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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**AFLURIA, Influenza Virus Vaccine
Suspension for Intramuscular Injection
2011-2012 Formula
Initial U.S. Approval: 2007**

RECENT MAJOR CHANGES

Indications and Usage (1)	11/2011
Dosage and Administration (2)	11/2011
Warnings and Precautions (5)	11/2011

INDICATIONS AND USAGE

- AFLURIA is an inactivated influenza virus 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 (0.5 mL). (2.2)

Children

- 5 years through 8 years of age**
Previously unvaccinated children, or vaccinated for the first time last season with only one dose: two 0.5 mL doses, one on Day 1 followed by another approximately 4 weeks later. (2.1)
Children vaccinated with two doses last season or with at least one dose two or more years ago: one 0.5 mL dose. (2.1)
- 9 years of age and older**
A single 0.5 mL dose. (2.1)

Adults

A single 0.5 mL dose. (2.1)

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 to less than 9 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 were pain (≥60%), redness (≥20%) and swelling (≥10%). The most common systemic adverse reactions were headache, myalgia (≥20%), malaise and fever (≥10%). (6.1)
- In adults 18 through 64 years of age, the most common injection-site adverse reactions were tenderness (≥60%) and pain (≥40%). The most common systemic adverse reactions were headache, malaise, and muscle aches (≥20%). (6.1)
- In adults 65 years of age and older, the most common injection-site adverse reactions were tenderness (≥30%) and pain (≥10%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. at 1-877-888-4231 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: 11/2011

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AFLURIA® is an inactivated influenza virus 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 (0.5 mL).

2.1 Dose and Schedule

Children

Children 5 years through 8 years of age not previously vaccinated with an influenza vaccine, or vaccinated for the first time last season with only one dose: Administer two 0.5 mL doses, one on Day 1 and another approximately 4 weeks later.

Children 5 years through 8 years of age given two doses last season, or at least one dose two or more years ago: Administer a single 0.5 mL dose.

Children 9 years of age and older: Administer a single 0.5 mL dose.

Adults

Administer a single 0.5 mL dose.

2.2 Administration

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.

When using a single-dose 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. Use a separate sterile needle and syringe for each individual patient.

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

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3 DOSAGE FORMS AND STRENGTHS

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

AFLURIA is supplied in two presentations:

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS**5.1 Fever and Febrile Seizures**

Administration of CSL's 2010 Southern Hemisphere influenza vaccine was associated with postmarketing reports of increased rates of fever and febrile seizures in children predominantly below the age of 5 years as compared to previous years; these increased rates were confirmed by postmarketing studies. Febrile events were also observed in children 5 to less than 9 years of age.

5.2 Guillain-Barré Syndrome

Guillain-Barré Syndrome (GBS) has occurred following vaccination with AFLURIA. If 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.

5.3 Preventing and Managing Allergic Reactions

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

5.4 Altered Immunocompetence

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

5.5 Limitations of Vaccine Effectiveness

Vaccination with AFLURIA may not protect all individuals.

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89 **6 ADVERSE REACTIONS**

90

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

95

96 In adults 18 through 64 years of age, the most common injection-site adverse reactions
97 observed in clinical studies with AFLURIA were tenderness ($\geq 60\%$) and pain ($\geq 40\%$). The
98 most common systemic adverse events observed were headache, malaise, and muscle aches
99 ($\geq 20\%$).

100

101 In adults 65 years of age and older, the most common injection-site adverse reactions observed
102 in clinical studies with AFLURIA were tenderness ($\geq 30\%$) and pain ($\geq 10\%$).

103

104 **6.1 Clinical Trials Experience**

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

108

109 ***Children***

110 In clinical studies, AFLURIA has been administered to, and safety information collected for,
111 3,009 children ages 6 months to less than 18 years. Clinical safety data for AFLURIA in
112 children is presented from three clinical studies (Studies 1, 2 and 3). Data from a comparator-
113 controlled trial (Study 1) are presented, followed by pooled data from two open label studies
114 (Studies 2 and 3). Subjects 6 months through 8 years of age received one or two vaccinations
115 as determined by previous vaccination history (for further details on clinical study design, dosing
116 and demographics *see Clinical Studies [14]*).

117

118 Study 1 included 1,468 subjects for safety analysis, ages 6 months to less than 18 years,
119 randomized to receive AFLURIA (735 subjects) or another U.S.-licensed trivalent inactivated
120 influenza vaccine (manufactured by Sanofi Pasteur, Inc.) (733 subjects).

121

122 Study 2 included 1,976 subjects for safety analysis, ages 6 months to less than 18 years. All
123 subjects received AFLURIA.

124

125 Study 3 included 298 subjects for safety analysis, ages 6 months to less than 9 years. All
126 subjects received AFLURIA.

127

128 The safety assessment was similar for the three pediatric studies. Local (injection site) and
129 systemic adverse events were solicited for 7 days post-vaccination (Tables 1 and 2).

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130 Unsolicited adverse events were collected for 30 days post-vaccination. All adverse events are
131 presented regardless of any treatment causality assigned by study investigators.

132

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

135

136 In the comparator-controlled trial (Study 1), the rate of fever after the first dose of AFLURIA
137 in subjects aged 5 to less than 9 years was 16% as compared to 8% in subjects who received
138 the comparator. The rate of fever in subjects aged 9 to less than 18 years following a single
139 dose of AFLURIA was 6% as compared to 4% in subjects who received the comparator. In all
140 three pediatric studies, the rates of fever in subjects aged 5 to less than 9 years who received
141 AFLURIA were lower after dose 2 than dose 1.

142

143 Data in Tables 1 and 2 are presented for children 5 years and older.

144

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145 **Table 1: Proportion of Subjects 5 through 17 Years of Age with Solicited Local or**
 146 **Systemic Adverse Events within 7 Days after Administration of First or Second**
 147 **Dose of AFLURIA, Irrespective of Causality (Study 1)**
 148

Solicited Adverse Event	Age Group			
	Subjects ≥ 5 to < 9 years		Subjects ≥ 9 to < 18 years	
	AFLURIA N=161	Comparator N=166	AFLURIA N=254	Comparator N=250
After the First Dose				
Local				
Pain	63%	60%	66%	60%
Redness	23%	27%	17%	17%
Induration	17%	17%	15%	16%
Systemic				
Myalgia	34%	30%	40%	37%
Malaise	24%	13%	22%	20%
Headache	21%	20%	27%	26%
Any Fever	16%	8%	6%	4%
Fever ≥102.2°F	5%	1%	3%	1%
Nausea/ vomiting	12%	8%	9%	10%
Diarrhea	7%	7%	8%	10%
After the Second Dose				
	AFLURIA N=39	Comparator N=53		
Local				
Pain	36%	38%	-	-
Redness	10%	19%	-	-
Induration	8%	17%	-	-
Systemic				
Diarrhea	13%	6%	-	-
Headache	13%	13%	-	-
Myalgia	13%	17%	-	-
Malaise	5%	8%	-	-
Nausea/ vomiting	3%	8%	-	-
Any Fever	0%	2%	-	-
Fever ≥102.2°F	0%	0%	-	-

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150 **Table 2: Proportion of Subjects 5 through 17 Years of Age with Solicited Local or**
 151 **Systemic Adverse Events Within 7 Days after Administration of AFLURIA,**
 152 **Irrespective of Causality (Studies 2 and 3)**
 153

Solicited Adverse Event	Studies 2 and 3 Subjects ≥ 5 years to < 9 years		Study 2 Subjects ≥ 9 years to < 18 years
	Dose 1 N=595	Dose 2 N=430	Dose 1 N=398
Local			
Pain	61%	55%	68%
Erythema	24%	23%	17%
Swelling	18%	17%	13%
Systemic			
Headache	17%	10%	27%
Malaise or feeling generally unwell*	16%	8%	17%
Any Fever	13%	6%	5%
Fever ≥ 102.2°F	2%	2%	1%
General Muscle Ache (Myalgia)	12%	8%	20%
Nausea/vomiting*	7%	3%	5%
Vomiting/Diarrhea**	5%	6%	-
Diarrhea*	4%	2%	5%
Irritability	3%	3%	-
Loss of appetite	1%	1%	-

154 *These preferred terms were used to describe Solicited Adverse Events in Study 2.
 155 **These preferred terms were used to describe Solicited Adverse Events in Study 3.

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156 In Study 1, unsolicited adverse events that occurred in $\geq 5\%$ of subjects who received
157 AFLURIA in ages 5 years to less than 9 years following the first or second dose included
158 cough (15%) and pyrexia (9%). Unsolicited adverse events that occurred in $\geq 5\%$ of subjects
159 who received AFLURIA in ages 9 years to less than 18 years following the first dose included
160 cough (7%), oropharyngeal pain (7%), headache (7%) and nasal congestion (6%).

161
162 In Studies 2 and 3, unsolicited adverse events that occurred in $\geq 5\%$ subjects ages 5 years to
163 less than 9 years after the first or second dose included the following: upper respiratory tract
164 infection (13%), cough (10%), rhinorrhoea (7%), headache (5%), nasopharyngitis (5%) and
165 pyrexia (5%). Unsolicited adverse events that occurred in $\geq 5\%$ of subjects who received
166 AFLURIA in ages 9 years to less than 18 years following the first dose included upper
167 respiratory tract infection (9%) and headache (8%).

168
169 **Adults**
170 In clinical studies, a single dose of AFLURIA was administered to, and safety information
171 collected for, 11,104 subjects ages 18 to less than 65 years and 836 subjects ages 65 years and
172 older. Clinical safety data for AFLURIA in adults are presented from three clinical studies
173 (Studies 4 through 6). In all adult studies, there were no vaccine-related deaths or vaccine-
174 related serious adverse events reported.

175
176 Study 4 included 1,357 subjects for safety analysis, ages 18 to less than 65 years, randomized
177 to receive AFLURIA (1,089 subjects) or placebo (268 subjects) (see *Clinical Studies [14]*).

178
179 Study 5 included 15,020 subjects for safety analysis, ages 18 to less than 65 years, randomized
180 to receive AFLURIA (10,015 subjects) or placebo (5,005 subjects) (see *Clinical Studies [14]*).

181
182 Study 6 included 1,266 subjects for safety analysis, ages 65 years and older, randomized to
183 receive AFLURIA (630 subjects) or another U.S.-licensed trivalent inactivated influenza
184 vaccine (manufactured by Sanofi Pasteur SA) as an active control (636 subjects). (see *Clinical*
185 *Studies [14]*).

186
187 The safety assessment was identical for the three adult studies. Local (injection-site) and
188 systemic adverse events were solicited for 5 days post-vaccination (Table 3). Unsolicited
189 adverse events were collected for 21 days post-vaccination. All adverse events are presented
190 regardless of any treatment causality assigned by study investigators.

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192 **Table 3: Proportion of Subjects 18 Years of Age and Older with Solicited Local or**
 193 **Systemic Adverse Events within 5 Days after Administration of AFLURIA or**
 194 **Placebo, Irrespective of Causality (Studies 4, 5 and 6)**
 195

Solicited Adverse Event	Study 4 Subjects ≥ 18 to < 65 years		Study 5 Subjects ≥ 18 to < 65 years		Study 6 Subjects ≥ 65 years	
	AFLURIA N = 1089	Placebo N = 268	AFLURIA N=10,015	Placebo N=5005	AFLURIA N=630	Comparator N=636
Local						
Tenderness (Pain on touching)	60%	18%	69%	17%	36%	31%
Pain (without touching)	40%	9%	48%	11%	15%	14%
Redness	16%	8%	4%	<1%	3%	1%
Swelling	9%	1%	4%	<1%	7%	8%
Bruising	5%	1%	1%	<1%	1%	1%
Systemic						
Headache	26%	26%	25%	23%	9%	10%
Malaise	20%	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%	0%	0%

196
 197 In Study 4, headache was the only unsolicited adverse event that occurred in ≥ 5% of subjects
 198 who received AFLURIA or placebo (8% versus 6%, respectively).
 199

200 In Study 5, headache was the only unsolicited adverse event that occurred in ≥ 5% of subjects
 201 who received AFLURIA or placebo (12% versus 11%, respectively).
 202

203 In Study 6, unsolicited adverse events that occurred in ≥ 5% of subjects who received
 204 AFLURIA included headache (8%), nasal congestion (7%), cough (5%), rhinorrhea (5%), and
 205 pharyngolaryngeal pain (5%).
 206

207 **6.2 Postmarketing Experience**

208 Because postmarketing reporting of adverse reactions is voluntary and from a population of
 209 uncertain size, it is not always possible to reliably estimate their frequency or establish a causal
 210 relationship to vaccine exposure. The adverse reactions described have been included in this
 211 section because they: 1) represent reactions that are known to occur following immunizations
 212 generally or influenza immunizations specifically; 2) are potentially serious; or 3) have been
 213 reported frequently. These adverse reactions reflect experience in both children and adults and
 214 include those identified during post-approval use of AFLURIA outside the US since 1985.
 215

216 **Blood and lymphatic system disorders**

217 Transient thrombocytopenia
 218

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219 **Immune system disorders**

220 Allergic reactions including anaphylactic shock and serum sickness

221

222 **Nervous system disorders**

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

225

226 **Vascular disorders**

227 Vasculitis with transient renal involvement

228

229 **Skin and subcutaneous tissue disorders**

230 Pruritus, urticaria, and rash

231

232 **6.3 Adverse Reactions Associated With Influenza Vaccination**

233 Anaphylaxis has been reported after administration of AFLURIA. Egg protein can induce
234 immediate hypersensitivity reactions among persons who have severe egg allergy. Allergic
235 reactions include hives, angioedema, asthma, and systemic anaphylaxis (*see Contraindications*
236 *[4]*).

237

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

242

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

246

247 Microscopic polyangiitis (vasculitis) has been reported temporally associated with influenza
248 vaccination.

249

250

251 **7 DRUG INTERACTIONS**

252

253 **7.1 Concurrent Use With Other Vaccines**

254 There are no data to assess the concomitant administration of AFLURIA with other vaccines.
255 If AFLURIA is to be given at the same time as another injectable vaccine(s), the vaccine(s)
256 should be administered at different injection sites.

257

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

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7.2 Concurrent Use With Immunosuppressive Therapies

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

8 USE IN SPECIFIC POPULATIONS**8.1 Pregnancy**

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

AFLURIA is not approved for use in children less than 5 years of age. In a clinical study in which children received AFLURIA or a US-licensed comparator vaccine (Study 1, *see Clinical Trials Experience, [6.1]*), the incidence of fever in children 6 months to less than 3 years of age following the first and second doses of AFLURIA were 37% and 15%, respectively, as compared to 14% following each dose in the comparator group. Among children 3 years to less than 5 years of age, the incidence of fever following the first and second doses of AFLURIA were 32% and 14%, respectively, as compared to 11% and 16% in the comparator. In an open-label study (Study 2), fever, irritability, loss of appetite, and vomiting/diarrhea occurred more frequently in children 6 months to less than 3 years of age as compared to older children. Across three pediatric studies of AFLURIA (Studies 1, 2, and 3), 1.2% of eligible children (n=1,764) were discontinued from the second vaccination because of severe fever ($\geq 104^{\circ}\text{F}$) within 48 hours of the first vaccination. Across the three pediatric studies, two

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302 children, a 7-month old and a 3-year old, experienced vaccine-related febrile seizures (rate of
303 0.07% across studies), one of which was serious.

304

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

309

310 **8.5 Geriatric Use**

311 In clinical studies, AFLURIA has been administered to, and safety information collected for,
312 836 subjects ages 65 years and older (see *Clinical Trials Experience [6.1]*). After
313 administration of AFLURIA, hemagglutination-inhibiting antibody responses in persons 65
314 years of age and older were lower as compared to younger adult subjects (see *Clinical Studies*
315 *[14]*).

316

317

318 **11 DESCRIPTION**

319

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

328

329 AFLURIA is standardized according to USPHS requirements for the 2011-2012 influenza
330 season and is formulated to contain 45 mcg hemagglutinin (HA) per 0.5 mL dose in the
331 recommended ratio of 15 mcg HA for each of the three influenza strains recommended for the
332 2011-2012 Northern Hemisphere influenza season: A/California/7/2009, NYMC X-181
333 (H1N1), A/Victoria/210/2009, NYMC X-187 (H3N2) (an A/Perth/16/2009-like strain), and
334 B/Brisbane/60/2008.

335

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

339

340 A single 0.5 mL dose of AFLURIA contains sodium chloride (4.1 mg), monobasic sodium
341 phosphate (80 mcg), dibasic sodium phosphate (300 mcg), monobasic potassium phosphate
342 (20 mcg), potassium chloride (20 mcg), and calcium chloride (1.5 mcg). From the
343 manufacturing process, each 0.5 mL dose may also contain residual amounts of sodium

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344 taurodeoxycholate (≤ 10 ppm), ovalbumin (≤ 1 mcg), neomycin sulfate (≤ 3 nanograms [ng]),
345 polymyxin B (≤ 0.5 ng), and beta-propiolactone (≤ 2 ng).

346

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

349

350

351 **12 CLINICAL PHARMACOLOGY**

352

353 **12.1 Mechanism of Action**

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

361

362 Antibody against one influenza virus type or subtype confers limited or no protection against
363 another. Furthermore, antibody to one antigenic variant of influenza virus might not protect
364 against a new antigenic variant of the same type or subtype. Frequent development of
365 antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the
366 reason for the usual change to one or more new strains in each year's influenza vaccine.
367 Therefore, inactivated influenza vaccines are standardized to contain the HA of three strains
368 (i.e., typically two type A and one type B) representing the influenza viruses likely to be
369 circulating in the US during the upcoming winter.

370

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

374

375

376 **13 NONCLINICAL TOXICOLOGY**

377

378 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

379 AFLURIA has not been evaluated for carcinogenic or mutagenic potential.

380

381

382 **14 CLINICAL STUDIES**

383

384 **14.1 Efficacy Against Laboratory-Confirmed Influenza**

385 In Study 5, the efficacy of AFLURIA was demonstrated in a randomized, observer-blind,
386 placebo-controlled study conducted in 15,044 subjects. Healthy subjects 18 to less than 65

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387 years of age were randomized in a 2:1 ratio to receive a single dose of AFLURIA (enrolled
388 subjects: 10,033; evaluable subjects: 9,889) or placebo (enrolled subjects: 5,011; evaluable
389 subjects: 4,960). The mean age of all randomized subjects was 35.5 years. 54.4% were female
390 and 90.2% were White. Laboratory-confirmed influenza was assessed by active and passive
391 surveillance of influenza-like illness (ILI) beginning 2 weeks post-vaccination until the end of
392 the influenza season, approximately 6 months post-vaccination. ILI was defined as at least one
393 respiratory symptom (e.g., cough, sore throat, nasal congestion) and at least one systemic
394 symptom (e.g., oral temperature of 100.0°F or higher, feverishness, chills, body aches). Nasal
395 and throat swabs were collected from subjects who presented with an ILI for laboratory
396 confirmation by viral culture and real-time reverse transcription polymerase chain reaction.
397 Influenza virus strain was further characterized using gene sequencing and pyrosequencing.

398
399 Attack rates and vaccine efficacy, defined as the relative reduction in the influenza infection
400 rate for AFLURIA compared to placebo, were calculated using the per protocol population.
401 Vaccine efficacy against laboratory-confirmed influenza infection due to influenza A or B
402 virus strains contained in the vaccine was 60% with a lower limit of the 95% CI of 41% (Table
403 4).

404
405 **Table 4: Laboratory-confirmed Influenza Infection Rate and Vaccine Efficacy in Adults**
406 **18 to less than 65 Years of Age (Study 5)**
407

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

408 Abbreviations: CI, confidence interval
409 * The Per Protocol Population was identical to the Evaluable Population in this study.
410 ** Vaccine efficacy = 1 minus the ratio of AFLURIA/placebo infection rates. The objective of the study was to demonstrate
411 that the lower limit of the CI for vaccine efficacy was greater than 40%.

412
413 **14.2 Immunogenicity in Children**

414 Study 1 was a randomized, observer-blind, comparator-controlled study to evaluate the
415 immunological non-inferiority of AFLURIA to a U.S.-licensed trivalent inactivated influenza
416 vaccine (manufactured by Sanofi Pasteur, Inc.) in subjects 6 months to less than 18 years of
417 age. Results are presented for children 5 to less than 18 years of age (Table 5). A total of 832
418 subjects (aged 5 to less than 18 years) were enrolled. Subjects were randomized in a 1:1 ratio
419 to receive AFLURIA (enrolled subjects: 417; evaluable subjects: 383) or the comparator
420 vaccine (enrolled subjects: 415; evaluable subjects: 383).

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421
422 Children 6 months to less than 9 years of age with no history of influenza vaccination received 2
423 doses approximately 28 days apart. Children 6 months to less than 9 years of age with a history of
424 influenza vaccination and children 9 years of age and older received 1 dose. Children 6 months to
425 less than 3 years of age received 0.25 mL of AFLURIA or comparator influenza vaccine, and
426 children 3 years of age and older received 0.5 mL of AFLURIA or comparator influenza vaccine.
427 Nearly equal proportions of subjects were male (49.9%) and female (50.1%), and the majority
428 were White (85.0%) or Black (10.3%).

429
430 Immunogenicity assessments were performed prior to vaccination and at 21 days after
431 vaccination. The co-primary endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted
432 for baseline HI titers) and the difference in seroconversion rates for each vaccine strain 21 days
433 after the final vaccination. Pre-specified non-inferiority criteria required that the upper bound
434 of the 2-sided 95% CI of the GMT ratio (Comparator/AFLURIA) did not exceed 1.5 and the
435 upper bound of the 2-sided 95% CI of the seroconversion rate difference (Comparator minus
436 AFLURIA) did not exceed 10.0% for each strain. As shown in Table 5, non-inferiority of
437 AFLURIA to the comparator vaccine was demonstrated in the per protocol population for
438 influenza A subtypes A(H1N1) and A(H3N2), but not for influenza type B. For influenza type
439 B, non-inferiority was demonstrated for HI GMTs, but not for seroconversion rates. Note that
440 the study was powered to assess the pre-specified non-inferiority criteria based on 1400
441 evaluable subjects. Analysis of the 761 subjects aged 5 to less than 18 years reduced the power
442 of the study and widened the confidence intervals. In the pre-specified analysis, AFLURIA
443 was not inferior to the comparator vaccine for all three virus strains. Post hoc analyses of
444 immunogenicity by gender did not demonstrate significant differences between males and
445 females. The study was not sufficiently diverse to assess differences between races or
446 ethnicities.

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449 **Table 5: Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of**
 450 **Non-Inferiority of AFLURIA to a U.S. Licensed Comparator, Subjects 5 to less**
 451 **than 18 Years of Age (Study 1)**
 452

Strain	Post-vaccination GMT		GMT Ratio*	Seroconversion %**		Difference	Met both pre-defined non-inferiority criteria? †
	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

453 Abbreviations: CI, confidence interval; GMT, geometric mean titer.
 454 *GMT ratios are adjusted for baseline HI titers
 455 **Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer $\geq 1:10$ or
 456 an increase in titer from $< 1:10$ to $\geq 1:40$.
 457 † Note that the study was powered to assess the pre-specified non-inferiority criteria based on 1400 evaluable subjects.
 458

459 **14.3 Immunogenicity in Adults and Older Adults**

460 Two randomized, controlled clinical studies of AFLURIA evaluated the immune responses by
 461 measuring HI antibody titers to each virus strain in the vaccine in adults. In these studies, post-
 462 vaccination immunogenicity was evaluated on sera obtained 21 days after administration of a
 463 single dose of AFLURIA.
 464

465 Study 4 was a randomized, double-blinded, placebo-controlled, multicenter study in healthy
 466 subjects ages 18 to less than 65 years. A total of 1,357 subjects were vaccinated (1,089
 467 subjects with AFLURIA and 268 with a placebo). Subjects who received AFLURIA were
 468 vaccinated using either the preservative-free or thimerosal-containing presentation. The
 469 evaluable population consisted of 1,341 subjects (1,077 in the AFLURIA group and 264 in the
 470 placebo group). The mean age of the entire evaluable population receiving AFLURIA was 38
 471 years. 62.5% of subjects were female, 81.3% were White, 12.1% were Black, and 6.2% were
 472 Asian.
 473

474 Serum HI antibody responses to AFLURIA met the pre-specified co-primary endpoint criteria
 475 for all three virus strains (Table 6). Similar responses were observed between genders. The
 476 study was not sufficiently diverse to assess immunogenicity by race or ethnicity.
 477

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478 **Table 6: Serum Antibody Responses in Subjects 18 through 64 Years of Age Receiving**
479 **AFLURIA (Study 4)**
480

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

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

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

486
487 Study 6 was a randomized, observer-blind, comparator-controlled study that enrolled 1,268
488 subjects 65 years of age and older (Table 7). This study compared the immune response
489 following administration of AFLURIA to that following a US-licensed trivalent inactivated
490 influenza vaccine (manufactured by Sanofi Pasteur SA). Subjects were randomized in a 1:1
491 ratio to receive a single vaccination of AFLURIA (enrolled subjects: 631; evaluable subjects:
492 605) or the comparator vaccine (enrolled subjects: 637; evaluable subjects: 610).
493 Immunogenicity assessments were performed prior to vaccination and at 21 days after
494 vaccination. Most of the subjects in the per-protocol immunogenicity population were female
495 (56.7%) and White (97.4%). 2.0% were Black and less than 1.0% were of other races or
496 ethnicities.

497
498 The co-primary endpoints were HI GMT ratios (adjusted for baseline HI titers) and the
499 difference in seroconversion rates for each vaccine strain 21 days after vaccination. Pre-
500 specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the
501 GMT ratio (Comparator/AFLURIA) did not exceed 1.5 and the upper bound of the 2-sided
502 95% CI of the seroconversion rate difference (Comparator minus AFLURIA) did not exceed
503 10.0% for each strain. As shown in Table 7, non-inferiority of AFLURIA to the comparator
504 vaccine was demonstrated in the per protocol population for influenza A subtypes A(H1N1)
505 and A(H3N2), but not for influenza type B. For the B strain, non-inferiority was demonstrated
506 for HI GMTs, but not for seroconversion rates. Post hoc analyses of immunogenicity by

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507 gender did not demonstrate significant differences between males and females. The study was
508 not sufficiently diverse to assess differences between races or ethnicities.
509

510 **Table 7: Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of**
511 **Non-Inferiority of AFLURIA to a U.S. Licensed Comparator, Adults 65 Years of**
512 **Age and Older (Study 6)**

Strain	Post-vaccination GMT		GMT Ratio*	Seroconversion %**		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

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

514 *Post-vaccination GMTs were adjusted for baseline HI titers.

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

517

518 **15 REFERENCES**

519

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528

529

530 **16 HOW SUPPLIED/STORAGE AND HANDLING**

531

How Supplied	NDC Number
Package of ten 0.5 mL single-dose, prefilled syringes without needles	33332-011-01
Package of one 5 mL multi-dose vial, which contains ten 0.5 mL doses	33332-111-10

532

533 Store refrigerated at 2–8°C (36–46°F). Do not freeze. Discard if product has been frozen.
534 Protect from light. Do not use AFLURIA beyond the expiration date printed on the label.

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535 Once the stopper of the multi-dose vial has been pierced, the vial must be discarded within 28
536 days.

537
538

539 17 PATIENT COUNSELING INFORMATION

540 The vaccine recipient or guardian should be:

- 541 • informed of the potential benefits and risks of immunization with AFLURIA.
- 542 • informed that AFLURIA is an inactivated vaccine that cannot cause influenza but
543 stimulates the immune system to produce antibodies that protect against influenza, and
544 that the full effect of the vaccine is generally achieved approximately 3 weeks after
545 vaccination.
- 546 • instructed to report any severe or unusual adverse reactions to their healthcare
547 provider.
- 548 • provided with Vaccine Information Statements which are required by the National
549 Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These
550 materials are available free of charge at the Centers for Disease Control and
551 Prevention (CDC) website (www.cdc.gov/vaccines).
- 552 • instructed that annual revaccination is recommended.

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555

556 Manufactured by:

557 **CSL Limited**
558 Parkville, Victoria, 3052, Australia
559 US License No. 1764

560
561

562 Distributed by:

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564 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

565
566

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