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

AFLURIA QUADRIVALENT, Influenza Vaccine
Suspension for Intramuscular Injection
2017-2018 Formula
Initial U.S. Approval (AFLURIA QUADRIVALENT): 2016

----------INDICATIONS AND USAGE----------
- AFLURIA QUADRIVALENT is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. (1)
- AFLURIA QUADRIVALENT is approved for use in persons 18 years of age and older. (1)

----------DOSAGE AND ADMINISTRATION----------
For intramuscular injection only, by needle and syringe (18 years of age and older) or by PharmaJet® Stratis® Needle-Free Injection System (18 through 64 years of age). Administer as a single 0.5 mL dose. (2)

----------DOSAGE FORMS AND STRENGTHS----------
AFLURIA QUADRIVALENT 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----------
- If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give AFLURIA QUADRIVALENT should be based on careful consideration of the potential benefits and risks. (5.1)
- Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. (5.2)

----------ADVERSE REACTIONS----------
- In adults 18 through 64 years, the most commonly reported injection-site adverse reaction when AFLURIA QUADRIVALENT was administered by needle and syringe was pain (≥40%). The most common systemic adverse events were myalgia and headache (≥20%). (6.1)
- In adults 65 years of age and older, the most commonly reported injection-site adverse reaction when AFLURIA QUADRIVALENT was administered by needle and syringe was pain (≥20%). The most common systemic adverse event was myalgia (≥10%). (6.1)
- In adults 18 through 64 years of age, the most commonly reported injection-site adverse reactions when AFLURIA® (trivalent formulation) was administered by the PharmaJet Stratis Needle-Free Injection System were tenderness (≥80%), swelling, pain, redness (≥60%), itching (≥20%) and bruising (≥10%). The most common systemic adverse events were myalgia, malaise (≥30%), and headache (≥20%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Seqirus at 1-855-358-8966 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

----------USE IN SPECIFIC POPULATIONS----------
- Antibody responses were lower in geriatric subjects than in younger adults. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.
Revised: 3/2017

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FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AFLURIA® QUADRIVALENT is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

AFLURIA QUADRIVALENT is approved for use in persons 18 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular (IM) use only.

- By needle and syringe (18 years of age and older)
- By PharmaJet® Stratis® Needle-Free Injection System (18 through 64 years of age)

Administer as a single 0.5 mL dose.

Immediately before use, shake thoroughly and inspect visually. 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.

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

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

It is recommended that small syringes (0.5 mL or 1 mL) be used to minimize any product loss.

To use the PharmaJet Stratis Needle-Free Injection System, refer to the Instructions for Use for the PharmaJet Stratis Needle-Free Injection System.

3 DOSAGE FORMS AND STRENGTHS

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

AFLURIA QUADRIVALENT 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 QUADRIVALENT 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 Guillain-Barré Syndrome

If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give AFLURIA QUADRIVALENT 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.

5.2 Preventing and Managing Allergic Reactions

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

5.3 Altered Immunocompetence

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

5.4 Limitations of Vaccine Effectiveness

Vaccination with AFLURIA QUADRIVALENT may not protect all individuals.

6 ADVERSE REACTIONS

In adults 18 through 64 years of age, the most commonly reported injection-site adverse reaction observed in clinical studies with AFLURIA QUADRIVALENT administered by needle and syringe was pain (≥40%). The most common systemic adverse events observed were myalgia and headache (≥20%).

In adults 65 years of age and older, the most commonly reported injection-site adverse reaction observed in clinical studies with AFLURIA QUADRIVALENT administered by needle and syringe was pain (≥20%). The most common systemic adverse event observed was myalgia (≥10%).

The safety experience with AFLURIA (trivalent formulation) is relevant to AFLURIA QUADRIVALENT because both vaccines are manufactured using the same process and have overlapping compositions (see *Description [11]*).

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

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.

Clinical safety data for AFLURIA QUADRIVALENT have been collected in one clinical trial, Study 1, a randomized, double-blind, active-controlled trial conducted in the US in 3449 subjects ages 18 years and older. Subjects in the safety population received one dose of either AFLURIA QUADRIVALENT (N=1721) or one of two formulations of comparator trivalent influenza vaccine (AFLURIA, TIV-1 N=864 or TIV-2 N=864) each containing an influenza type B virus that corresponded to one of the two B viruses in AFLURIA QUADRIVALENT (a type B virus of the Yamagata lineage or a type B virus of the Victoria lineage), respectively. The mean age of the population was 58 years, 57% were female, and racial groups consisted of 82% White, 16% Black, and 2% other; 5% of subjects were Hispanic/Latino. The age sub-groups were 18 through 64 years and 65 years and older with mean ages of 43 years and 73 years, respectively. In this study, AFLURIA QUADRIVALENT and comparator trivalent influenza vaccines were administered by needle and syringe (*see Clinical Studies [14]*).

Local (injection-site) adverse reactions and systemic adverse events were solicited for 7 days post-vaccination (Table 1). Injection site cellulitis, cellulitis-like reactions (defined as concurrent Grade 3 pain, redness, and swelling/lump), and Grade 3 swelling/lump were monitored for 28 days post-vaccination. Unsolicited adverse events were collected for 28 days post-vaccination. Serious adverse events (SAEs), including deaths, were collected for 180 days post-vaccination.

Table 1: Proportion of Subjects Per Age Cohort with Any Solicited Local Adverse Reactions or Systemic Adverse Events within 7 Days after Administration of AFLURIA QUADRIVALENT or Trivalent Influenza Vaccine (Study 1)[a]

	Percentage (%) [b] of Subjects in each Age Cohort Reporting an Event											
	Subjects 18 through 64 years						Subjects ≥ 65 years					
	AFLURIA Quadrivalent N= 854 [c]		TIV-1 N= 428 [c]		TIV-2 N= 430 [c]		AFLURIA Quadrivalent N= 867 [c]		TIV-1 N= 436 [c]		TIV-2 N= 434 [c]	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
Local Adverse Reactions [d]												
Pain	47.9	0.7	43.7	1.4	50.7	1.2	24.6	0.1	22.7	0	21.0	0.2
Swelling/Lump	3.7	0.1	2.3	0	3.5	0.2	3.2	0.5	1.8	0	1.6	0
Redness	2.9	0	2.8	0	2.8	0	4.2	0.3	2.1	0	2.5	0.2
Systemic Adverse Events [e]												
Myalgia (muscle ache)	25.5	1.9	23.4	1.4	24.2	1.2	12.7	0.3	14.0	0.7	12.2	0.5
Headache	21.7	1.7	15.2	0.9	19.1	1.2	8.4	0	7.1	0.2	7.8	0.7
Malaise	8.9	0.7	9.1	0	9.3	0.7	4.4	0.5	5.0	0.2	5.1	0.2
Nausea	6.9	0.6	7.7	0.5	6.3	1.2	1.6	0	1.8	0	2.1	0.2
Chills	4.8	0.6	4.4	0.2	4.7	0.5	2.0	0	2.1	0.5	1.4	0.2
Vomiting	1.5	0.4	0.9	0	2.3	0.7	0.5	0.1	0	0	0.7	0.2
Fever	1.1	0.4	0.9	0	0.5	0	0.2	0	0.9	0	0.5	0.2

Abbreviations: Gr 3, Grade 3.

[a] NCT02214225

[b] Proportion of subjects reporting each solicited local adverse reaction or systemic adverse event by study vaccine group based on the number of subjects contributing any follow up safety information for at least one data value of an individual sign/symptom.

[c] N = number of subjects in the Safety Population for each study vaccine group.

[d] Local adverse reactions: Grade 3 pain is that which prevents daily activity; Swelling/Lump and redness: any = ≥ 20mm diameter, Grade 3 = ≥ 100mm diameter.

[e] Systemic adverse events: Fever: any = ≥ 100.4°F, Grade 3 = ≥ 102.2°F; Grade 3 for all other adverse events is that which prevents daily activity.

In the 28 days following vaccination, no subject experienced cellulitis or a cellulitis-like reaction. All Grade 3 swelling/lump reactions began within 7 days of vaccination and are included in Table 1.

In the 28 days following vaccination, 20.5%, 20.1%, and 20.7% of adults 18 through 64 years and 20.3%, 24.1%, and 20.0% of adults ≥65 years who received AFLURIA QUADRIVALENT, TIV-1, and TIV-2, respectively, reported unsolicited adverse events. Rates of individual events were similar between treatment groups, and most events were mild to moderate in severity.

In the 180 days following vaccination, 2.3%, 1.6%, and 1.5% of all subjects who received

AFLURIA QUADRIVALENT, TIV-1, and TIV-2, respectively, experienced SAEs, including six deaths, five in the AFLURIA QUADRIVALENT group and one in the TIV-2 group. The majority of SAEs occurred after Study Day 28 and in subjects ≥65 years of age who had co-morbid illnesses. No SAEs or deaths appeared related to the study vaccines.

Safety information has also been collected in a clinical study of AFLURIA (trivalent formulation) administered using the PharmaJet Stratis Needle-Free Injection System (Study 2). Study 2 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 2. Local (injection-site) adverse reactions and systemic adverse events were solicited for 7 days post-vaccination (Table 2).

Table 2: 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 (trivalent formulation) by PharmaJet Stratis Needle-Free Injection System or Needle and Syringe (Study 2)[a]

	Percentage [b] of Subjects Reporting Event			
	Study 2 Subjects 18 through 64 years			
	AFLURIA (trivalent formulation)			
	PharmaJet Stratis Needle-Free Injection System N=540-616 [c]		Needle and Syringe N=599-606 [c]	
	Any	Grade 3	Any	Grade 3
Local Adverse Reactions [d]				
Tenderness	89.4	2.1	77.9	1.0
Swelling	64.8	1.7	19.7	0.2
Pain	64.4	0.8	49.3	0.7
Redness	60.1	1.3	19.2	0.3
Itching [f]	28.0	0.0	9.5	0.2
Bruising	17.6	0.2	5.3	0.0
Systemic Adverse Events [e]				
Myalgia	36.4	0.8	35.5	1.0
Malaise	31.2	0.7	28.4	0.5
Headache	24.7	1.3	22.1	1.3
Chills	7.0	0.2	7.2	0.2
Nausea	6.6	0.2	6.5	0.0
Vomiting	1.3	0.0	1.8	0.2
Fever	0.3	0.0	0.3	0.0

[a] NCT01688921

[b] 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).

[c] 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.

[d] Local adverse reactions: Grade 3 is pain, tenderness or itching that prevents daily activity; Swelling, redness or bruising: any = ≥ 25mm diameter, Grade 3 = > 100mm diameter.

[e] Systemic adverse events: Fever: any = ≥ 100.4°F, Grade 3 = ≥ 102.2°F; Grade 3 for all other adverse events is that which prevents daily activity.

[f] 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 adults 18 through 64 years who received AFLURIA (trivalent formulation) administered via PharmaJet Stratis Needle-Free Injection System, commonly reported unsolicited adverse events were headache (4.2%), injection site hematoma (1.8%), injection site erythema (1.1%), myalgia (1.0%) and nausea (1.0%).

6.2 Postmarketing Experience

Because postmarketing reporting of adverse events 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 events 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. There are no postmarketing data available for AFLURIA QUADRIVALENT. The adverse events listed below reflect experience in both children and adults and include those identified during post-approval use of AFLURIA (trivalent formulation) outside the US since 1985.

The post-marketing experience with AFLURIA (trivalent formulation) included the following:

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

7 DRUG INTERACTIONS

No interaction studies have been performed on interaction between influenza vaccines in general and other vaccines or medications.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. There are no data for AFLURIA QUADRIVALENT administered to pregnant women to inform vaccine-associated

risks in pregnancy. Available data on AFLURIA (trivalent formulation) administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

There were no developmental toxicity studies of AFLURIA QUADRIVALENT performed in animals. The developmental effects of AFLURIA (trivalent formulation) are relevant to AFLURIA QUADRIVALENT because both vaccines are manufactured using the same process and have overlapping compositions. A developmental toxicity study of AFLURIA (trivalent formulation) has been performed in female rats administered 0.5 mL (divided) of AFLURIA (trivalent formulation) prior to mating and during gestation. This study revealed no evidence of harm to the fetus due to AFLURIA (trivalent formulation) (*see 8.1 Data*).

Clinical Considerations

Disease-associated Maternal and/or Embryo-Fetal Risk

Pregnant women are at increased risk for severe illness due to influenza compared to non-pregnant women. Pregnant women with influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

Data

Animal Data

In a developmental toxicity study, female rats were administered 0.5 mL (divided) of AFLURIA (trivalent formulation) by intramuscular injection 21 days and 7 days prior to mating, and on gestation day 6. Some rats were administered an additional dose on gestation day 20. No vaccine-related fetal malformations or variations and no adverse effects on pre-weaning development were observed in the study.

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to AFLURIA QUADRIVALENT during pregnancy. To enroll in or obtain information about the registry, women are encouraged to contact Seqirus by calling 1-855-358-8966 or send an email to us.medicalinformation@seqirus.com

8.2 Lactation

Risk Summary

It is not known whether AFLURIA QUADRIVALENT is excreted in human milk. Data are not available to assess the effects of AFLURIA QUADRIVALENT on the breastfed infant or on milk production/excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AFLURIA QUADRIVALENT and any potential adverse effects on the breastfed child from AFLURIA QUADRIVALENT or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine or the effects on milk production.

8.4 Pediatric Use

The safety and efficacy of AFLURIA QUADRIVALENT in persons less than 18 years has not been established in clinical trials.

Administration of CSL's 2010 Southern Hemisphere trivalent 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.

8.5 Geriatric Use

In clinical studies, AFLURIA QUADRIVALENT has been administered to, and safety information collected for, 867 subjects aged 65 years and older *(see Adverse Reactions [6])*. The 65 years and older age group included 539 subjects 65 through 74 years and 328 subjects 75 years and older. After administration of AFLURIA QUADRIVALENT, hemagglutination-inhibiting antibody responses were non-inferior to comparator trivalent influenza (TIV-1 and TIV-2) in persons 65 years of age and older, but were lower than younger adult subjects (*see Clinical Studies [14]*).

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

11 DESCRIPTION

AFLURIA QUADRIVALENT, 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 QUADRIVALENT 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 QUADRIVALENT is standardized according to USPHS requirements for the 2017-2018 influenza season and is formulated to contain 60 mcg hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 mcg HA for each of the four influenza strains recommended for the 2017-2018 Northern Hemisphere influenza season: A/Singapore/GP1908/2015 (H1N1), IVR-180A, A/Hong Kong/4801/2014 (H3N2), NYMC X-263B, B/Phuket/3073/2013 BVR-1B and B/Brisbane/46/2015.

Thimerosal, a mercury derivative, is not used in the manufacturing process for the single dose presentation. This presentation does not contain 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 QUADRIVALENT 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 (0.5 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 (≤ 81.8 nanograms [ng]), polymyxin B (≤ 14 ng), and beta-propiolactone (≤ 1.5 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. Since 2001, two distinct lineages of influenza B (Victoria and Yamagata lineages) have co-circulated worldwide. 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 four strains (i.e., typically two type A and two 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 QUADRIVALENT has not been evaluated for carcinogenic or mutagenic potential, or male infertility in animals. A developmental toxicity study conducted in rats vaccinated with AFLURIA (trivalent formulation) revealed no impact on female fertility (see *Pregnancy [8.1]*).

14 CLINICAL STUDIES

14.1 Efficacy Against Laboratory-Confirmed Influenza

The efficacy of AFLURIA (trivalent formulation) is relevant to AFLURIA QUADRIVALENT because both vaccines are manufactured using the same process and have overlapping compositions (*see Description [11]*).

The efficacy of AFLURIA (trivalent formulation) was demonstrated in Study 3, 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 (trivalent formulation) (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 (trivalent formulation) 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 3).

Table 3: AFLURIA (trivalent formulation): Laboratory-Confirmed Influenza Infection Rate and Vaccine Efficacy in Adults 18 through 64 Years of Age (Study 3)[a]

	Subjects [b]	Laboratory-Confirmed Influenza Cases	Influenza Infection Rate	Vaccine Efficacy [c]	
	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] NCT00562484
[b] The Per Protocol Population was identical to the Evaluable Population in this study.
[c] Vaccine efficacy = 1 minus the ratio of AFLURIA (trivalent formulation) /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 of Afluria Quadrivalent Administered via Needle and Syringe

Study 1 was a randomized, double-blind, active-controlled trial conducted in the US in adults aged 18 years of age and older. Subjects received one dose of either AFLURIA QUADRIVALENT (N=1691) or one of two formulations of comparator trivalent influenza vaccine (Afluria, TIV-1 N=854 or TIV-2 N=850) each containing an influenza type B virus that corresponded to one of the two B viruses in AFLURIA QUADRIVALENT (a type B virus of the Yamagata lineage or a type B virus of the Victoria lineage, respectively).

Post-vaccination immunogenicity was evaluated on sera obtained 21 days after administration of a single dose of AFLURIA QUADRIVALENT or TIV comparator. 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 vaccination. Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the GMT ratio (TIV/AFLURIA QUADRIVALENT) did not exceed 1.5 and the upper bound of the 2-sided 95% CI of the seroconversion rate difference (TIV minus AFLURIA QUADRIVALENT) did not exceed 10.0% for each strain.

Serum HI antibody responses to AFLURIA QUADRIVALENT were non-inferior to both TIVs for all influenza strains for subjects 18 years of age and older. Additionally, non-inferiority was demonstrated for both endpoints in both age sub-groups, adults aged 18 through 64 years and 65 years and older, for all strains (Table 4). Superiority of the immune response to each of the influenza B strains contained in AFLURIA QUADRIVALENT was shown relative to the antibody response after vaccination with TIV formulations not containing that B lineage strain for subjects 18 years of age and older. Superiority against the alternate B strain was also demonstrated for each of the influenza B strains in both age sub-groups; 18 through 64 years and 65 years and older. Post-hoc analyses of immunogenicity endpoints by gender did not

demonstrate meaningful differences between males and females. The study population was not sufficiently diverse to assess differences between races or ethnicities.

Table 4: Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of Non-Inferiority of AFLURIA QUADRIVALENT Relative to Trivalent Influenza Vaccine (TIV) by Age Cohort (Study 1)[a]

	Post-vaccination GMT		GMT Ratio [b]	Seroconversion % [c]		Difference	
Strain	**AFLURIA Quadrivalent**	**Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria)**	**Pooled TIV or TIV-1 or TIV-2 over AFLURIA Quadrivalent (95% CI)**	**AFLURIA Quadrivalent N=1691**	**Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria)**	**Pooled TIV or TIV-1 or TIV-2 minus AFLURIA Quadrivalent (95% CI)**	**Met both pre-defined non-inferiority criteria? [d]**
18 through 64 years	**AFLURIA Quadrivalent N=835, Pooled TIV N=845, TIV-1 N=424, TIV-2 N=421**						
A(H1N1)	432.7	402.8	0.93 [e] (0.85, 1.02)	51.3	49.1	-2.1 [h] (-6.9, 2.7)	Yes
A(H3N2)	569.1	515.1	0.91 [e] (0.83, 0.99)	56.3	51.7	-4.6 [h] (-9.4, 0.2)	Yes
B/Massachusetts/ 2/2012 (B Yamagata)	92.3	79.3	0.86 [f] (0.76, 0.97)	45.7	41.3	-4.5 [i] (-10.3, 1.4)	Yes
B/Brisbane/ 60/2008 (B Victoria)	110.7	95.2	0.86 [g] (0.76, 0.98)	57.6	53.0	-4.6 [j] (-10.5, 1.2)	Yes
≥ 65 years	**AFLURIA Quadrivalent N=856, Pooled TIV N=859, TIV-1 N=430, TIV-2 N=429**						
A(H1N1)	211.4	199.8	0.95 [e] (0.88, 1.02)	26.6	26.4	-0.2 [h] (-5.0, 4.5)	Yes
A(H3N2)	419.5	400.0	0.95 [e] (0.89, 1.02)	25.9	27.0	1.1 [h] (-3.7, 5.8)	Yes
B/Massachusetts/ 2/2012 (B Yamagata)	43.3	39.1	0.90 [f] (0.84, 0.97)	16.6	14.4	-2.2 [i] (-8.0, 3.6)	Yes
B/Brisbane/ 60/2008 (B Victoria)	66.1	68.4	1.03 [g] (0.94, 1.14)	23.5	24.7	1.2 [j] (-4.6, 7.0)	Yes

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

[a] NCT02214225

[b] GMT ratio was computed after fitting a multi-variable model on the post-vaccination titers including sex, vaccination history, pre-vaccination HI titers and other factors.

[c] 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.

[d] The non-inferiority (NI) criteria for the GMT ratio: upper bound of 2-sided 95% CI on the ratio of Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria)/AFLURIA Quadrivalent. GMT should not exceed 1.5. NI criteria for the SCR difference: upper bound of 2-sided 95% CI on the difference between SCR Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria) minus AFLURIA Quadrivalent should not exceed 10%.

[e] Pooled TIV/AFLURIA Quadrivalent

[f] TIV-1 (B Yamagata)/AFLURIA Quadrivalent

[g] TIV-2 (B Victoria)/AFLURIA Quadrivalent

[h] Pooled TIV - Afluria Quadrivalent

[i] TIV-1 (B Yamagata) - AFLURIA Quadrivalent

[j] TIV-2 (B Victoria) - AFLURIA Quadrivalent

14.3 Immunogenicity of Afluria (trivalent formulation) Administered via PharmaJet Stratis Needle-Free Injection System

Study 2 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 (trivalent formulation) when delivered intramuscularly 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 (1130 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 5, non-inferiority of administration of AFLURIA (trivalent formulation) by the PharmaJet Stratis Needle-Free Injection System compared to administration of AFLURIA (trivalent formulation) 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 sex 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 5: Baseline and Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of Non-Inferiority of AFLURIA (trivalent formulation) Administered by PharmaJet Stratis Needle-Free Injection System or Needle and Syringe, Adults 18 through 64 Years of Age (Study 2)[a]

	Baseline GMT		Post-vaccination GMT		GMT Ratio [b]	Seroconversion % [c]		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? [d]
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] NCT01688921
[b] GMT ratio is defined as post-vaccination GMT for Needle and Syringe/PharmaJet Stratis Needle-Free Injection System.
[c] 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.

[d] 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

1. Centers for Disease Control and Prevention. Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2010;59 (RR-8):1-62.
2. Hannoun C, Megas F, Piercy J. Immunogenicity and Protective Efficacy of Influenza Vaccination. *Virus Res* 2004;103:133-138.
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	33332-317-01	• Ten 0.5 mL single-dose syringes fitted with a Luer-Lok™ attachment without needles [NDC 33332-317-02]
Multi-Dose Vial	33332-417-10	• One 5 mL vial, which contains ten 0.5 mL doses [NDC 33332-417-11]

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 QUADRIVALENT beyond the expiration date printed on the label.
- Between uses, return the multi-dose vial to the recommended storage conditions.
- 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 of the potential benefits and risks of immunization with AFLURIA QUADRIVALENT.
- Inform the vaccine recipient that AFLURIA QUADRIVALENT 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 to report any severe or unusual adverse reactions to their healthcare provider.
- There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to AFLURIA QUADRIVALENT during pregnancy. For contact information necessary to enroll, see Pregnancy [8.1])
- Provide the vaccine recipient Vaccine Information Statements 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 that annual revaccination is recommended.

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