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®.


INDICATIONS AND USAGE

• AFLURIA® is an inactivated influenza virus vaccine indicated for active immunization of persons ages 18 years and older against influenza disease caused by influenza virus subtypes A and type B present in the vaccine. (1)

• This indication is based on the immune response elicited by AFLURIA®; there have been no controlled clinical studies demonstrating a decrease in influenza disease after vaccination with AFLURIA®. (14)

DOSAGE AND ADMINISTRATION

• A single 0.5 mL dose for intramuscular injection. (2)

DOSAGE FORMS AND STRENGTHS

AFLURIA®, a sterile suspension for intramuscular injection, is supplied in two presentations:

• 0.5 mL preservative-free, single-dose, pre-filled syringe. (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)

Each 0.5 mL dose contains 15 mcg of influenza virus hemagglutinin (HA) from each of the three strains: A/Solomon Islands/3/2006 (H1N1), A/Wisconsin /67/2005 (H3N2), and B/Malaysia/2506/2004. (3, 11)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

• 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. (5.1)

• Immunocompromised persons may have a diminished immune response to AFLURIA®. (5.2)

ADVERSE REACTIONS

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)

To report SUSPECTED ADVERSE REACTIONS, contact CSL Biotherapies at 1-888-435-8633 or VAERS at 1-800-822-7967 and 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 AFLURIA®. (7.2)

USE IN SPECIFIC POPULATIONS

• Safety and effectiveness of AFLURIA® have not been established in pregnant women or nursing mothers and in the pediatric population. (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.

Issued: 09/2007

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*Sections or subsections omitted from the full prescribing information are not listed.
1 INDICATIONS AND USAGE
AFLURIA® is an inactivated influenza virus vaccine indicated for active immunization of persons ages 18 years and older against influenza disease caused by influenza virus subtypes A and type B present in the vaccine.

This indication is based on the immune response elicited by AFLURIA®, 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
AFLURIA® 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 the 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. AFLURIA® should be administered as a single 0.5 mL intramuscular injection, preferably in the deltoid muscle of the upper arm.

3 DOSAGE FORMS AND STRENGTHS
AFLURIA® is a sterile suspension for intramuscular injection. Each 0.5 mL dose contains 15 micrograms (mcg) of influenza virus hemagglutinin (HA) from each of the three influenza virus strains included in the vaccine (see Description [11]). AFLURIA® is supplied in two presentations:
- 0.5 mL preservative-free, single-dose, pre-filled syringe.
- 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
AFLURIA® is contraindicated in individuals with known hypersensitivity to eggs or chicken protein, neomycin, or polymyxin, or in anyone who has had a life-threatening reaction to previous influenza vaccination.

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 AFLURIA® should be based on careful consideration of the potential benefits and risks.

5.2 Altered Immunocompetence
If AFLURIA® 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 AFLURIA® may not protect all individuals.

6 ADVERSE REACTIONS
6.1 Overall Adverse Reactions
Serious allergic reactions, including anaphylactic shock, have been observed during postmarketing surveillance in individuals receiving AFLURIA®.

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.

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 safety data for AFLURIA® have been obtained in two clinical studies (see Clinical Studies [14]).

A US study (Study 1) included 1,357 subjects for safety analysis, ages 18 to less than 65 years, randomized to receive AFLURIA®, Influenza Virus Vaccine Suspension for Intramuscular Injection, (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.

The safety assessment was identical for the two studies. Local (injection-site) and systemic adverse reactions were solicited by completion of a symptom diary card for 5 days post-vaccination (Table 1). Unsolicited local and systemic 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.

Table 1: Proportion of Subjects With Solicited Local or Systemic Adverse Events* Within 5 Days After Administration of AFLURIA® or Placebo, Irrespective of Causality†

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjects ≥ 18 to &lt; 65 Years</td>
<td>Subjects ≥ 65 Years</td>
</tr>
<tr>
<td>Local</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenderness†</td>
<td>60%</td>
<td>18%</td>
</tr>
<tr>
<td>Pain*</td>
<td>40%</td>
<td>9%</td>
</tr>
<tr>
<td>Redness</td>
<td>16%</td>
<td>8%</td>
</tr>
<tr>
<td>Swelling</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>Bruising</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Systemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>Malaise</td>
<td>20%</td>
<td>19%</td>
</tr>
<tr>
<td>Muscle aches</td>
<td>13%</td>
<td>9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>Chills†</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Shivering</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever ≥ 37.7°C† (99.8°F)</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

* 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, 20.3% 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.
¶ 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†

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjects ≥ 18 to &lt; 65 years</td>
<td>Subjects ≥ 65 years</td>
</tr>
<tr>
<td>Headache</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Cough</td>
<td>1%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Pharyngolaryngeal Pain</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Reactionsogeny Event</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>2%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Pulmonary Infection</td>
<td>0.4%</td>
<td>1%</td>
</tr>
<tr>
<td>Lower Respiratory Tract Infection</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

* 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 2% were severe. In both studies, most unsolicited adverse events lasted no longer than 5 days.
† Values greater than 0.5% 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.

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. The following adverse reactions also include those identified during postapproval use of AFLURIA®, Influenza Virus Vaccine Suspension for Intramuscular Injection, outside the US since 1985.

6.4 Other Adverse Reactions Associated With Influenza Vaccination
Anaphylaxis has been reported after administration of AFLURIA®. Although AFLURIA® contains only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Allergic reactions include hives, angioedema, allergic asthma, and systemic anaphylaxis (see Containments [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.

7.1 Concurrent Use With Other Vaccines
There are no data to assess the concomitant administration of AFLURIA® with other vaccines. If AFLURIA® is to be given at the same time as another injectable vaccine(s), the vaccine(s) should be administered at different injection sites. AFLURIA® 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 AFLURIA® may be diminished in individuals receiving corticosteroid or immunosuppressive therapies.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C: Animal reproduction studies have not been conducted with AFLURIA®. It is also not known whether AFLURIA® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. AFLURIA® should be given to a pregnant woman only if clearly needed.

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
Safety and effectiveness in the pediatric population have not been established.

8.5 Geriatric Use
In four clinical studies, 343 subjects ages 65 years and older received AFLURIA®. Hemagglutination-inhibiting (HI) 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
AFLURIA®, Influenza Virus 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. AFLURIA® 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.

AFLURIA®, Influenza Virus Vaccine Suspension for Intramuscular Injection, is standardized according to USPHS requirements for the 2007-2008 influenza season and is formulated to contain 45 mcg HA per 0.5 mL dose in the recommended ratio of 15 mcg HA for each of the three influenza strains recommended for the 2007-2008 Northern Hemisphere influenza season: A/H1N1 (A/Solomon Islands/3/2006), A/H3N2 (A/Wisconsin/67/2005), and influenza B (B/Malaysia/2506/2004).

The single-dose formulation is preservative-free; thimerosal, a mercury derivative, is not used in the manufacturing process for this formulation. The multi-dose formulation contains thimerosal, added as a preservative; each 0.5 mL dose contains 24.5 mcg of mercury.

A single 0.5 mL dose of AFLURIA® 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). From the manufacturing process, each dose may also contain residual amounts of sodium taurodeoxycholate (≤10 ppm), ovalbumin (≤0.10 mcg), neomycin sulfate (≤0.2 picograms [pg]), polymyxin B (≤0.03 pg), and beta-propiolactone (<25 nanograms).

The rubber tip cap and plungers 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 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. 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. Therefore, inactivated influenza vaccines are standardized to contain the HA of three strains (i.e., typically two type A and one type B) representing the influenza viruses likely to be circulating in the US during the upcoming winter. Annual revaccination with the current vaccine is recommended because immunity declines during the year after vaccination and circulating strains of influenza virus change from year to year.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
AFLURIA® has not been evaluated for carcinogenic or mutagenic potential or for impairment of fertility.

14 CLINICAL STUDIES
Three randomized, controlled clinical studies of AFLURIA® have evaluated the immune responses (specifically, 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...
subjects ages 65 years and older. This study compared AFLURIA® to 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.

The post-hoc 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.

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING
AFLURIA®, Influenza Virus Vaccine Suspension for Intramuscular Injection, is supplied as a 0.5 mL preservative-free, single-dose pre-filled syringe (packaged without needles) and as a 5 mL multi-dose vial containing ten 0.5 mL doses, with thimerosal, a mercury derivative, added as a preservative; each 0.5 mL dose contains 24.5 mcg of mercury.

Product Description
Package of ten 0.5 mL preservative-free, prefilled syringes
5 mL multi-dose vial

Store refrigerated at 2−8°C (36−46°F). Do not freeze. Protect from light. Do not use AFLURIA® beyond the expiration date printed on the label.

17 PATIENT COUNSELING INFORMATION
• Inform the patient that AFLURIA® 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. Annual revaccination is recommended.
• Instruct the patient to report any severe or unusual adverse reactions to their healthcare provider.

Manufactured by:
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US License No. 1764

Distributed by:
CSL Biotherapies Inc.
King of Prussia, PA 19406 USA

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