Influenza A (H1N1) 2009 Monovalent Vaccine

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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 (≥ 10%) local (injection-site) adverse reactions were tenderness, pain, redness, and swelling. The most common (≥ 10%) systemic adverse reactions were headache, malaise, and muscle aches. (6)
- In children, the most common (≥ 10%) local (injection-site) adverse reactions were pain, redness, and swelling. The most common (≥ 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

Package insert

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 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.

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 (*see Clinical Studies [14]*).

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Administration

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

2.2 Administration

When using a preservative-free, 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. Between uses, store the vial at 2 –8°C (36–46°F) (*see How Supplied/Storage and Handling [16]*). Once the stopper has been pierced, the vial must be discarded within 28 days.

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

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

Children

Children 6 months through 35 months of age should receive two 0.25 mL doses approximately 4 weeks apart.[2]

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

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

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

Adults

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

3 DOSAGE FORMS AND STRENGTHS

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

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

- 0.25 mL single-dose, pre-filled syringe, no preservative.
- 0.5 mL single-dose, pre-filled syringe, no preservative.
- 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 mcg of mercury.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome (GBS)

If 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.

5.2 Altered Immunocompetence

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

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 Limitations of Vaccine Effectiveness

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

6 ADVERSE REACTIONS

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

6.1 Overall Adverse Reactions

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

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

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

6.2 Safety Experience from Clinical Studies

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.

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

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

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

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

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

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

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

	Study 1 Subjects ≥ 18 to < 65 years		Study 2 Subjects ≥ 65 years
Solicited Adverse event	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%

* In Study 1, 87% of solicited local and systemic adverse events were mild, 12% were moderate, and 1% were severe. In Study 2, 76.5% were mild, 20.5% were moderate, and 3% were severe. In both studies, most solicited local and systemic adverse events lasted no longer than 2 days.

† Values rounded to the nearest whole percent.

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

§ Thimerosal-containing placebo.

‖ Tenderness defined as pain on touching.

¶ Pain defined as spontaneously painful without touch.

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

	Study 1 Subjects ≥ 18 to < 65 years		Study 2 Subjects ≥ 65 years
Adverse Event	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%

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

† Values rounded to the nearest whole percent.

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

§ Thimerosal-containing placebo.

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)

	Subjects ≥ 6 months to < 3 years (n = 151)[‡]		Subjects ≥ 3 years to < 9 years (n = 147)[§]	
Solicited Adverse Event	**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.

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

	Subjects ≥ 6 months to < 3 years (n = 151)†		Subjects ≥ 3 to < 9 years (n = 147)‡	
Adverse Event	**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.

6.3 Postmarketing Experience

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

Blood and lymphatic system disorders
Transient thrombocytopenia

Immune system disorders
Allergic reactions including anaphylactic shock and serum sickness

Nervous system disorders
Neuralgia, paresthesia, and convulsions; encephalopathy, neuritis or neuropathy, transverse myelitis, and GBS

Vascular disorders
Vasculitis with transient renal involvement

Skin and subcutaneous tissue disorders
Pruritus, urticaria, and rash

6.4 Other Adverse Reactions Associated With Influenza Vaccination

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

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

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

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

7 DRUG INTERACTIONS

7.1 Concurrent Use With Other Vaccines

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

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

7.2 Concurrent Use With Immunosuppressive Therapies

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

8 USE IN SPECIFIC POPULATIONS

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

8.1 Pregnancy

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

11 DESCRIPTION

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

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

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

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

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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

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

14.1 Immunogenicity in the Adult and Geriatric Populations

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

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

Black, and 6% Asian.

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

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

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

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)

* 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. Lower bound of 95% CI for seroconversion should be > 40% for the study population.

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

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

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

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

Table 6: Study 2 – Serum HI Antibody Responses in Subjects ≥ 65 Years Receiving AFLURIA

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)

* 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. Lower bound of 95% CI for seroconversion should be > 30% for the study population.

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

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

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

14.2 Immunogenicity in a Pediatric Population

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

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

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

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)

* 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.

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

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.

17 PATIENT COUNSELING INFORMATION

- 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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