Package insert

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

AFLURIA, Influenza Vaccine
Suspension for Intramuscular Injection
2016-2017 Formula
Initial U.S. Approval: 2007

----------INDICATIONS AND USAGE----------

- AFLURIA is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B present in the vaccine. (1)
- AFLURIA is approved for use in persons 5 years of age and older. (1)

----------DOSAGE AND ADMINISTRATION----------

For intramuscular (IM) injection only, by needle and syringe (5 years of age and older) or by PharmaJet® Stratis® Needle-Free Injection System (18 through 64 years of age). A single dose is 0.5 mL. (2)

Age	Schedule
5 years through 8 years	One dose or two doses at least 1 month apart[a]
9 years and older	One dose

[a]1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines. (2)

----------DOSAGE FORMS AND STRENGTHS----------

AFLURIA is a suspension for injection supplied in two presentations:

- 0.5 mL pre-filled syringe (single dose) (3, 11)
- 5 mL multi-dose vial (ten 0.5 mL doses) (3, 11)

----------CONTRAINDICATIONS----------

- Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine including egg protein, or to a previous dose of any influenza vaccine. (4, 11)

----------WARNINGS AND PRECAUTIONS----------

- Administration of CSL's 2010 Southern Hemisphere influenza vaccine was associated with increased rates of fever and febrile seizures in children predominantly below the age of 5 years as compared to previous years. Febrile events were also observed in children 5 through 8 years of age. (5.1)
- If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give AFLURIA should be based on careful consideration of the potential benefits and risks. (5.2)
- Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. (5.3)
- Immunocompromised persons may have a diminished immune response to AFLURIA. (5.4)

----------ADVERSE REACTIONS----------

- In children 5 through 17 years of age, the most common injection-site adverse reactions when administered by needle and syringe were pain (≥60%), redness (≥20%) and swelling (≥10%). The most common systemic adverse events were headache, myalgia (≥20%), irritability, malaise and fever (≥10%). (6.1)
- In adults 18 through 64 years of age, the most common injection-site adverse reactions when administered by needle and syringe were tenderness (≥60%), pain (≥40%), swelling (≥20%), and redness, itching (≥10%). The most common systemic adverse events were muscle aches (≥30%) and headache, malaise (≥20%). (6.1)
- In adults 18 through 64 years of age, the most common injection-site adverse reactions when administered by the PharmaJet Stratis Needle-Free Injection System up to 7 days post-vaccination were tenderness (≥80%), swelling, pain, redness (≥60%), itching (≥20%) and bruising (≥10%). The most common systemic adverse events within this period were myalgia, malaise (≥30%), and headache (≥20%). (6.1)
- In adults 65 years of age and older, when administered by needle and syringe the most common injection-site adverse reactions were tenderness (≥30%) and pain (≥10%). No systemic adverse events occurred in ≥10% of subjects in this age group (6.1)

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

----------USE IN SPECIFIC POPULATIONS----------

- 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)
- Antibody responses were lower in geriatric subjects than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2016

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

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

2 DOSAGE AND ADMINISTRATION

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

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

Table 1: AFLURIA Schedule

Age	Schedule
5 years through 8 years	One dose or two doses at least 1 month apart [a]
9 years and older	One dose

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

Shake thoroughly and inspect visually before use. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever suspension and container permit. If either of these conditions exists, the vaccine should not be administered.

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

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

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

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

- PharmaJet Stratis Needle-Free Injection System: For instructions on withdrawal of a 0.5 mL dose and use of the PharmaJet Stratis Needle-Free Injection System, refer to the Instructions For Use for the PharmaJet Stratis Needle-Free Injection System.

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

Between uses, return the multi-dose vial to the recommended storage conditions between 2-8°C (36–46°F). **Do not freeze.** Discard if the vaccine has been frozen.

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 through 8 years of age.

5.2 Guillain-Barré Syndrome

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.

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.

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.

6 ADVERSE REACTIONS

In children 5 through 17 years of age, the most common injection-site reactions observed in clinical studies with AFLURIA administered by needle and syringe were pain (≥60%), redness (≥20%) and swelling (≥10%). The most common systemic adverse events were headache, myalgia (≥20%), irritability, malaise and fever (≥10%).

In adults 18 through 64 years of age, the most common injection-site adverse reactions observed in clinical studies with AFLURIA administered by needle and syringe were tenderness (≥60%), pain (≥40%), swelling (≥20%), redness and itching (≥10%). The most common systemic adverse events observed were muscle aches (≥30%), headache and malaise (≥20%).

In adults 18 through 64 years of age, using the PharmaJet Stratis Needle-Free Injection System, the most common injection-site adverse reactions observed in a clinical study with AFLURIA up to 7 days post-vaccination were tenderness (≥80%), swelling, pain, redness (≥60%), itching (≥20%) and bruising (≥10%). The most common systemic adverse events within this period were myalgia, malaise (≥30%) and headache (≥20%).

In adults 65 years of age and older, the most common injection-site adverse reactions observed in clinical studies with AFLURIA administered by needle and syringe were tenderness (≥30%) and pain (≥10%). No systemic adverse reactions occurred in ≥10% of subjects in this age group.

6.1 Clinical Trials Experience

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

Children

In clinical studies, AFLURIA has been administered to, and safety information collected for, 3,009 children ages 6 months through 17 years. The exposure in children includes 1,601 aged 6 months to less than 5 years, 756 children ages 5 years to less than 9 years and 652 children ages 9 years through 17 years. Clinical safety data for AFLURIA in children are presented from three clinical studies (Studies 1, 2 and 3). Data from a comparator-controlled trial (Study 1) are presented, followed by pooled data from two open label studies (Studies 2 and 3). Subjects 6 months through 8 years of age received one or two vaccinations, administered by needle and syringe, as determined by previous vaccination history (for further details on clinical study design, dosing and demographics *see Clinical Studies [14]*).

Study 1 included 1,468 subjects for safety analysis, ages 6 months through 17 years, randomized to receive AFLURIA (735 subjects) or another U.S.-licensed trivalent inactivated influenza vaccine (manufactured by Sanofi Pasteur, Inc.) (733 subjects).

Study 2 included 1,976 subjects for safety analysis, ages 6 months through 17 years. All subjects received AFLURIA.

Study 3 included 298 subjects for safety analysis, ages 6 months through 8 years. All subjects received AFLURIA.

The safety assessment was similar for the three pediatric studies. Local (injection site) adverse reactions and systemic adverse events were solicited for 7 days post-vaccination (Tables 2 and 3). Unsolicited adverse events were collected for 30 days post-vaccination. All adverse events are presented regardless of any treatment causality assigned by study investigators.

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

In this section, safety data from the pediatric studies are limited to children 5 years of age and older. AFLURIA is not approved for use in children less than 5 years of age. See Warnings and Precautions [5.1] and Use in Specific Populations [8.4] for risks of AFLURIA in children less than 5 years of age.

In the comparator-controlled trial (Study 1), the rate of fever after the first dose of AFLURIA in subjects aged 5 through 8 years was 16% as compared to 8% in subjects who received the comparator. The rate of fever in subjects aged 9 through 17 years following a single dose of

AFLURIA was 6% as compared to 4% in subjects who received the comparator. In all three pediatric studies, the rates of fever in subjects aged 5 through 8 years who received AFLURIA were lower after dose 2 than dose 1.

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

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

	Percentage [a] of Subjects in each Age Group Reporting Event			
	Subjects 5 through 8 years		Subjects 9 through 17 years	
	AFLURIA N=161 [b]	Comparator N=165 [b]	AFLURIA N=254 [b]	Comparator N=250 [b]
After the First Dose				
Local Adverse Reactions				
Pain	63	60	66	60
Redness	23	27	17	17
Induration	17	17	15	16
Systemic Adverse Events				
Myalgia	34	30	40	37
Malaise	24	13	22	20
Headache	21	19	27	26
Any Fever Fever ≥102.2°F	16 5	8 1	6 3	4 1
Nausea/Vomiting	12	8	9	10
Diarrhea	7	7	8	10
	AFLURIA N=39 [b]	Comparator N=53 [b]		
After the Second Dose				
Local Adverse Reactions				
Pain	36	38	-	-
Redness	10	19	-	-
Induration	8	17	-	-
Systemic Adverse Events				
Diarrhea	13	6	-	-
Headache	13	13	-	-
Myalgia	13	17	-	-
Malaise	5	8	-	-
Nausea/Vomiting	3	8	-	-
Any Fever Fever ≥102.2°F	0 0	2 0	- -	- -

[a] Proportion of subjects reporting each solicited local adverse reaction or systemic adverse event by treatment group based on the number of subjects contributing at least one data value for an individual sign/symptom (individual event denominators).
[b] N = number of subjects in the Safety Population for each treatment group.

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

	Percentage [a] of Subjects in each Age Group Reporting Event		
	Studies 2 and 3 Subjects 5 through 8 years		Study 2 Subjects 9 through 17 years
	Dose 1 N=82-595 [b]	Dose 2 N=82-426 [b]	Dose 1 N=397 [b]
Local Adverse Reactions			
Pain	61	56	68
Erythema	24	23	17
Swelling	17	17	13
Systemic Adverse Events			
Irritability [d]	18	16	-
Headache	16	10	27
Malaise or feeling generally unwell [c]	16	8	17
Any Fever Fever ≥ 102.2°F	13 3	6 2	5 1
General Muscle Ache (Myalgia)	12	8	20
Nausea/Vomiting [c]	7	3	5
Vomiting/Diarrhea [d]	5	6	-
Loss of appetite [d]	5	4	-
Diarrhea [c]	4	2	5

[a] Proportion of subjects reporting each solicited local adverse reaction or systemic adverse event by treatment group based on the number of subjects contributing at least one data value for an individual sign/symptom (individual event denominators).
[b] N = number of subjects in the Safety Population for each treatment group. Denominators for Dose 1 were: N=82 for Vomiting/Diarrhea, Irritability, Loss of appetite, N=513 for Malaise, Diarrhea, Nausea/Vomiting and N=593-595 for all other parameters. Denominators for Dose 2 were: N=82 for Vomiting/Diarrhea, Irritability, Loss of appetite, N=344 for Malaise, Diarrhea and Nausea/Vomiting and N=421-426 for all other parameters.
[c] These preferred terms were used to describe Solicited Adverse Events in Study 2.
[d] These preferred terms were used to describe Solicited Adverse Events in Study 3.

In Study 1, unsolicited adverse events that occurred in ≥ 5% of subjects who received AFLURIA in ages 5 years through 8 years following the first or second dose included cough (15%) and pyrexia (9%). Unsolicited adverse events that occurred in ≥ 5% of subjects who received AFLURIA in ages 9 years through 17 years following the first dose included cough (7%), oropharyngeal pain (7%), headache (7%) and nasal congestion (6%).

In Studies 2 and 3, unsolicited adverse events that occurred in ≥ 5% of subjects ages 5 years through 8 years after the first or second dose included the following: upper respiratory tract

infection (13%), cough (10%), rhinorrhea (7%), headache (5%), nasopharyngitis (5%) and pyrexia (5%). Unsolicited adverse events that occurred in ≥ 5% of subjects who received AFLURIA in ages 9 years through 17 years following the first dose included upper respiratory tract infection (9%) and headache (8%).

Adults

In clinical studies comparing AFLURIA to placebo or a comparator trivalent inactivated influenza vaccine, a single dose of AFLURIA was administered to, and safety information collected for, 11,104 subjects ages 18 through 64 years and 836 subjects ages 65 years and older. Clinical safety data for AFLURIA in adults are presented from three clinical studies (Studies 4 through 6) conducted in the US and one clinical study (Study 7) conducted in the UK

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

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

Study 6 included 1,266 subjects for safety analysis, ages 65 years and older, randomized to receive AFLURIA (630 subjects) or another U.S.-licensed trivalent inactivated influenza vaccine (manufactured by Sanofi Pasteur Inc.) as an active comparator (636 subjects) (*see Clinical Studies [14]).* Study 7 included 275 subjects for safety analysis, ages 65 years and older, randomized to receive AFLURIA (206 subjects) or a UK-licensed trivalent inactivated influenza vaccine (manufactured by GSK) as an active comparator (69 subjects).

The safety assessment was identical for the four adult studies. Local (injection-site) adverse reactions and systemic adverse events were solicited for 5 days post-vaccination (Table 4, studies 4 through 6). Unsolicited adverse events were collected for 21 days post-vaccination. All adverse events are presented regardless of any treatment causality assigned by study investigators.

Among adult studies, there were no vaccine-related deaths or vaccine-related serious adverse events reported.

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

	Percentage [a] of Subjects in each Age Group Reporting Event					
	Study 4 Subjects 18 through 64 years		Study 5 Subjects 18 through 64 years		Study 6 Subjects ≥ 65 years	
	AFLURIA N=1087-1088 [b]	Placebo N=266 [b]	AFLURIA N=10,015 [b]	Placebo N=5005 [b]	AFLURIA N=630 [b]	Comparator N=636 [b]
Local Adverse Reactions						
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 Adverse Events						
Headache	26	26	25	23	9	11
Malaise	19	19	29	26	7	6
Muscle aches	13	9	21	12	9	8
Nausea	6	9	7	6	2	1
Chills/Shivering	3	2	5	4	2	2
Fever	1	1	3	2	<1	1

[a] Proportion of subjects reporting each solicited local adverse reaction or systemic adverse event by treatment group based on the number of subjects contributing at least one data value for an individual sign/symptom (individual event denominators).
[b] N = number of subjects in the Safety Population for each treatment group.

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

In Study 5, unsolicited adverse events that occurred in ≥ 5% of subjects who received AFLURIA or placebo included headache (AFLURIA 12%, placebo 11%) and oropharyngeal pain (AFLURIA 5%, placebo 5%).

In Study 6, headache was the only unsolicited adverse event that occurred in ≥ 5% of subjects who received AFLURIA (5%).

Studies 1 to 7 were all conducted when AFLURIA was administered by needle and syringe.

Additionally, safety information has been collected in a clinical study of AFLURIA administered using the PharmaJet Stratis Needle-Free Injection System (Study 8). Study 8 included 1,247 subjects for safety analysis, ages 18 through 64 years, randomized to receive AFLURIA by either the PharmaJet Stratis Needle-Free Injection System (624 subjects) or

needle and syringe (623 subjects). No deaths or vaccine-related serious adverse events were reported in Study 8. Local (injection-site) adverse reactions and systemic adverse events were solicited for 7 days post-vaccination (Table 5).

Table 5: Proportion of Subjects 18 through 64 Years of Age with Solicited Local Adverse Reactions or Systemic Adverse Events within 7 Days after Administration of AFLURIA by PharmaJet Stratis Needle-Free Injection System or Needle and Syringe Irrespective of Causality (Study 8).

	Percentage [a] of Subjects Reporting Event	
	Study 8 Subjects 18 through 64 years	
	AFLURIA	
	PharmaJet Stratis Needle-Free Injection System N=540-616 [b]	Needle and Syringe N=599-606 [b]
Local Adverse Reactions		
Tenderness	89	78
Swelling	65	20
Pain	64	49
Redness	60	19
Itching [c]	28	10
Bruising	18	5
Systemic Adverse Events		
Myalgia	36	36
Malaise	31	28
Headache	25	22
Chills	7	7
Nausea	7	7
Vomiting	1	2
Fever	0	0

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

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

[c] A total of 155 subjects (approximately randomly distributed between PharmaJet Stratis Needle-Free Injection System and needle and syringe groups) received Diary Cards without itching listed as a solicited symptom.

In Study 8, no unsolicited adverse events occurred in $\geq 5\%$ of subjects who received AFLURIA administered via PharmaJet Stratis Needle-Free Injection System up to 28 days post-vaccination.

6.2 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
Thrombocytopenia

Immune system disorders
Allergic or immediate hypersensitivity reactions including anaphylactic shock and serum sickness

Nervous system disorders
Neuralgia, paresthesia, convulsions (including febrile seizures), encephalomyelitis, encephalopathy, neuritis or neuropathy, transverse myelitis, and GBS

Vascular disorders
Vasculitis which may be associated with transient renal involvement

Skin and subcutaneous tissue disorders
Pruritus, urticaria, and rash

General disorders and administration site conditions
Cellulitis and large injection site swelling
Influenza-like illness

6.3 Adverse Reactions Associated With Influenza Vaccination

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

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 AFLURIA with other vaccines. If AFLURIA is given at the same time as another injectable vaccine(s), the vaccine(s) should be administered in separate syringes and a separate arm should be used.

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

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.

Pregnancy exposure and safety surveillance

An exposure and surveillance study which monitors pregnancy outcomes in women exposed to AFLURIA during pregnancy has been established. Women who are vaccinated with AFLURIA during pregnancy should be encouraged to contact the pregnancy study center by calling 1-877-311-8972 or visit the website http://www.pregnancystudies.org.

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 through 35 months 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 through 4 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 through 35 months 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 ($\geq 104^{o}$F) within 48 hours of the first vaccination. Across the three pediatric studies, two children, a 7-month old and a 3-year old, experienced vaccine-related febrile seizures (rate of 0.07% across studies), one of which was serious.

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

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

8.5 Geriatric Use

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

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

11 DESCRIPTION

AFLURIA, Influenza 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 continuous flow zonal centrifugation. 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 is standardized according to USPHS requirements for the 2016-2017 influenza season and is formulated to contain 45 mcg hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 mcg HA for each of the three influenza strains recommended for the 2016-2017 Northern Hemisphere influenza season: A/California/7/2009 (H1N1), NYMC X-181, A/Hong Kong/4801/2014 (H3N2), NYMC X-263B, and B/Brisbane/60/2008.

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 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 0.5 mL dose may also contain residual amounts of sodium taurodeoxycholate (≤ 10 ppm), ovalbumin (< 1 mcg), sucrose (< 10 mcg), neomycin sulfate (≤ 3 nanograms [ng]), polymyxin B (≤ 0.5 ng), and beta-propiolactone (≤ 2 ng).

The rubber tip cap and plunger used for the preservative-free, single-dose syringes and the rubber stoppers used for the multi-dose vial were not made with natural rubber 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 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.[2,3]

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.[1]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

14.1 Efficacy Against Laboratory-Confirmed Influenza

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

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

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

	Subjects [a]	Laboratory-Confirmed Influenza Cases	Influenza Infection Rate	Vaccine Efficacy [b]	
	N	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		

Abbreviations: CI, confidence interval

[a] The Per Protocol Population was identical to the Evaluable Population in this study.

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

14.2 Immunogenicity in Children – Administration via Needle and Syringe

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

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

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

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

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

	Post-vaccination GMT		GMT Ratio [a]	Seroconversion % [b]		Difference	Met both pre-defined non-inferiority criteria? [c]
Strain	Comparator N=381	AFLURIA N=380	Comparator over AFLURIA (95% CI)	Comparator N=381	AFLURIA N=380	Comparator minus AFLURIA (95% CI)	
A(H1N1)	526.2	507.4	1.03 (0.88, 1.21)	62.7	62.6	0.1 (-6.8, 7.0)	Yes
A(H3N2)	1060.0	961.3	1.07 (0.94, 1.23)	72.2	69.7	2.4 (-4.0, 8.9)	Yes
B	123.3	110.1	1.10 (0.94, 1.29)	75.1	70.0	5.1 (-1.3, 11.4)	No

Abbreviations: CI, confidence interval; GMT, geometric mean titer.
[a] GMT ratios are adjusted for baseline HI titers
[b] 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.
[c] Note that the study was powered to assess the pre-specified non-inferiority criteria based on 1400 evaluable subjects.

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

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

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

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

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

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

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

[a] 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.

[b] 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.

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

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

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

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

	Post-vaccination GMT		GMT Ratio [a]	Seroconversion % [b]		Difference	Met both pre-defined non-inferiority criteria?
Strain	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

Abbreviations: CI, confidence interval; GMT, geometric mean titer.
[a] Post-vaccination GMTs were adjusted for baseline HI titers.
[b] 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.

14.4 Immunogenicity in Adults – Administration via PharmaJet Stratis Needle-Free Injection System

Study 8 was a randomized, comparator-controlled non-inferiority study that enrolled 1,250 subjects 18 through 64 years of age. This study compared the immune response following administration of AFLURIA when delivered IM using either the PharmaJet Stratis Needle-Free Injection System or needle and syringe. Immunogenicity assessments were performed prior to vaccination and at 28 days after vaccination in the immunogenicity population (1,130 subjects, 562 PharmaJet Stratis Needle-Free Injection System group, 568 needle and syringe group). The co-primary endpoints were HI GMT ratios for each vaccine strain and the absolute difference in seroconversion rates for each vaccine strain 28 days after vaccination. As shown in Table 10, non-inferiority of administration of AFLURIA by the PharmaJet Stratis Needle-Free Injection System compared to administration of AFLURIA by needle and syringe was demonstrated in the immunogenicity population for all strains. Post-hoc analyses of

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

Table 10: Baseline and Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of Non-Inferiority of AFLURIA Administered by PharmaJet Stratis Needle-Free Injection System or Needle and Syringe, Adults 18 through 64 Years of Age (Study 8)

	Baseline GMT		Post-vaccination GMT		GMT Ratio [a]	Seroconversion % [b]		Difference	
Strain	Needle and Syringe N=568	PharmaJet Stratis Needle-Free Injection System N=562	Needle and Syringe N=568	PharmaJet Stratis Needle-Free Injection System N=562	Needle and Syringe over PharmaJet Stratis Needle-Free Injection System (95% CI)	Needle and Syringe N=568	PharmaJet Stratis Needle-Free Injection System N=562	Needle and Syringe minus PharmaJet Stratis Needle-Free Injection System (95% CI)	Met both pre-defined non-inferiority criteria? [c]
A(H1N1)	79.5	83.7	280.6	282.9	0.99 (0.88, 1.12)	38.4	37.5	0.8 (-4.8, 6.5)	Yes
A(H3N2)	75.4	68.1	265.9	247.3	1.08 (0.96, 1.21)	45.1	43.8	1.3 (-4.5, 7.1)	Yes
B	12.6	13.5	39.7	42.5	0.94 (0.83, 1.06)	35.2	34.9	0.3 (-5.2, 5.9)	Yes

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

[a] GMT ratio is defined as post-vaccination GMT for Needle and Syringe/PharmaJet Stratis Needle-Free Injection System

[b] 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.

[c] Non-inferiority (NI) criteria for the GMT ratio: upper bound of 2-sided 95% CI on the ratio of Needle and Syringe/PharmaJet Stratis Needle-Free Injection System. GMT should not exceed 1.5. NI criteria for the seroconversion rate (SCR) difference: upper bound of 2-sided 95% CI on the difference between SCR Needle and Syringe – SCR PharmaJet Stratis Needle-Free Injection System should not exceed 10%.

15 REFERENCES

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3. 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

16.1 How Supplied

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

Presentation	Carton NDC Number	Components
Pre-Filled Syringe	33332-016-01	• Ten 0.5 mL single-dose syringes fitted with a Luer-Lok™ attachment without needles [NDC 33332-016-02]
Multi-Dose Vial	33332-116-10	• One 5 mL vial, which contains ten 0.5 mL doses [NDC 33332-116-11]

16.2 Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

- Inform the vaccine recipient or guardian of the potential benefits and risks of immunization with AFLURIA.
- Inform the vaccine recipient or guardian that AFLURIA is an inactivated vaccine that cannot cause influenza but stimulates the immune system to produce antibodies that protect against influenza, and that the full effect of the vaccine is generally achieved approximately 3 weeks after vaccination.
- Instruct the vaccine recipient or guardian to report any severe or unusual adverse reactions to their healthcare provider.
- Encourage women who receive AFLURIA while pregnant to participate in the exposure and surveillance study. Pregnant women can contact the pregnancy study center by calling 1-877-311-8972 or visiting the website http://www.pregnancystudies.org.
- Provide the vaccine recipient or guardian with Vaccine Information Statements which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

- Instruct the vaccine recipient or guardian that annual revaccination is recommended.

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