated influenza virus vaccine
7 indicated for active immunization of persons ages 6 months and older against influenza
8 disease caused by pandemic (H1N1) 2009 virus.

10 This indication is based on the immune response elicited by the seasonal trivalent
11 Influenza Virus Vaccine manufactured by CSL (AFLURIA®). CSL's Influenza A
12 (H1N1) 2009 Monovalent Vaccine and AFLURIA are manufactured by the same process.
13 There have been no controlled clinical studies demonstrating a decrease in influenza
14 disease after vaccination with AFLURIA (*see Clinical Studies [14]*).

17 **2 DOSAGE AND ADMINISTRATION**19 **2.1 Prior to Administration**

20 Influenza A (H1N1) 2009 Monovalent Vaccine should be inspected visually for
21 particulate matter and discoloration prior to administration (*see Description [11]*),
22 whenever suspension and container permit. If either of these conditions exists, the
23 vaccine should not be administered. Any vaccine that has been frozen or is suspected of
24 being frozen must not be used.

26 **2.2 Administration**

27 When using a preservative-free, single-dose syringe, shake the syringe thoroughly and
28 administer the dose immediately.

30 When using the multi-dose vial, shake the vial thoroughly before withdrawing each dose,
31 and administer the dose immediately. Between uses, store the vial at 2 –8°C (36–46°F)
32 (*see How Supplied/Storage and Handling [16]*). Once the stopper has been pierced, the
33 vial must be discarded within 28 days.

35 Clinical studies are ongoing with Influenza A (H1N1) 2009 Monovalent Vaccine to
36 determine the optimal dosage, number of doses and schedule.

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37
38 Available data show that children 9 years of age and younger are largely serologically
39 naïve to the pandemic (H1N1) 2009 virus.¹ Based upon these data Influenza A (H1N1)
40 2009 Monovalent Vaccine should be administered as follows:

41

Children

42
43 Children 6 months through 35 months of age should receive two 0.25 mL doses
44 approximately 4 weeks apart.²

45

46 Children 36 months through 9 years of age should receive two 0.5 mL doses
47 approximately 4 weeks apart.²

48

49 Children 10 years of age and older should receive a single 0.5 mL intramuscular dose.²

50

51 The preferred sites for intramuscular injections are the anterolateral aspect of the thigh in
52 infants or the deltoid muscle of the upper arm in toddlers and young children.

53

Adults

54

55
56 Persons 18 years of age and older should receive a single 0.5 mL intramuscular injection,
57 preferably in the deltoid muscle of the upper arm.

58

59

3 DOSAGE FORMS AND STRENGTHS

60

61
62 Influenza A (H1N1) 2009 Monovalent Vaccine is a sterile suspension for intramuscular
63 injection (*see Description [11]*).

64

65 Influenza A (H1N1) 2009 Monovalent Vaccine is supplied in three presentations:

66

- 67 • 0.25 mL single-dose, pre-filled syringe, no preservative.
- 68 • 0.5 mL single-dose, pre-filled syringe, no preservative.
- 69 • 5 mL multi-dose vial containing ten doses. Thimerosal, a mercury derivative,
70 is added as a preservative; each 0.5 mL dose contains 24.5 mcg of mercury.

71

72

4 CONTRAINDICATIONS

73

74
75 Influenza A (H1N1) 2009 Monovalent Vaccine is contraindicated in individuals with
76 known hypersensitivity to eggs, neomycin, or polymyxin, or in anyone who has had a
77 life-threatening reaction to previous influenza vaccination (*see Description [11]*).

78

79

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80 **5 WARNINGS AND PRECAUTIONS**

81

82 **5.1 Guillain-Barré Syndrome (GBS)**

83 If GBS has occurred within 6 weeks of previous influenza vaccination, the decision to
84 give Influenza A (H1N1) 2009 Monovalent Vaccine should be based on careful
85 consideration of the potential benefits and risks.

86

87 **5.2 Altered Immunocompetence**

88 If Influenza A (H1N1) 2009 Monovalent Vaccine is administered to
89 immunocompromised persons, including those receiving immunosuppressive therapy, the
90 immune response may be diminished.

91

92 **5.3 Preventing and Managing Allergic Reactions**

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

95

96 **5.4 Limitations of Vaccine Effectiveness**

97 Vaccination with Influenza A (H1N1) 2009 Monovalent Vaccine may not protect all
98 individuals.

99

100

101 **6 ADVERSE REACTIONS**

102

103 CSL's Influenza A (H1N1) 2009 Monovalent Vaccine and seasonal trivalent Influenza
104 Virus Vaccine (AFLURIA) are manufactured by the same process. The data in this
105 section were obtained from clinical studies and postmarketing experience with
106 AFLURIA.

107

108 **6.1 Overall Adverse Reactions**

109 Serious allergic reactions, including anaphylactic shock, have been observed during
110 postmarketing surveillance in individuals receiving AFLURIA.

111

112 In adults, the most common local (injection-site) adverse reactions observed in clinical
113 studies with AFLURIA were tenderness, pain, redness and swelling. The most common
114 systemic adverse reactions observed were headache, malaise, and muscle aches.

115

116 In children, the most common local (injection-site) adverse reactions observed in a
117 clinical study with AFLURIA were pain, redness and swelling. The most common
118 systemic adverse reactions observed were irritability, rhinitis, fever, cough, loss of
119 appetite, vomiting/diarrhea, headache, muscle aches and sore throat.

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121 **6.2 Safety Experience from Clinical Studies**

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

126
127 Clinical data for AFLURIA have been obtained in four clinical studies, three in adult
128 populations and one in a pediatric population (*see Clinical Studies [14]*). Safety data are
129 provided for two of the adult studies and the pediatric study.

130
131 A US study (Study 1) included 1,357 subjects for safety analysis, ages 18 to less than 65
132 years, randomized to receive AFLURIA (1,089 subjects) or placebo (268 subjects) (*see*
133 *Clinical Studies [14] for study demographics*). There were no deaths or serious adverse
134 events reported in this study.

135
136 A UK study (Study 2) included 275 subjects, ages 65 years and older, randomized to
137 receive preservative-free AFLURIA (206 subjects) or a European-licensed trivalent
138 inactivated influenza vaccine as an active control (69 subjects) (*see Clinical Studies*
139 *[14]*). There were no deaths or serious adverse events reported in this study.

140
141 An open-label, uncontrolled study in children, conducted in Australia (Study 4), included
142 298 subjects, ages 6 months to less than 9 years. All subjects received preservative-free
143 AFLURIA administered as two doses, one month apart (*see Clinical Studies [14]*).
144 Subjects were subdivided into two age groups: children ages 6 months to less than 3
145 years (151 subjects) received two 0.25 mL doses of AFLURIA and children ages 3 years
146 to less than 9 years (147 subjects) received two 0.5 mL doses of AFLURIA. There were
147 no deaths or vaccine-related serious adverse events reported in this study.

148
149 The safety assessment was identical for the two adult studies. Local (injection-site) and
150 systemic adverse events were solicited by completion of a symptom diary card for 5 days
151 post-vaccination (Table 1). Unsolicited adverse events were collected for 21 days post-
152 vaccination (Table 2). These unsolicited adverse events were reported either
153 spontaneously or when subjects were questioned about any changes in their health post-
154 vaccination. All adverse events are presented regardless of any treatment causality
155 assigned by study investigators.

156
157 In the pediatric study, solicited adverse events were recorded for up to 7 days (Table 3)
158 and unsolicited adverse events were recorded for 30 days post-vaccination (Table 4).
159 Data are presented following each dose for each age group. All adverse events are
160 presented regardless of any treatment causality assigned by study investigators.

161

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162 **Table 1: Proportion of Subjects With Solicited Local or Systemic Adverse Events***
 163 **Within 5 Days After Administration of AFLURIA or Placebo, Irrespective**
 164 **of Causality† (Studies 1 and 2, Adult Populations)**
 165

Solicited Adverse event	Study 1 Subjects ≥ 18 to < 65 years		Study 2 Subjects ≥ 65 years
	AFLURIA‡ n=1089	Placebo § n=268	AFLURIA n=206
Local			
Tenderness¶	60%	18%	34%
Pain¶	40%	9%	9%
Redness	16%	8%	23%
Swelling	9%	1%	11%
Bruising	5%	1%	4%
Systemic			
Headache	26%	26%	15%
Malaise	20%	19%	10%
Muscle aches	13%	9%	14%
Nausea	6%	9%	3%
Chills/ Shivering	3%	2%	7%
Fever ≥ 37.7°C (99.9°F)	1%	1%	1%
Vomiting	1%	1%	0%

166 * In Study 1, 87% of solicited local and systemic adverse events were mild, 12% were moderate, and 1% were severe.
 167 In Study 2, 76.5% were mild, 20.5% were moderate, and 3% were severe. In both studies, most solicited local and
 168 systemic adverse events lasted no longer than 2 days.
 169 † Values rounded to the nearest whole percent.
 170 ‡ Includes subjects who received either the single-dose (preservative-free) or multi-dose formulation of AFLURIA.
 171 § Thimerosal-containing placebo.
 172 ¶ Tenderness defined as pain on touching.
 173 ¶ Pain defined as spontaneously painful without touch.

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174 **Table 2: Adverse Events* Reported Spontaneously by ≥ 1% of Subjects Within 21**
 175 **Days After Administration of AFLURIA or Placebo, Irrespective of**
 176 **Causality† (Studies 1 and 2, Adult Populations)**
 177

Adverse Event	Study 1 Subjects ≥ 18 to < 65 years		Study 2 Subjects ≥ 65 years
	AFLURIA‡ n=1089	Placebo § n=268	AFLURIA n=206
Headache	8%	6%	8%
Nasal Congestion	1%	1%	7%
Cough	1%	0.4%	5%
Rhinorrhea	1%	1%	5%
Pharyngolaryngeal Pain	3%	1%	5%
Reactogenicity Event	3%	3%	0%
Diarrhea	2%	3%	1%
Back Pain	2%	0.4%	2%
Upper Respiratory Tract Infection	2%	1%	0.5%
Viral Infection	0.4%	1%	0%
Lower Respiratory Tract Infection	0%	0%	1%
Myalgia	1%	1%	1%
Muscle Spasms	0.4%	1%	0%

178 * In Study 1, 63% of unsolicited adverse events were mild, 35% were moderate, and 2% were severe. In Study 2,
 179 47% were mild, 51% were moderate, and 3% were severe. In both studies, most unsolicited adverse events lasted no
 180 longer than 5 days.

181 † Values rounded to the nearest whole percent.

182 ‡ Includes subjects who received either the single-dose (preservative-free) or multi-dose formulation of AFLURIA.

183 § Thimerosal-containing placebo.

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Table 3: Proportion of Subjects With Solicited Local or Systemic Adverse Events* Within 7 Days After Administration of AFLURIA, Irrespective of Causality† (Study 4, Pediatric Population)

Solicited Adverse Event	Subjects ≥ 6 months to < 3 years (n = 151)‡		Subjects ≥ 3 years to < 9 years (n = 147)§	
	Dose 1	Dose 2	Dose 1	Dose 2
Local				
Pain	36%	37%	59%	62%
Erythema	36%	38%	37%	46%
Swelling	16%	21%	25%	27%
Systemic				
Irritability	48%	41%	20%	17%
Rhinitis	37%	48%	21%	29%
Fever¶	23%	23%	16%	8%
Cough	21%	32%	19%	19%
Loss of appetite	19%	24%	8%	5%
Vomiting/Diarrhea	15%	14%	8%	7%
Headache	2%¶	3%**	14%	11%
Myalgia	1%#	3%**	14%	8%
Sore throat	2%¶	5%**	8%	11%
Wheezing/ Shortness of breath	3%	9%	3%	2%
Ear ache	3%**	3%#	4%	1%

* In Study 4, 78% of all local and systemic solicited events experienced by children ages 6 months to less than 3 years were mild, 19% were moderate and 3% were severe; 76% of all events experienced by children ages 3 years to less than 9 years were mild, 20% moderate and 4% severe. Severe pain was reported by < 1% of children ages 6 months to less than 3 years and 3% in children ages 3 years to less than 9 years. Severe fever (> 103.1°F axillary or > 104.0°F oral) was reported by < 1% of subjects in children ages 6 months to less than 3 years and 1% of subjects in children ages 3 years to less than 9 years.

† Values rounded to the nearest whole percent.

‡ Dosage in children 6 months to less than 3 years of age was 0.25 mL.

§ Dosage in children 3 years to less than 9 years of age was 0.5 mL.

¶ Axillary Temperature ≥ 37.5°C (99.5°F) or Oral Temperature ≥ 38.0°C (100.4°F).

¶ Data obtained from a total of 148 subjects.

Data obtained from a total of 149 subjects.

** Data obtained from a total of 150 subjects.

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190 **Table 4: Adverse Events* Reported Spontaneously by ≥ 5% of Subjects Within 30**
 191 **Days After Administration of AFLURIA, Irrespective of Causality (Study**
 192 **4, Pediatric Population)**
 193

Adverse Event	Subjects ≥ 6 months to < 3 years (n = 151) [†]		Subjects ≥ 3 to < 9 years (n = 147) [‡]	
	Dose 1	Dose 2	Dose 1	Dose 2
Nasopharyngitis	5.3%	7.9%	5.4%	5.4%
Rhinitis	13.2%	9.9%	6.8%	10.9%
Upper Respiratory Tract Infection	9.9%	7.3%	6.1%	6.1%
Irritability	3.3%	5.3%	0.7%	0.7%
Headache	1.3%	0.7%	6.1%	4.1%
Cough	10.6%	13.2%	10.9%	13.6%
Rhinorrhea	7.3%	6.0%	6.8%	4.8%
Teething	14.6%	9.9%	0.0%	0.0%
Vomiting	5.3%	2.6%	2.0%	2.7%
Influenza-like Illness	13.9%	10.6%	6.8%	3.4%
Pyrexia	2.6%	9.3%	2.7%	4.1%

* In Study 4, for both doses and both groups combined, 47% of unsolicited adverse events were mild, 42% were moderate, and 12% were severe.

[†] Dosage in children 6 months to less than 3 years of age was 0.25 mL.

[‡] Dosage in children 3 years to less than 9 years of age was 0.5 mL.

194
 195 **6.3 Postmarketing Experience**
 196 Because postmarketing reporting of adverse reactions is voluntary and from a population
 197 of uncertain size, it is not always possible to reliably estimate their frequency or establish
 198 a causal relationship to vaccine exposure. The adverse reactions described have been
 199 included in this section because they: 1) represent reactions that are known to occur
 200 following immunizations generally or influenza immunizations specifically; 2) are
 201 potentially serious; or 3) have been reported frequently. These adverse reactions reflect
 202 experience in both children and adults and include those identified during post-approval
 203 use of AFLURIA outside the US since 1985.

204
 205 **Blood and lymphatic system disorders**

206 Transient thrombocytopenia

207
 208 **Immune system disorders**

209 Allergic reactions including anaphylactic shock and serum sickness

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210

211 Nervous system disorders

212 Neuralgia, paresthesia, and convulsions; encephalopathy, neuritis or neuropathy,
213 transverse myelitis, and GBS

214

215 Vascular disorders

216 Vasculitis with transient renal involvement

217

218 Skin and subcutaneous tissue disorders

219 Pruritus, urticaria, and rash

220

221 6.4 Other Adverse Reactions Associated With Influenza Vaccination

222 Anaphylaxis has been reported after administration of AFLURIA. Although AFLURIA
223 and Influenza A (H1N1) 2009 Monovalent Vaccine contain only a limited quantity of egg
224 proteins, these proteins can induce immediate hypersensitivity reactions among persons
225 who have severe egg allergy. Allergic reactions include hives, angioedema, asthma, and
226 systemic anaphylaxis (*see Contraindications [4]*).

227

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

232

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

236

237 Microscopic polyangiitis (vasculitis) has been reported temporally associated with
238 influenza vaccination.

239

240

241 7 DRUG INTERACTIONS

242

243 7.1 Concurrent Use With Other Vaccines

244 There are no data to assess the concomitant administration of Influenza A (H1N1) 2009
245 Monovalent Vaccine with other vaccines. If Influenza A (H1N1) 2009 Monovalent
246 Vaccine is to be given at the same time as another injectable vaccine(s), the vaccine(s)
247 should be administered at different injection sites.

248

249 Influenza A (H1N1) 2009 Monovalent Vaccine should not be mixed with any other
250 vaccine in the same syringe or vial.

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252 **7.2 Concurrent Use With Immunosuppressive Therapies**

253 The immunological response to Influenza A (H1N1) 2009 Monovalent Vaccine may be
254 diminished in individuals receiving corticosteroid or immunosuppressive therapies.

255

256

257 **8 USE IN SPECIFIC POPULATIONS**

258

259 CSL's Influenza A (H1N1) 2009 Monovalent Vaccine and seasonal trivalent Influenza
260 Virus Vaccine (AFLURIA) are manufactured by the same process. Available information
261 for AFLURIA is provided in this section.

262

263 **8.1 Pregnancy**

264 Pregnancy Category C: Animal reproduction studies have not been conducted with
265 Influenza A (H1N1) 2009 Monovalent Vaccine or AFLURIA. It is also not known
266 whether these vaccines can cause fetal harm when administered to a pregnant woman or
267 can affect reproduction capacity. Influenza A (H1N1) 2009 Monovalent Vaccine should
268 be given to a pregnant woman only if clearly needed.

269

270 **8.3 Nursing Mothers**

271 Neither Influenza A (H1N1) 2009 Monovalent Vaccine nor AFLURIA has been
272 evaluated in nursing mothers. It is not known whether Influenza A (H1N1) 2009
273 Monovalent Vaccine or AFLURIA is excreted in human milk. Because many drugs are
274 excreted in human milk, caution should be exercised when Influenza A (H1N1) 2009
275 Monovalent Vaccine is administered to a nursing woman.

276

277 **8.4 Pediatric Use**

278 Safety and effectiveness of Influenza A (H1N1) 2009 Monovalent Vaccine and
279 AFLURIA in children below 6 months of age have not been established. The safety and
280 immunogenicity of AFLURIA was evaluated in 298 children between the ages of 6
281 months and 9 years (*see Adverse Reactions [6.2] and Clinical Studies [14]*).

282

283 **8.5 Geriatric Use**

284 In four clinical studies, 343 subjects ages 65 years and older received AFLURIA.
285 Hemagglutination-inhibiting antibody responses in geriatric subjects were lower after
286 administration of AFLURIA in comparison to younger adult subjects (*see Clinical
287 Studies [14]*). Adverse event rates were generally similar in frequency to those reported
288 in subjects ages 18 to less than 65 years, although some differences were observed (*see
289 Adverse Reactions [6.2]*).

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292 **11 DESCRIPTION**

293

294 Influenza A (H1N1) 2009 Monovalent Vaccine, for intramuscular injection, is a sterile,
295 clear, colorless to slightly opalescent suspension with some sediment that resuspends
296 upon shaking to form a homogeneous suspension. Influenza A (H1N1) 2009 Monovalent
297 Vaccine is prepared from influenza virus propagated in the allantoic fluid of embryonated
298 chicken eggs. Following harvest, the virus is purified in a sucrose density gradient using
299 a continuous flow zonal centrifuge. The purified virus is inactivated with beta-
300 propiolactone, and the virus particles are disrupted using sodium taurodeoxycholate to
301 produce a “split virion”. The disrupted virus is further purified and suspended in a
302 phosphate buffered isotonic solution.

303

304 Influenza A (H1N1) 2009 Monovalent Vaccine is formulated to contain 15 mcg
305 hemagglutinin (HA) per 0.5 mL dose of influenza A/California/7/2009 (H1N1)v-like
306 virus.

307

308 Thimerosal, a mercury derivative, is not used in the manufacturing process for the single
309 dose presentations; therefore these products contain no preservative. The multi-dose
310 presentation contains thimerosal, added as a preservative; each 0.5 mL dose contains
311 24.5 mcg of mercury.

312

313 A single 0.5 mL dose of Influenza A (H1N1) 2009 Monovalent Vaccine contains sodium
314 chloride (4.1 mg), monobasic sodium phosphate (80 mcg), dibasic sodium phosphate
315 (300 mcg), monobasic potassium phosphate (20 mcg), potassium chloride (20 mcg), and
316 calcium chloride (1.5 mcg). A single 0.25 mL dose of Influenza A (H1N1) 2009
317 Monovalent Vaccine contains half of these quantities. From the manufacturing process,
318 each 0.5 mL dose may also contain residual amounts of sodium taurodeoxycholate (≤ 10
319 ppm), ovalbumin (≤ 1 mcg), neomycin sulfate (≤ 0.2 picograms [pg]), polymyxin B
320 (≤ 0.03 pg), and beta-propiolactone (< 25 nanograms).

321

322 The rubber tip cap and plunger used for the preservative-free, single-dose syringes and
323 the rubber stoppers used for the multi-dose vial contain no latex.

324

325

326 **12 CLINICAL PHARMACOLOGY**

327

328 **12.1 Mechanism of Action**

329 Influenza illness and its complications follow infection with influenza viruses. Global
330 surveillance of influenza identifies yearly antigenic variants. For example, since 1977
331 antigenic variants of influenza A (H1N1 and H3N2) and influenza B viruses have been in
332 global circulation. Specific levels of hemagglutination inhibition (HI) antibody titers
333 post-vaccination with inactivated influenza virus vaccine have not been correlated with

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334 protection from influenza virus. In some human studies, antibody titers of 1:40 or greater
335 have been associated with protection from influenza illness in up to 50% of subjects.^{3,4}

336

337 Antibody against one influenza virus type or subtype confers limited or no protection
338 against another. Furthermore, antibody to one antigenic variant of influenza virus might
339 not protect against a new antigenic variant of the same type or subtype. Frequent
340 development of antigenic variants through antigenic drift is the virologic basis for
341 seasonal epidemics and the reason for the usual change to one or more new strains in
342 each year's influenza vaccine.

343

344

345 **13 NONCLINICAL TOXICOLOGY**

346

347 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

348 Neither Influenza A (H1N1) 2009 Monovalent Vaccine nor AFLURIA has been
349 evaluated for carcinogenic or mutagenic potential or for impairment of fertility.

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352 **14 CLINICAL STUDIES**

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354 CSL's Influenza A (H1N1) 2009 Monovalent Vaccine and seasonal trivalent Influenza
355 Virus Vaccine (AFLURIA) are manufactured by the same process. Data in this section
356 were obtained in clinical studies conducted with AFLURIA.

357

358 **14.1 Immunogenicity in the Adult and Geriatric Populations**

359 Three randomized, controlled clinical studies of AFLURIA have evaluated the immune
360 responses by measuring HI antibody titers to each virus strain in the vaccine. In these
361 studies, post-vaccination immunogenicity was evaluated on sera obtained 21 days after
362 administration of AFLURIA. No controlled clinical studies demonstrating a decrease in
363 influenza disease after vaccination with AFLURIA have been performed.

364

365 The US study (Study 1) was a randomized, double-blinded, placebo-controlled,
366 multicenter study in healthy subjects ages 18 to less than 65 years. A total of 1,357
367 subjects were vaccinated (1,089 subjects with AFLURIA and 268 with a thimerosal-
368 containing placebo). Subjects receiving AFLURIA were vaccinated using either a single-
369 dose (preservative-free) or multi-dose (one of three lots) formulation. The evaluable
370 efficacy population consisted of 1,341 subjects (1,077 in the AFLURIA group and 264 in
371 the placebo group) with complete serological data who had not received any
372 contraindicated medications before the post-vaccination immunogenicity assessment.
373 Among the evaluable efficacy population receiving AFLURIA, 37.5% were men and
374 62.5% were women. The mean age of the entire evaluable population receiving
375 AFLURIA was 38 years; 73% were ages 18 to less than 50 years and 27% were ages 50
376 to less than 65 years. Additionally, 81% of AFLURIA recipients were White, 12%

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377 Black, and 6% Asian.

378

379 In Study 1, the following co-primary immunogenicity endpoints were assessed: 1) the
380 lower bounds of the 2-sided 95% confidence intervals (CI) for the proportion of subjects
381 with HI antibody titers of 1:40 or greater after vaccination, which should exceed 70% for
382 each vaccine antigen strain; and 2) the lower bounds of the 2-sided 95% CI for rates of
383 seroconversion (defined as a 4-fold increase in post-vaccination HI antibody titers from
384 pre-vaccination titers of 1:10 or greater, or an increase in titers from less than 1:10 to
385 1:40 or greater), which should exceed 40% for each vaccine antigen strain.

386

387 In subjects ages 18 to less than 65 years, serum HI antibody responses to AFLURIA met
388 the pre-specified co-primary endpoint criteria for all three virus strains (Table 5).
389 Clinical lot-to-lot consistency was demonstrated for the single-dose (preservative-free)
390 and multi-dose formulations of AFLURIA, showing that these formulations elicited
391 similar immune responses.

392

393 **Table 5: Study 1 – Serum HI Antibody Responses in Subjects ≥ 18 to < 65 Years**
394 **Receiving AFLURIA**

395

Treatment Arm	Number Enrolled/ Evaluable	Vaccine Strain	Seroconversion Rate* (95% CI)	HI Titer ≥ 1:40† (95% CI)
All active AFLURIA influenza vaccine formulations‡	1089/1077	H1N1	48.7% (45.6, 51.7)	97.8% (96.7, 98.6)
		H3N2	71.5% (68.7, 74.2)	99.9% (99.5, 100.0)
		B	69.7% (66.9, 72.5)	94.2% (92.7, 95.6)
Placebo	270/264	H1N1	2.3% (0.8, 4.9)	74.6% (68.9, 79.8)
		H3N2	0.0% (N/A)	72.0% (66.1, 77.3)
		B	0.4% (< 0.1, 2.1)	47.0% (40.8, 53.2)

396 * Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-
397 vaccination titer ≥ 1:10, or an increase in titer from < 1:10 to ≥ 1:40. Lower bound of 95% CI for
398 seroconversion should be > 40% for the study population.

399 † HI titer ≥ 1:40 is defined as the proportion of subjects with a minimum post-vaccination HI antibody titer of
400 1:40. Lower bound of 95% CI for HI antibody titer ≥ 1:40 should be > 70% for the study population.

401 ‡ Active formulations include aggregated results for the single-dose (preservative-free) and multi-dose
402 formulations of AFLURIA.

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404 The UK study (Study 2) was a randomized, controlled study that enrolled 275 healthy
 405 subjects ages 65 years and older. This study compared AFLURIA with a European-
 406 licensed trivalent inactivated influenza vaccine as an active control. The evaluable
 407 efficacy population consisted of 274 subjects (206 in the AFLURIA group and 68 in the
 408 control group). Among these subjects, 50% were men and 50% were women, with a
 409 mean age of 72 years (range: 65 to 93 years).

410
 411 The co-primary immunogenicity endpoints for the seroconversion rate and the proportion
 412 of subjects with a minimum post-vaccination HI antibody titer of 1:40 are presented in
 413 Table 6.

414
 415 **Table 6: Study 2 – Serum HI Antibody Responses in Subjects ≥ 65 Years Receiving**
 416 **AFLURIA**
 417

Number of Subjects	Vaccine Strain	Seroconversion Rate* (95% CI)	HI Titer ≥ 1:40† (95% CI)
206	H1N1	34.0% (27.5, 40.9)	85.0% (79.3, 89.5)
	H3N2	44.2% (37.3, 51.2)	99.5% (97.3, 100.0)
	B	45.6% (38.7, 52.7)	77.7% (71.4, 83.2)

418 * Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-
 419 vaccination titer ≥ 1:10, or an increase in titer from < 1:10 to ≥ 1:40. Lower bound of 95% CI for
 420 seroconversion should be > 30% for the study population.

421 † HI titer ≥ 1:40 is defined as the proportion of subjects with a minimum post-vaccination HI antibody titer of
 422 1:40. Lower bound of 95% CI for HI antibody titer ≥ 1:40 should be > 60% for the study population.

423
 424 A second UK study (Study 3) was a randomized, controlled study that enrolled 406
 425 healthy subjects ages 18 years and older (stratified by age from 18 to less than 60 years
 426 and 60 years and older). This study compared AFLURIA with a European-licensed
 427 trivalent inactivated influenza vaccine as an active control. In a post-hoc analysis of
 428 different age ranges, among subjects ages 18 to less than 65 years receiving AFLURIA
 429 (146 subjects), 47% were men and 53% were women, with a mean age of 48 years for all
 430 subjects. Among subjects ages 65 years and older receiving AFLURIA (60 subjects),
 431 53% were men and 47% were women, with a mean age of 71 years.

432
 433 Analysis of serum HI antibody responses showed that the lower bound of the 95% CI for
 434 subjects with HI antibody titers of 1:40 or greater after vaccination exceeded 70% for
 435 each strain. HI antibody responses were lower in subjects, ages 65 years and older after
 436 administration of AFLURIA. Serum HI antibody responses to the active control were
 437 similar to those for AFLURIA in both age groups.

438

439 **14.2 Immunogenicity in a Pediatric Population**

440

441 An open-label, uncontrolled, multi-center study (Study 4) to evaluate the safety,
442 tolerability and immunogenicity of AFLURIA in children 6 months to 9 years of age was
443 conducted in Australia. The study subjects were subdivided into two groups dependent
444 upon age at time of enrollment. A total of 298 subjects were enrolled, including 151
445 subjects, 6 months to less than 3 years (mean age 1.7 years with 51.0% females) and 147
446 subjects, 3 years to less than 9 years (mean age 5 years with 55.1% females).

447

448 Two doses of AFLURIA were administered to all subjects, with a 30 day interval
449 between each dose. Children ages 6 months to less than 3 years received two 0.25 mL
450 doses of AFLURIA. Children ages 3 years to less than 9 years were administered two 0.5
451 mL doses of AFLURIA. Sera for immunological assessment were taken 30 days (± 3)
452 following each vaccination. Immunogenicity endpoints were the seroconversion rate and
453 the proportion of subjects with a minimum post-vaccination HI antibody titer of 1:40.
454 The results for each dose are presented in Table 7.

455

456 For both age groups, the vaccine met FDA acceptance criteria for immunogenicity
457 developed for healthy adults for all three influenza strains following two doses. These
458 criteria are: 1) that the lower bound of the 2-sided 95% CI for the seroconversion rate
459 should be at least 40%; and 2) the lower bound of the 2-sided 95% CI for the proportion
460 of subjects with a post-vaccination HI titer of $\geq 1:40$ should be at least 70%.

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Table 7: Study 4 – Serum HI Antibody Responses in Subjects ≥ 6 months to < 9 Years Receiving AFLURIA

	Vaccine Strain	Vaccine Dose	Seroconversion Rate* (lower 95% CI)	HI Titer ≥ 1:40† (lower 95% CI)
Subjects ≥ 6 months to < 3 years n=143‡ n=139§	H1N1	Dose 1	16.1% (> 11.3)	16.1% (> 11.3)
		Dose 2	95.0% (> 90.8)	95.7% (> 91.7)
	H3N2	Dose 1	86.0% (> 80.3)	97.9% (> 94.7)
		Dose 2	90.6% (> 85.6)	100.0% (> 97.9)
	B	Dose 1	20.3% (> 14.9)	21.0% (> 15.5)
		Dose 2	94.2% (> 89.9)	95.7% (> 91.7)
Subjects ≥ 3 years to < 9 years n=144‡ n=132§	H1N1	Dose 1	24.3% (> 18.5)	25.7% (> 19.8)
		Dose 2	93.9% (> 89.3)	95.5% (> 91.2)
	H3N2	Dose 1	68.1% (> 61.1)	98.6% (> 95.7)
		Dose 2	70.5% (> 63.2)	100.0% (> 97.8)
	B	Dose 1	32.6% (> 26.2)	34.0% (> 27.5)
		Dose 2	93.2% (> 88.4)	94.7% (> 90.3)

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* Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer ≥ 1:10, or an increase in titer from < 1:10 to ≥ 1:40. The lower 95% confidence limits were determined. Lower bound of 95% CI for seroconversion was taken as > 40% for the study population (as applied to adults 18 to 64 years of age).

† HI titer ≥ 1:40 is defined as the proportion of subjects with a minimum post-vaccination HI antibody titer of 1:40. The lower 95% confidence limits were determined. Lower bound of 95% CI for HI antibody titer ≥ 1:40 was taken as > 70% for the study population (as applied to adults 18 to 64 years of age).

‡ Evaluable population post-dose 1.

§ Evaluable population post-dose 2.

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15 REFERENCES

1. Centers for Disease Control and Prevention. Serum Cross-Reactive Antibody Response to a Novel Influenza A (H1N1) Virus After Vaccination with Seasonal Influenza Vaccine. *MMWR* 2009;58 (19): 521-524.
2. Centers for Disease Control and Prevention. Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2009;58 (RR-8):1-52.
3. Hannoun C, Megas F, Piercy J. Immunogenicity and Protective Efficacy of Influenza Vaccination. *Virus Res* 2004;103:133-138.
4. Hobson D, Curry RL, Beare AS, et al. The Role of Serum Hemagglutination-Inhibiting Antibody in Protection Against Challenge Infection with Influenza A2 and B Viruses. *J Hyg Camb* 1972;70:767-777.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

NDC Number

Package of ten 0.25 mL single-dose, prefilled syringes without needles	33332-519-25
Package of ten 0.5 mL single-dose, prefilled syringes without needles	33332-519-01
Package of one 5 mL multi-dose vial, which contains ten 0.5 mL doses	33332-629-10

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The rubber tip cap and plunger used for the preservative-free, single-dose syringes and the rubber stoppers used for the multi-dose vial contain no latex.

Store refrigerated at 2–8°C (36–46°F). Do not freeze. Protect from light. Do not use Influenza A (H1N1) 2009 Monovalent Vaccine beyond the expiration date printed on the label.

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17 PATIENT COUNSELING INFORMATION

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- Inform the patient that Influenza A (H1N1) 2009 Monovalent Vaccine is an inactivated vaccine that cannot cause influenza but stimulates the immune system to produce antibodies that protect against influenza. The full effect of the vaccine is generally achieved approximately 3 weeks after vaccination.
- Instruct the patient to report any severe or unusual adverse reactions to their healthcare provider.
- Inform vaccine recipients that there are two influenza vaccine formulations for this influenza season, the monovalent vaccine against influenza disease caused by pandemic (H1N1) 2009 influenza virus and seasonal trivalent influenza vaccine.



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517 Manufactured by:

518 **CSL Limited**

519 Parkville, Victoria, 3052, Australia

520 US License No. 1764

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523 Distributed by:

524 **CSL Biotherapies Inc.**

525 King of Prussia, PA 19406 USA

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