flu360™ WE'VE GOT FLU COVERED™

Terms That Help to Support Your Influenza Immunization Goals

PRE-BOOK YOUR INFLUENZA VACCINE BY MAY 1, 2020 FOR THE 2020-2021 SEASON TO RECEIVE THE BELOW OFFER*

FIRM DOSE DISCOUNT

3% discount on orders placed by May 1, 2020

PROMPT PAY DISCOUNT

2% discount on orders paid within 60 days

RISK SHARING

25% return of each brand ordered and unused by the end of the season

2020-2021 INFLUENZA VACCINES DELIVERY EXPECTATIONS:

August 31, 2020	September 30, 2020	October 15, 2020
35%	75%	100%

	FLUAD® QUADRIVALENT influenza vaccine, adjuvanted	Influenza Vaccine FLUCELVAX® QUADRIVALENT		Influenza Vaccine afluria® QUADRIVALENT		
	65 years and older	4 years and older		6+ months	6–35 months	36+ months
	0.5 mL Pre-filled Syringe	0.5 mL Pre-filled Syringe	5 mL Multi-Dose Vial	5 mL Multi-Dose Vial	0.25 mL Pre-filled Syringe (Pediatric Dose)	0.5 mL Pre-filled Syringe
NET PRICE/UNIT†	$405.02	$167.52	$157.53	Sold Out	$146.20	Sold Out

†Inclusive of firm dose discount. Does not include Federal Excise Tax. Additional discount may apply.

COUNT ON THESE EASY ORDERING METHODS WHEN PURCHASING SEQIRUS PRODUCTS

Directly order, manage, and access your account online at **flu.seqirus.com**

Contact your Seqirus account manager

*Terms and conditions apply. See **flu.seqirus.com** for additional details.

Seqirus™ A CSL COMPANY

FLUAD® QUADRIVALENT (Influenza Vaccine, Adjuvanted) Important Safety Information

INDICATIONS AND USAGE

FLUAD QUADRIVALENT is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and types B contained in the vaccine. FLUAD QUADRIVALENT is approved for use in persons 65 years of age and older.

This indication is approved under accelerated approval based on the immune response elicited by FLUAD QUADRIVALENT. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

CONTRAINDICATIONS

Severe allergic reaction to any component of the vaccine, including egg protein, or after a previous dose of any influenza vaccine.

WARNINGS AND PRECAUTIONS

- If Guillain-Barré Syndrome (GBS) has occurred within six weeks of previous influenza vaccination, the decision to give FLUAD QUADRIVALENT should be based on careful consideration of the potential benefits and risks.
- Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.
- The immune response to FLUAD QUADRIVALENT in immunocompromised persons, including individuals receiving immunosuppressive therapy, may be lower than in immunocompetent individuals.
- Syncope (fainting) may occur in association with administration of injectable vaccines including FLUAD QUADRIVALENT. Ensure procedures are in place to avoid injury from falling associated with syncope.

ADVERSE REACTIONS

- The most common (≥ 10%) local and systemic reactions in elderly subjects 65 years of age and older were injection site pain (16.3%), headache (10.8%) and fatigue (10.5%).

Other adverse events may occur. For a comprehensive list of local and systemic adverse reactions, please see full Prescribing Information.

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

Before administration, please see the full Prescribing Information for FLUAD QUADRIVALENT.

FLUAD® QUADRIVALENT is a registered trademark of Seqirus UK Limited or its affiliates.

FLUCELVAX® QUADRIVALENT Important Safety Information

INDICATION AND USAGE FOR FLUCELVAX® QUADRIVALENT (INFLUENZA VACCINE)

FLUCELVAX QUADRIVALENT is an inactivated vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. FLUCELVAX QUADRIVALENT is approved for use in persons 4 years of age and older.

CONTRAINDICATIONS

- Do not administer FLUCELVAX QUADRIVALENT to anyone with a history of severe allergic reaction (e.g. anaphylaxis) to any component of the vaccine.

WARNINGS & PRECAUTIONS

- **Guillain-Barré Syndrome (GBS):** If GBS has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLUCELVAX QUADRIVALENT should be based on careful consideration of the potential benefits and risks.

ADVERSE REACTIONS

- The most common (≥10%) local and systemic reactions in adults 18-64 years of age were injection site pain (45.4%), headache (18.7%), fatigue (17.8%), myalgia (15.4%), injection site erythema (13.4%), and induration (11.6%).
- The most common (≥10%) local and systemic reactions in adults ≥65 years of age were injection site pain (21.6%) and injection site erythema (11.9%).
- The most common (≥10%) local and systemic reactions in children 4 to <6 years of age were tenderness at the injection site (46%), injection site erythema (18%), sleepiness (19%), irritability (16%), injection site induration (13%), and change in eating habits (10%).
- The most common (≥10%) local and systemic reactions in children 6 through 8 years of age were pain at the injection site (54%), injection site erythema (22%), injection site induration (16%), headache (14%), fatigue (13%), and myalgia (12%).
- The most common (≥10%) local and systemic reactions in children and adolescents 9 through 17 years of age were pain at the injection site (58%), headache (22%), injection site erythema (19%), fatigue (18%), myalgia (16%), and injection site induration (15%).

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

Please see accompanying US full Prescribing Information for FLUCELVAX QUADRIVALENT.

FLUCELVAX QUADRIVALENT is a registered trademark of Seqirus UK Limited or its affiliates.

AFLURIA® QUADRIVALENT (Influenza Vaccine) Important Safety Information

INDICATION

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 6 months of age and older.

CONTRAINDICATIONS

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

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.
- Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.
- Immunocompromised persons may have a diminished immune response to AFLURIA QUADRIVALENT.

ADVERSE REACTIONS

- In adults 18 through 64 years, the most commonly reported injection-site adverse reaction when administered by needle and syringe was pain (≥40%). The most common systemic adverse events were myalgia and headache (≥20%).
- In adults 65 years of age and older, the most commonly reported injection-site adverse reaction when administered by needle and syringe was pain (≥20%). The most common systemic adverse event was myalgia (≥10%).
- In children 5 through 8 years, the most commonly reported injection-site adverse reactions when administered by needle and syringe were pain (≥50%), redness and swelling (≥10%). The most common systemic adverse event was headache (≥10%).
- In children 9 through 17 years, the most commonly reported injection-site adverse reactions when administered by needle and syringe were pain (≥50%), redness and swelling (≥10%). The most common systemic adverse events were headache, myalgia, and malaise and fatigue (≥10%).
- In children 6 months through 35 months of age, the most commonly reported injection-site reactions were pain and redness (≥ 20%). The most common systemic adverse events were irritability (≥ 30%), diarrhea and loss of appetite (≥ 20%).
- In children 36 through 59 months of age, the most commonly reported injection site reactions were pain (≥ 30%) and redness (≥ 20%). The most commonly reported systemic adverse events were malaise and fatigue, and diarrhea (≥ 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:

- In adults 18 through 64 years of age, the most commonly reported injection-site adverse reactions with AFLURIA (trivalent formulation) when 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%).

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

Please see accompanying full Prescribing Information for AFLURIA QUADRIVALENT.

AFLURIA is a registered trademark of Seqirus UK Limited or its affiliates.

PharmaJet® and STRATIS® are registered trademarks of PharmaJet.

AFLURIA, flu360, FLUAD QUADRIVALENT, FLUCELVAX, and WE'VE GOT FLU COVERED are registered trademarks of Seqirus UK Limited or its affiliates.
Manufactured by: Seqirus Inc., 475 Green Oaks Parkway, Holly Springs, NC 27540, USA
Distributed by: Seqirus USA Inc., 25 Deforest Avenue, Summit, NJ 07901, USA
©2020 Seqirus USA Inc.
February 2020 US/CORP/1219/0194

Seqirus™
A CSL COMPANY

----------HIGHLIGHTS OF PRESCRIBING INFORMATION----------

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

FLUAD QUADRIVALENT (Influenza Vaccine, Adjuvanted)
Injectable Emulsion for Intramuscular Use
20XX-20XX Formula
Initial U.S. Approval: 2020

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

FLUAD QUADRIVALENT is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and types B contained in the vaccine. FLUAD QUADRIVALENT is approved for use in persons 65 years of age and older. (1)

This indication is approved under accelerated approval based on the immune response elicited by FLUAD QUADRIVALENT (1). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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

A single 0.5 mL dose for intramuscular injection. (2.1)

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

Injectable emulsion supplied in 0.5 mL single-dose pre-filled syringes. (3)

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

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

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

If Guillain-Barré Syndrome (GBS) has occurred within six weeks of previous influenza vaccination, the decision to give FLUAD QUADRIVALENT should be based on careful consideration of the potential benefits and risks. (5.1)

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

The most common (≥ 10%) local and systemic reactions in elderly subjects 65 years of age and older were injection site pain (16.3%), headache (10.8%) and fatigue (10.5%). (6)

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: 02/2020

FULL PRESCRIBING INFORMATION: CONTENTS

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FLUAD QUADRIVALENT is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and types B contained in the vaccine. FLUAD QUADRIVALENT is approved for use in persons 65 years of age and older. This indication is approved under accelerated approval based on the immune response elicited by FLUAD QUADRIVALENT *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only

2.1. Dosage and Schedule

Administer FLUAD QUADRIVALENT as a single 0.5 mL intramuscular injection in adults 65 years of age and older.

2.2. Administration

- Gently shake each syringe. FLUAD QUADRIVALENT has a milky-white appearance. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit *[see Description (11)]*. If either condition exists, FLUAD QUADRIVALENT should not be administered.
- The vaccine should be administered by intramuscular injection, preferably in the region of the deltoid muscle of the upper arm. Do not inject the vaccine in the gluteal region or areas where there may be a major nerve trunk.

3 DOSAGE FORMS AND STRENGTHS

FLUAD QUADRIVALENT is a sterile injectable emulsion supplied in 0.5 mL single-dose pre-filled syringes.

4 CONTRAINDICATIONS

Do not administer FLUAD QUADRIVALENT to anyone with a history of severe allergic reaction (e.g. anaphylaxis) to any component of the vaccine, including egg protein *[see Description (11)]*, or to a previous influenza vaccine.

5 WARNINGS AND PRECAUTIONS

5.1. Guillain-Barré Syndrome

If Guillain-Barré syndrome (GBS) has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give FLUAD QUADRIVALENT should be based on careful consideration of the potential benefits and risks. The 1976 swine influenza vaccine was associated with an elevated risk of GBS. *[see References (1)]* Evidence for a causal relationship of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 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

The immune response to FLUAD QUADRIVALENT in immunocompromised persons, including individuals receiving immunosuppressive therapy, may be lower than in immunocompetent individuals. *[see Concurrent Use With Immunosuppressive Therapies (7.2)]*

5.4 Syncope

Syncope (fainting) may occur in association with administration of injectable vaccines including FLUAD QUADRIVALENT. Ensure procedures are in place to avoid injury from falling associated with syncope.

5.5 Limitations of Vaccine Effectiveness

Vaccination with FLUAD QUADRIVALENT may not protect all vaccine recipients against influenza disease.

6 ADVERSE REACTIONS

The most common (≥10%) local and systemic reactions in elderly subjects 65 years of age and older were injection site pain (16.3%), headache (10.8%) and fatigue (10.5%).

6.1. Clinical Trials Experience

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

The safety of FLUAD QUADRIVALENT was evaluated in two clinical studies in 4269 elderly subjects 65 years of age and older. Study 1 (NCT02587221) was a multi-center, randomized, observer-blind, non-influenza comparator-controlled efficacy and safety study conducted in 12 countries during the 2016-2017 Northern Hemisphere and 2017 Southern Hemisphere seasons. In this study, 3381 subjects received FLUAD QUADRIVALENT and 3380 subjects received a US-licensed non-influenza comparator vaccine (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Boostrix® [GlaxoSmithKline Biologicals]).

The mean age of subjects at enrollment was 72 years, 62% were female, 48% White, 34% Asian, 16% Other, 2% American Indian/Alaska Native, and 18% of Hispanic/Latino ethnicity.

Solicited local and systemic adverse reactions were collected for 7 days after vaccination in a subset of 665 subjects who received FLUAD QUADRIVALENT and 667 subjects who received the comparator vaccine. The percentages of subjects reporting solicited local and systemic adverse reactions are presented in Table 1. Onset usually occurred within the first 2 days after vaccination. The majority of solicited reactions resolved within 3 days.

Table 1. Percentages of Subjects Reporting Solicited Local and Systemic Adverse Reactions[a] in the Solicited Safety Population[b] within 7 Days of Vaccination (Study 1)

Local (Injection site) Reactions[c]	FLUAD QUADRIVALENT N=595-659	Non-Influenza Comparator Vaccine N=607-664
Injection site pain	16.3	11.2
Erythema ≥25mm	3.8	1.8
Induration ≥25mm	4.0	2.6
Ecchymosis ≥25mm	0.5	0.7
Systemic Reactions[c]	**FLUAD QUADRIVALENT N=595-659**	**Non-Influenza Comparator Vaccine N=607-664**
Headache	10.8	8.3
Fatigue	10.5	8.8
Myalgia	7.7	6.1
Arthralgia	7.3	6.6
Chills	5.0	3.9
Diarrhea	4.1	3.0
Nausea	3.8	2.3
Loss of appetite	3.6	3.6
Fever ≥100.4°F (38°C)	1.7	1.2
Vomiting	0.8	1.1

Study 1: NCT02587221
Abbreviation: N=number of subjects with solicited safety data
Non-Influenza Comparator Vaccine = combined Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Boostrix® (GlaxoSmithKline Biologicals)
[a] All solicited local and systemic adverse events reported within 7 days of vaccination are included
[b] Solicited Safety Population: all subjects in the exposed population who received a study vaccine and provided post-vaccination solicited safety data
[c] Severe reactions of each type were reported in 1.1% or fewer subjects receiving FLUAD QUADRIVALENT; severe reactions of each type were also reported in the comparator group at similar percentages. Severe definitions: Erythema, Induration and Ecchymosis = >100 mm diameter; Injection site pain, Nausea, Fatigue, Myalgia, Arthralgia, Headache, and Chills = prevents daily activity; Loss of appetite = not eating at all; Vomiting = 6 or more times in 24 hours or requires intravenous hydration; Diarrhea = 6 or more loose stools in 24 hours or requires intravenous hydration; Fever = ≥102.2°F (39°C).

Unsolicited adverse events (AEs) were collected for all subjects for 21 days after vaccination. Related unsolicited AEs were reported by 303 (9.0%) and by 261 (7.7%) of the subjects for FLUAD QUADRIVALENT and Boostrix, respectively. For FLUAD QUADRIVALENT, injection site pain and influenza-like illness were the only unsolicited adverse reactions reported in ≥ 1% of subjects (1.7% and 1.5%, respectively).

Serious adverse events (SAEs) and potentially immune-mediated adverse events of special interest (AESIs) were collected up to 366 days after vaccination. SAEs were reported by 238 (7.0%) FLUAD QUADRIVALENT recipients and 234 (6.9%) comparator recipients. There were no SAEs, AESIs or deaths in this study that were related to FLUAD QUADRIVALENT.

Study 2 (NCT03314662) was a multicenter, randomized, double-blind, comparator-controlled study conducted during the 2017-18 Northern Hemisphere influenza season. In this study, 888 subjects received FLUAD QUADRIVALENT, 444 subjects received the licensed adjuvanted trivalent vaccine (aTIV-1 - FLUAD® (trivalent formulation)) and 444 subjects received an adjuvanted trivalent influenza vaccine with an alternate B strain (aTIV-2).

The mean age of subjects at enrollment who received FLUAD QUADRIVALENT was 72.5 years. Female subjects represented 56.6% of the study population and the racial distribution of subjects was 91.6% Caucasian, 7.0% Black or African American, and ≤ 1% each for Asian, Native Hawaiian or Pacific Islander, American Indian or Alaska Native or Other.

Solicited local and systemic adverse reactions reported within 7 days after vaccination were similar to those reported for Study 1. Unsolicited AEs were collected for 21 days after vaccination. Related unsolicited AEs were reported by 39 (4.4%) and by 17-19 (3.8%-4.3%) of subjects administered FLUAD QUADRIVALENT or aTIV, respectively. For FLUAD QUADRIVALENT, injection site bruising (1.0%) was the only unsolicited adverse reaction reported in ≥ 1% of subjects.

Serious AEs and AESIs were collected up to 181 days after vaccination. Within 6 months after vaccination, 37 (4.2%) FLUAD QUADRIVALENT recipients and 18-28 (4.1%-6.3%) aTIV recipients experienced an SAE. There were no SAEs, AESIs or deaths in this study that were related to the study vaccine. There were no AEs leading to withdrawal from the study.

6.2. Postmarketing Experience

There are no postmarketing data available for FLUAD QUADRIVALENT. However, the postmarketing experience with FLUAD (trivalent formulation) is relevant to FLUAD QUADRIVALENT because both vaccines are manufactured using the same process and have overlapping compositions.

Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Blood and lymphatic system disorders:
Thrombocytopenia (some cases were severe with platelet counts less than 5,000 per mm^3), lymphadenopathy

General disorders and administration site conditions:
Extensive swelling of injected limb lasting more than one week, injection site cellulitis-like reactions (some cases of swelling, pain, and redness extending more than 10 cm and lasting more than 1 week)

Immune system disorders:
Allergic reactions including anaphylactic shock, anaphylaxis, and angioedema

Musculoskeletal and connective tissue disorders:
Muscular weakness

Nervous system disorders:
Encephalomyelitis, Guillain-Barré Syndrome, convulsions, neuritis, neuralgia, parasthesia, syncope, presyncope

Skin and subcutaneous tissue disorders:
Generalized skin reactions including erythema multiforme, urticaria, pruritus or non-specific rash

Vascular disorders:
Vasculitis, renal vasculitis

7 DRUG INTERACTIONS

7.1. Concomitant Use With Other Vaccines

No clinical data on concomitant administration of FLUAD QUADRIVALENT with other vaccines is available.

If FLUAD QUADRIVALENT is given at the same time as other injectable vaccine(s), the vaccine(s) should be administered at different injection sites.

Do not mix FLUAD QUADRIVALENT with any other vaccine in the same syringe.

7.2. Concurrent Use With Immunosuppressive Therapies

Immunosuppressive or corticosteroid therapies may reduce the immune response to FLUAD QUADRIVALENT.

8 USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

FLUAD QUADRIVALENT is not approved for use in persons < 65 years of age. There are insufficient human data to establish whether there is a vaccine-associated risk with use of FLUAD QUADRIVALENT in pregnancy.

There were no developmental toxicity studies of FLUAD QUADRIVALENT performed in animals. A developmental toxicity study has been performed in female rabbits administered FLUAD (trivalent formulation) prior to mating and during gestation. A 0.5 mL dose was injected on each occasion (a single human dose is 0.5 mL). (see 8.1 Animal Data).

Animal Data

In a developmental toxicity study, the effect of FLUAD (trivalent formulation) was evaluated in pregnant rabbits. Animals were administered FLUAD (trivalent formulation) by intramuscular injection twice prior to gestation, during the period of organogenesis (gestation day 7) and later in pregnancy (gestation day 20), 0.5 mL (45 mcg)/rabbit/ occasion. No vaccine-related fetal malformations or variations and no adverse effects on pre-weaning development were observed in the study.

8.2. Lactation

FLUAD QUADRIVALENT is not approved for use in persons < 65 years of age. No human or animal data are available to assess the effects of FLUAD QUADRIVALENT on the breastfed infant or on milk production/excretion.

8.4. Pediatric Use

The safety and effectiveness of FLUAD QUADRIVALENT in the pediatric population have not been established.

8.5. Geriatric Use

Safety and immunogenicity of FLUAD QUADRIVALENT have been evaluated in adults 65 years of age and older. *[See Adverse Reactions (6.1) and Clinical Studies (14)]*

11 DESCRIPTION

FLUAD QUADRIVALENT (Influenza Vaccine, Adjuvanted), a sterile injectable emulsion for intramuscular use, is a quadrivalent, inactivated influenza vaccine prepared from virus propagated in the allantoic cavity of embryonated hens' eggs inoculated with a specific type of influenza virus.

FLUAD QUADRIVALENT is standardized according to United States Public Health Service requirements and each 0.5 mL dose is formulated to contain 15 mcg of hemagglutinin (HA) from each of the following four influenza strains recommended for the XXXX/XXXX influenza season: XXXX (H1N1) (an XXXX-like virus); XXXX (H3N2) (an XXXX-like virus); XXXX (B1) (a XXXX-like virus) and B/ XXXX (B2) (a XXXX-like virus). FLUAD QUADRIVALENT also contains MF59C.1 adjuvant (MF59®), a squalene based oil-in-water emulsion.

Each of the strains is harvested and clarified separately by centrifugation and filtration prior to inactivation with formaldehyde. The inactivated virus is concentrated and purified by zonal centrifugation. The surface antigens, hemagglutinin and neuraminidase, are obtained from the influenza virus particle by further centrifugation in the presence of cetyltrimethylammonium bromide (CTAB). The antigen preparation is further purified.

FLUAD QUADRIVALENT is prepared by combining the four virus antigens with the MF59C.1 adjuvant. After combining, FLUAD QUADRIVALENT is a sterile, milky-white injectable emulsion supplied in single-dose pre-filled syringes containing 0.5 mL dose. Each 0.5 mL dose contains 15 mcg of hemagglutinin (HA) from each of the four recommended influenza strains and MF59C.1 adjuvant (9.75 mg squalene, 1.175 mg of polysorbate 80, 1.175 mg of sorbitan trioleate, 0.66 mg of sodium citrate dihydrate and 0.04 mg of citric acid monohydrate) at pH 6.9-7.7.

FLUAD QUADRIVALENT may contain trace amounts of neomycin (≤ 0.02 mcg by calculation), kanamycin (≤ 0.03 mcg by calculation) and hydrocortisone (≤ 0.005 ng by calculation) which are used during the initial stages of manufacture, as well as residual egg protein (ovalbumin) (≤ 1.0 mcg), formaldehyde (≤ 10 mcg) or CTAB (≤ 12 mcg).

FLUAD QUADRIVALENT does not contain a preservative. The syringe, syringe plunger stopper and tip caps are 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) viruses and influenza B viruses have been in global circulation. Specific levels of hemagglutination inhibition (HI) antibody titers induced by vaccination with inactivated influenza virus vaccine have not been correlated with protection from influenza illness. In some human studies, HI antibody titers of 1:40 or greater have been associated with protection from influenza illness in up to 50% of subjects. *[see References (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 of one or more new strains in each year's influenza vaccine. Therefore, inactivated quadrivalent influenza vaccines are standardized to contain the hemagglutinin of influenza virus strains (two subtypes A and two types B), representing the influenza viruses likely to be circulating in the United States in the upcoming influenza season.

Annual influenza vaccination is recommended because immunity declines during the year after vaccination, and because circulating strains of influenza virus change from year to year.

13 NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

FLUAD QUADRIVALENT has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility in animals. FLUAD (trivalent formulation) did not affect female fertility in a rabbit developmental toxicity study *[see Pregnancy (8.1)]*.

14 CLINICAL STUDIES

14.1 Immunogenicity of FLUAD QUADRIVALENT

Immunogenicity of FLUAD QUADRIVALENT was evaluated in Study 1 (NCT02587221), a randomized, observer-blind, non-influenza comparator-controlled multicenter efficacy study conducted in 12 countries during the 2016-2017 Northern Hemisphere and 2017 Southern Hemisphere seasons. In this study, elderly subjects 65 years of age and older received one dose of either FLUAD QUADRIVALENT (N=3379) or a US-licensed non-influenza comparator vaccine (Boostrix; N=3382). Immunogenicity was evaluated 21 days after vaccination in a subgroup of subjects in a 4:1 ratio: FLUAD QUADRIVALENT (N=1324) and non-influenza control vaccines (N=332). In the immunogenicity set, the mean age across both vaccination groups was 72 years and females represented 59% of subjects. The racial distribution of subjects consisted of 89% Caucasian, 11% Asian and <1% American Indian or Alaska Native.

Immunogenicity endpoints measured 3 weeks after vaccination included percentage of subjects with HI titer ≥1:40 and percentage of subjects who achieved seroconversion. Success criteria required the lower bound of the 2-sided 95% CI for the proportion of subjects with an HI titer ≥1:40 to be ≥60% and for the lower bound of the 2-sided 95% CI for the proportion of subjects with seroconversion to be ≥30%. Antibody responses for all 4 strains are presented in Table 2.

Table 2: Immune Responses 21 Days After Vaccination with FLUAD QUADRIVALENT or a Non-Influenza Comparator Vaccine in Elderly Subjects 65 years of Age and Older (Study 1)

Strain	Proportion of subjects with HI titer ≥1:40[a] (95% CI) FLUAD QUADRIVALENT N=1324	Proportion of subjects with HI titer ≥1:40[a] (95% CI) Non-Influenza Comparator Vaccine N=332	Seroconversion[b] (95% CI) FLUAD QUADRIVALENT N=1324	Seroconversion[b] (95% CI) Non-Influenza Comparator Vaccine N=332
A/H1N1	96.2% (95.1%, 97.2%)	46.7% (41.2%, 52.2%)	78.0% (75.7%, 80.2%)	2.1% (0.9%, 4.3%)
A/H3N2	95.6% (94.4%, 96.7%)	41.7% (36.3%, 47.2%)	84.6% (82.5%, 86.5%)	3.9% (2.1%, 6.6%)
B/Yamagata	79.2% (77.0%, 81.4%)	21.5% (17.2%, 26.4%)	60.8% (58.1%, 63.4%)	3.6% (1.9%, 6.3%)
B/Victoria	81.6% (79.4%, 83.7%)	18.4% (14.4%, 23.0%)	65.5% (62.9%, 68.1%)	2.1% (0.9%, 4.3%)

Abbreviations: CI=Confidence Interval, N=number of subjects in full analysis immunogenicity set.
Non-Influenza Comparator Vaccine = combined Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Boostrix® (GlaxoSmithKline Biologicals)
[a]Success criteria: LB of the 95% CI for the % of subjects with HI titer ≥1:40 must be ≥60%
[b]Seroconversion is defined as a pre-vaccination HI titer <1:10 and post-vaccination HI titer ≥ 1:40 or at least a 4-fold increase in HI from pre-vaccination HI titer ≥ 1:10. Success criteria: the LB of the 95% CI for the SCR must be ≥30%.

15 REFERENCES

1. Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barre syndrome and the 1992-1993 and 1993-1994 influenza vaccines. N Engl J Med 1998; 339(25): 1797-1802.
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 A, et. al. The role of serum hemagglutinin-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. J Hyg Camb 1972; 767-777.

16 HOW SUPPLIED/STORAGE AND HANDLING

FLUAD QUADRIVALENT is supplied in the product presentation listed below:

Presentation	Carton NDC Number	Components
Pre-Filled Syringe	70461-1XX-03	0.5 mL dose in a pre-filled syringe (needle not supplied), package of 10 syringes per carton [NDC 70461-1XX-04]

Store FLUAD QUADRIVALENT refrigerated at 2°C to 8°C (36°F to 46°F). Protect from light. Do not freeze. Discard if the vaccine has been frozen. Do not use after expiration date.

The syringe, syringe plunger stopper and tip cap are not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

- Inform vaccine recipients of the potential benefits and risks of immunization with FLUAD QUADRIVALENT.
- Educate vaccine recipients regarding the potential side effects. Clinicians should emphasize that (1) FLUAD QUADRIVALENT contains non-infectious particles and cannot cause influenza and (2) FLUAD QUADRIVALENT is intended to help provide protection against illness due to influenza viruses only.
- Instruct vaccine recipients to report adverse reactions to their healthcare provider and/or to Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967 and www.vaers.hhs.gov. Provide vaccine recipients with the Vaccine Information Statements which are required by the National Childhood Vaccine Injury Act of 1986. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).
- Inform vaccine recipients that annual vaccination is recommended.

FLUAD QUADRIVALENT is a registered trademark of Seqirus UK Limited or its affiliates.

MF59® is a trademark of Novartis AG.

Manufactured by:
Seqirus Inc., 475 Green Oaks Parkway, Holly Springs, NC 27540, USA

Distributed by:
Seqirus USA Inc., 25 Deforest Avenue, Summit, NJ 07901, USA

Tel: 1-855-358-8966

US License No. 2049

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

FLUCELVAX QUADRIVALENT (Influenza Vaccine)
Suspension for Intramuscular Injection
2019-2020 Formula
Initial U.S. Approval: 23 May 2016

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

FLUCELVAX QUADRIVALENT is an inactivated vaccine indicated for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. (1)

(1) FLUCELVAX is approved for use in persons 4 years of age and older. (1)

For children and adolescents 4 through 17 years of age, approval is based on the immune response elicited by FLUCELVAX QUADRIVALENT. Data demonstrating a decrease in influenza disease after vaccination of children and adolescents 4 through 17 years of age with FLUCELVAX QUADRIVALENT are not available. (14)

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

For intramuscular use only

Age	Dose	Schedule
4 through 8 years of age	One or two doses[a], 0.5 mL each	If 2 doses, administer at least 4 weeks apart
9 years of age and older	One dose, 0.5 mL	Not Applicable

[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.

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

Suspension for injection supplied in two presentations:

- 0.5-mL single-dose pre-filled syringes. (3,11)
- 5 mL multi-dose vial containing 10 doses (each dose is 0.5mL). (3,11)

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

History of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine. (4, 11)

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

- If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLUCELVAX QUADRIVALENT should be based on careful consideration of the potential benefits and risks. (5.1)

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

- The most common (≥10%) local and systemic reactions in adults 18-64 years of age were injection site pain (45.4%) headache (18.7%), fatigue (17.8%) and myalgia (15.4%), injection site erythema (13.4%), and induration (11.6%). (6)
- The most common (≥10%) local and systemic reactions in adults ≥65 years of age were injection site pain (21.6%) and injection site erythema (11.9%). (6)
- The most common (≥10%) local and systemic reactions in children 4 to <6 years of age were tenderness at the injection site (46%), injection site erythema (18%), sleepiness (19%), irritability (16%), injection site induration (13%) and change in eating habits (10%). (6)
- The most common (≥10%) local and systemic reactions in children 6 through 8 years of age were pain at the injection site (54%), injection site erythema (22%), injection site induration (16%), headache (14%), fatigue (13%) and myalgia (12%). (6)
- The most common (≥10%) local and systemic reactions in children and adolescents 9 through 17 years of age were pain at the injection site (58%), headache (22%), injection site erythema (19%), fatigue (18%) myalgia (16%), and injection site induration (15%). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Seqirus at 1-855-358-8966 or VAERS at 1800 822 7967 or www.vaers.hhs.gov.

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

- Geriatric Use: Antibody responses were lower in adults 65 years and older than in younger adults. (8.5)
- Pregnancy: There is a pregnancy exposure registry that monitors outcomes in women exposed to FLUCELVAX QUADRIVALENT during pregnancy. Enroll in the pregnancy registry by calling 1-855-358-8966 or sending an email to us.medicalinformation@seqirus.com. (8.1)

See 17 for PATIENT COUNSELING INFORMATION **Revised: 09/2019**

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FLUCELVAX QUADRIVALENT is an inactivated vaccine indicated for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. FLUCELVAX QUADRIVALENT is approved for use in persons 4 years of age and older. For children and adolescents 4 through 17 years of age, approval is based on the immune response elicited by FLUCELVAX QUADRIVALENT. Data demonstrating a decrease in influenza disease after vaccination of this age group with FLUCELVAX QUADRIVALENT are not available. [*see Clinical Studies (14)*]

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Dosage and Schedule

Administer FLUCELVAX QUADRIVALENT as a single 0.5 mL intramuscular injection preferably in the region of the deltoid muscle of the upper arm. Do not inject the vaccine in the gluteal region or areas where there may be a major nerve trunk.

Table 1: Dosage and Schedule

Age	Dose	Schedule
4 through 8 years of age	One or two doses[1], 0.5 mL each	If 2 doses, administer at least 4 weeks apart
9 years of age and older	One dose, 0.5 mL	Not Applicable

[1]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.

2.2 Administration

Shake the syringe vigorously before administering and shake the multi-dose vial preparation each time before withdrawing a dose of vaccine. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. [*see Description (11)*] If either condition exists, do not administer the vaccine. Between uses, return the multi-dose vial to the recommended storage conditions between 2º and 8ºC (36º and 46ºF). **Do not freeze.** Discard if the vaccine has been frozen.

Attach a sterile needle to the pre-filled syringe.

For the multi-dose vial, a separate sterile syringe and needle must be used for each injection to prevent transmission of infectious agents from one person to another. Needles should be disposed of properly and not recapped. It is recommended that small syringes (0.5 mL or 1 mL) should be used to minimize any product loss.

Administer intramuscularly only. Do not administer this product intravenously, intradermally or subcutaneously.

3 DOSAGE FORMS AND STRENGTHS

FLUCELVAX QUADRIVALENT is a suspension for injection supplied in two presentations

- a 0.5 mL single-dose pre-filled Luer Lock syringe
- a 5 mL multi-dose vial containing 10 doses (each dose is 0.5 mL).

4 CONTRAINDICATIONS

Do not administer FLUCELVAX QUADRIVALENT to anyone with a history of severe allergic reaction (e.g. anaphylaxis) to any component of the vaccine [*see Description (11)*].

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

The 1976 swine influenza vaccine was associated with an elevated risk of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case per 1 million persons vaccinated.[1] If GBS has occurred after receipt of a prior influenza vaccine, the decision to give FLUCELVAX QUADRIVALENT should be based on careful consideration of the potential benefits and risks.

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 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including Flucelvax. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope by maintaining a supine or Trendelenburg position.

5.4 Altered Immunocompetence

After vaccination with FLUCELVAX QUADRIVALENT, immunocompromised individuals, including those receiving immunosuppressive therapy, may have a reduced immune response.

5.5 Limitations of Vaccine Effectiveness

Vaccination with FLUCELVAX QUADRIVALENT may not protect all vaccine recipients against influenza disease.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The most common (≥10%) local and systemic reactions in adults 18 through 64 years of age were injection site pain (45.4%), headache (18.7%), fatigue (17.8%) and myalgia (15.4%), injection site erythema (13.4%), and induration (11.6%).

The most common (≥10%) local and systemic reactions in adults ≥65 years of age were injection site pain (21.6%), and injection site erythema (11.9%).

The most common (≥10%) local and systemic reactions in children 4 through 5 years of age after first dose of vaccine were tenderness at the injection site (46%), injection site erythema (18%), sleepiness (19%), irritability (16%), injection site induration (13%) and change in eating habits (10%).

The most common (≥10%) local and systemic reactions in children 6 through 8 years of age after first dose of vaccine were pain at the injection site (54%), injection site erythema (22%), injection site induration (16%), headache (14%), fatigue (13%) and myalgia (12%).

The most common (≥10%) local and systemic reactions in children and adolescents 9 through 17 years of age were pain at the injection site (58%), headache (22%), injection site erythema (19%), fatigue (18%) and myalgia (16%), and injection site induration (15%).

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 clinical studies of another vaccine, and may not reflect rates observed in clinical practice.

Adults 18 years of age and older:

The safety of FLUCELVAX QUADRIVALENT in adults was evaluated in a randomized, double-blind, controlled study conducted in the US (Study 1). The safety population included a total of 2680 adults 18 years of age and older; 1340 adults 18 through 64 years of age and 1340 adults 65 years of age and older.

In this study, subjects received FLUCELVAX QUADRIVALENT or one of the two formulations of comparator trivalent influenza vaccine (TIV1c and TIV2c) (FLUCELVAX QUADRIVALENT (n=1335), TIV1c, n=676 or TIV2c, n= 669). The mean age of subjects who received FLUCELVAX QUADRIVALENT was 57.4 years of age; 54.8% of subjects were female and 75.6% were Caucasian, 13.4% were Black, 9.1% were Hispanics, 0.7% were American Indian and 0.3%, 0.1% and 0.7% were Asian, Native Hawaiian and others, respectively. The safety data observed are summarized in Table 2.

In this study, solicited local injection site and systemic adverse reactions were collected from subjects who completed a symptom diary card for 7 days following vaccination.

Solicited adverse reactions for FLUCELVAX QUADRIVALENT and comparator are summarized in Table 2.

Table 2: Incidence of Solicited Adverse Reactions in the Safety Population[1] Reported Within 7 Days of Vaccination (Study 1)

	18 through 64 years of age			≥ 65 years of age		
	Percentages (%)[2]					
	FLUCELVAX QUADRIVALENT N=663	Trivalent Influenza Vaccine		FLUCELVAX QUADRIVALENT N=656	Trivalent Influenza Vaccine	
		TIV1c N=330	TIV2c N=327		TIV1c N=340	TIV2c N=336
Local Adverse Reactions						
Injection site induration	11.6 (0)	9.7 (0.3)	10.4 (0)	8.7 (0)	6.8 (0)	7.7 (0)
Injection site erythema	13.4 (0)	13.3 (0)	10.1 (0)	11.9 (0)	10.6 (0)	10.4 (0)
Injection site ecchymosis	3.8 (0)	3.3 (0.3)	5.2 (0)	4.7 (0)	4.4 (0)	5.4 (0)
Injection site pain	45.4 (0.5)	37.0 (0.3)	40.7 (0)	21.6 (0)	18.8 (0)	18.5 (0)
Systemic Adverse Reactions						
Chills	6.2 (0.2)	6.4 (0.6)	6.4 (0)	4.4 (0.3)	4.1 (0.3)	4.5 (0.6)
Nausea	9.7 (0.3)	7.3 (0.9)	8.9 (1.2)	3.8 (0.2)	4.1 (0)	4.2 (0.3)
Myalgia	15.4 (0.8)	14.5 (0.9)	15.0 (1.2)	8.2 (0.2)	9.4 (0.3)	8.3 (0.6)
Arthralgia	8.1 (0.5)	8.2 (0)	9.5 (0.9)	5.5 (0.5)	5.0 (0.3)	6.8 (0.9)
Headache	18.7 (0.9)	18.5 (0.9)	18.7 (0.6)	9.3 (0.3)	8.5 (0.6)	8.3 (0.6)
Fatigue	17.8 (0.6)	22.1 (0.3)	15.6 (1.5)	9.1 (0.8)	10.6 (0.3)	8.9 (0.6)
Vomiting	2.6 (0)	1.5 (0.3)	0.9 (0)	0.9 (0.2)	0.3 (0)	0.6 (0)
Diarrhea	7.4 (0.6)	7.6 (0)	7.6 (0.6)	4.3 (0.5)	5.0 (0.9)	5.1 (0.3)
Loss of appetite	8.3 (0.3)	8.5 (0.3)	8.3 (0.9)	4.0 (0.2)	5.0 (0)	3.6 (0.3)
Fever: ≥38.0 °C (≥40.0°C)	0.8 (0)	0.6 (0)	0.3 (0)	0.3 (0)	0.9 (0)	0.6 (0)

[1] Safety population: all subjects in the exposed population who provided post-vaccination safety data

[2] Percentage of severe adverse reactions are presented in parenthesis

Study 1: NCT01992094

Unsolicited adverse events were collected for 21 days after vaccination. In adults 18 years of age and older, unsolicited adverse events were reported in 16.1% of subjects who received FLUCELVAX QUADRIVALENT, within 21 days after vaccination.

In adults 18 years of age and older, serious adverse events (SAEs) were collected throughout the study duration (until 6 months after vaccination) and were reported by 3.9%, of the subjects who received FLUCELVAX QUADRIVALENT. None of the SAEs were assessed as being related to study vaccine.

Children and Adolescents 4 through 17 years of age:

The safety of FLUCELVAX QUADRIVALENT in children was evaluated in a randomized, double-blind, controlled study conducted in the US (Study 2). The safety population included a total of 2332 children 4 through 17 years of age; 1161 children 4 through 8 years of age and 1171 children 9 through 17 years of age.

In this study, subjects received FLUCELVAX QUADRIVALENT or one of the two formulations of comparator trivalent influenza vaccine (FLUCELVAX QUADRIVALENT n=1159, TIV1c, n=593 or TIV2c, n= 580). Children 9 through 17 years of age received a single dose of FLUCELVAX QUADRIVALENT or comparator vaccine. Children 4 through 8 years of age received one or two doses (separated by 4 weeks) of FLUCELVAX QUADRIVALENT or comparator vaccine based on determination of the subject's prior influenza vaccination history. The mean age of subjects who received FLUCELVAX QUADRIVALENT was 9.6 years of age; 48% of subjects were female and 53% were Caucasian. The safety data observed are summarized in Table 3 and Table 4.

In this study, solicited local injection site and systemic adverse reactions were collected from subjects who completed a symptom diary card for 7 days following vaccination.

Solicited adverse reactions for FLUCELVAX QUADRIVALENT and comparator are summarized in Table 3 and Table 4.

Table 3: Incidence of Solicited Adverse Reactions in the Safety Population[1] (4 through 5 years of age) Reported Within 7 Days of the First dose of Vaccination (Study 2)

	Children 4 through 5 years		
	Percentages (%)[2]		
	FLUCELVAX QUADRIVALENT N=182	Trivalent Influenza Vaccine	
		TIV1c N=91	TIV2c N=93
Local Adverse Reactions			
Injection site induration	13 (1)	20 (2)	13 (0)
Injection site erythema	18 (1)	23 (1)	17 (0)
Injection site ecchymosis	9 (0)	11 (0)	8 (0)
Injection site tenderness	46 (1)	45 (1)	43 (0)
Systemic Adverse Reactions			
Change in eating habits	10 (1)	7	6
Sleepiness	19 (1)	12 (3)	10 (0)
Irritability	16 (2)	10 (2)	10 (1)
Chills	5 (1)	2 (0)	1 (0)
Vomiting	4 (0)	2 (0)	2 (0)
Diarrhea	4 (0)	2 (0)	2 (0)
Fever: ≥38.0 °C (≥40.0 °C)	4 (0)	4 (0)	3 (0)

[1] Safety population: all subjects in the exposed population who provided post-vaccination safety data.

[2] Percentage of subjects with severe adverse reactions are presented in parenthesis.

Study 2: NCT01992107

Table 4: Incidence of Solicited Adverse Reactions in the Safety Population[1] (Children 6 through 17 years of age) Reported Within 7 Days of Vaccination (Study 2)

	Children 6 through 8 years (after first dose)			Children 9 through 17 years		
	Percentages (%)[2]					
	FLU-CELVAX QUADRI-VALENT N=371-372	Trivalent Influenza vaccine		FLU-CELVAX QUADRI-VALENT N=579	Trivalent Influenza Vaccine	
		TIV1c N=185	TIV2c N=186		TIV1c N=294	TIV2c N=281-282
Local Adverse Reactions						
Injection site induration	16 (0)	19 (1)	13 (0)	15 (0)	15 (0)	13 (<1)
Injection site erythema	22 (0)	23 (1)	20 (0)	19 (<1)	17 (0)	15 (<1)
Injection site ecchymosis	9 (0)	9 (0)	8 (0)	4 (0)	5 (0)	5 (0)
Injection site pain	54 (1)	57 (1)	58 (2)	58 (1)	51(<1)	50 (0)
Systemic Adverse Reactions						
Chills	4 (1)	3 (0)	4 (0)	7 (0)	6 (1)	4 (1)
Nausea	8 (1)	5 (0)	5 (1)	9 (<1)	8 (1)	7 (1)
Myalgia	12 (1)	14 (0)	10 (0)	16 (<1)	17 (<1)	15 (<1)
Arthralgia	4 (0)	5 (0)	4 (0)	6 (0)	6 (0)	8 (<1)
Headache	14 (1)	13 (0)	12 (0)	22 (1)	23 (2)	18 (1)
Fatigue	13 (2)	14 (0)	18 (0)	18 (<1)	16 (1)	16 (<1)
Vomiting	3 (1)	3 (0)	3 (0)	2 (0)	1 (0)	2 (0)
Diarrhea	3 (<1)	6 (1)	5 (0)	4 (0)	4 (0)	3 (<1)
Loss of appetite	9 (<1)	5 (0)	8 (1)	9 (0)	9 (<1)	9 (0)
Fever: ≥38.0 °C (≥40.0 °C)	4 (0)	3 (0)	2 (0)	1 (<1)	3 (0)	1 (0)

[1]Safety population: all subjects in the exposed population who provided post-vaccination safety data.

[2]Percentage of subjects with severe adverse reactions are presented in parenthesis.

Study 2: NCT 01992107

In children who received a second dose of FLUCELVAX QUADRIVALENT, TIV1c, or TIV2c, the incidence of adverse reactions following the second dose of vaccine were similar to those observed with the first dose.

Unsolicited adverse events were collected for 21 days after last vaccination. In children 4 through 17 years of age, unsolicited adverse events were reported in 24.3% of subjects who received FLUCELVAX QUADRIVALENT, within 3 weeks after last vaccination.

In children 4 through 17 years of age, serious adverse events (SAEs) were collected throughout the study duration (until 6 months after last vaccination) and were reported by 0.5% of the subjects who received FLUCELVAX QUADRIVALENT. None of the SAEs were assessed as being related to study vaccine.

6.2 Postmarketing Experience

The following additional adverse events have been identified during post-approval use of FLUCELVAX QUADRIVALENT. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Immune system disorders: Allergic or immediate hypersensitivity reactions, including anaphylactic shock.

Nervous systems disorders: Syncope, presyncope, paresthesia.

Skin and subcutaneous tissue disorders: Generalized skin reactions including pruritus, urticaria or non-specific rash.

General disorders and administration site conditions: Extensive swelling of injected limb.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FLUCELVAX QUADRIVALENT during pregnancy. Women who are vaccinated with FLUCELVAX QUADRIVALENT during pregnancy are encouraged to enroll in the registry by calling 1-855-358-8966 or sending an email to Seqirus at us.medicalinformation@seqirus.com.

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 insufficient data for FLUCELVAX QUADRIVALENT in pregnant women to inform vaccine-associated risks in pregnancy.

There were no developmental toxicity studies of FLUCELVAX QUADRIVALENT performed in animals. A developmental toxicity study has been performed in female rabbits administered FLUCELVAX (trivalent formulation) prior to mating and during gestation. The dose was 0.5 mL on each occasion (a single human dose is 0.5 mL). This study revealed no evidence of harm to the fetus due to FLUCELVAX (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 rabbits were administered of FLUCELVAX (trivalent formulation) by intramuscular injection 1, 3, and 5 weeks prior to mating, and on gestation days 7 and 20. The dose was 0.5 mL on each occasion (a single human dose is 0.5 mL). No vaccine-related fetal malformations or variations and no adverse effects on pre-weaning development were observed in the study.

8.2 Lactation

Risk Summary

It is not known whether FLUCELVAX QUADRIVALENT is excreted in human milk. Data are not available to assess the effects of FLUCELVAX 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 FLUCELVAX QUADRIVALENT and any potential adverse effects on the breastfed child from FLUCELVAX 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

Safety and effectiveness have not been established in children less than 4 years of age.

8.5 Geriatric Use

Of the total number of subjects who received one dose of FLUCELVAX QUADRIVALENT in clinical studies and included in the safety population (2493), 26.47% (660) were 65 years of age and older and 7.7% (194) were 75 years of age or older.

Antibody responses to FLUCELVAX QUADRIVALENT were lower in the geriatric (adults 65 years and older) population than in younger subjects. [*see Clinical Studies (14.3)*]

11 DESCRIPTION

FLUCELVAX QUADRIVALENT (Influenza Vaccine) is a subunit influenza vaccine manufactured using cell derived candidate vaccine viruses (CVV) that are propagated in Madin Darby Canine Kidney (MDCK) cells, a continuous cell line. These cells were adapted to grow freely in suspension in culture medium. The virus is inactivated with ß-propiolactone, disrupted by the detergent cetyltrimethylammonium bromide and purified through several process steps. Each of the 4 virus strains is produced and purified separately then pooled to formulate the quadrivalent vaccine.

FLUCELVAX QUADRIVALENT is a sterile, slightly opalescent suspension in phosphate buffered saline. FLUCELVAX QUADRIVALENT is standardized according to United States Public Health Service requirements for the 2019-2020 influenza season and is formulated to contain a total of 60 micrograms (mcg) hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 mcg HA of each of the following four influenza strains:

A/Idaho/07/2018 (an A/Brisbane/02/2018 (H1N1)pdm09-like virus)

A/Indiana/08/2018 (an A/Kansas/14/2017 (H3N2)-like virus)

B/Iowa/06/2017 (a B/Colorado/06/2017-like virus)

B/Singapore/INFTT-16-0610/2016 (a B/Phuket/3073/2013-like virus)

Each dose of FLUCELVAX QUADRIVALENT may contain residual amounts of MDCK cell protein (≤ 25.2 mcg), protein other than HA (≤ 240 mcg), MDCK cell DNA (≤ 10 ng), polysorbate 80 (≤ 1500 mcg), cetyltrimethlyammonium bromide (≤ 18 mcg), and ß-propiolactone (<0.5 mcg), which are used in the manufacturing process.

FLUCELVAX QUADRIVALENT contains no egg protein or antibiotics.

FLUCELVAX QUADRIVALENT 0.5 mL pre-filled syringes contain no preservative.

FLUCELVAX QUADRIVALENT 5 mL multi-dose vials contain thimerosal, a mercury derivative, added as a preservative. Each 0.5 mL dose from the multi-dose vial contains 25 mcg mercury.

The tip caps and plungers of the prefilled syringes and the multi-dose vial stopper are 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 and analysis of influenza virus isolates permits identification of yearly antigenic variants. Since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. Specific levels of hemagglutination inhibition (HI) antibody titers induced by vaccination with inactivated influenza virus vaccine have not been correlated with protection from influenza illness. In some studies, HI antibody titers of ≥1:40 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 little 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 of one or more strains in each year's influenza vaccine. Therefore, inactivated influenza vaccines are standardized to contain the hemagglutinin of influenza virus strains representing the influenza viruses likely to circulate in the United States in the upcoming winter.

Annual influenza vaccination is recommended by the Advisory Committee on Immunization Practices because immunity declines during the year after vaccination, and because circulating strains of influenza virus change from year to year.[4]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

FLUCELVAX QUADRIVALENT has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility in animals.

FLUCELVAX (trivalent formulation) administered to female rabbits had no effect on fertility [*see Use in Specific Population (8.1)*]

14 CLINICAL STUDIES

14.1 Efficacy against Culture-Confirmed Influenza

The efficacy experience with FLUCELVAX is relevant to FLUCELVAX QUADRIVALENT because both vaccines are manufactured using the same process and have overlapping compositions.

A multinational (US, Finland, and Poland), randomized, observer-blind, placebo-controlled trial was performed to assess clinical efficacy and safety of FLUCELVAX during the 2007-2008 influenza season in adults aged 18 through 49 years. A total of 11,404 subjects were enrolled to receive FLUCELVAX (N=3828), AGRIFLU (N=3676) or placebo (N=3900) in a 1:1:1 ratio. Among the overall study population enrolled, the mean age was 33 years, 55% were female, 84% were Caucasian, 7% were Black, 7% were Hispanic, and 2% were of other ethnic origin.

FLUCELVAX efficacy was assessed by the prevention of culture-confirmed symptomatic influenza illness caused by viruses antigenically matched to those in the vaccine and prevention of influenza illness caused by all influenza viruses compared to placebo. Influenza cases were identified by active and passive surveillance of influenza-like illness (ILI). ILI was defined as a fever (oral temperature ≥100.0°F / 38°C) and cough or sore throat. Nose and throat swab samples were collected for analysis within 120 hours of onset of an influenza-like illness in the period from 21 days to 6 months after vaccination. Overall vaccine efficacy against all influenza viral subtypes and vaccine efficacy against individual influenza viral subtypes were calculated (Tables 5 and 6, respectively).

Table 5: Vaccine Efficacy against Culture-Confirmed Influenza

	Number of subjects per protocol	Number of subjects with influenza	Attack Rate (%)	Vaccine Efficacy (VE)[1,2]	
				%	Lower Limit of One- Sided 97.5% CI of VE[2, 3]
Antigenically Matched Strains					
FLUCELVAX	3776	7	0.19	83.8	61.0
Placebo	3843	44	1.14	--	--
All Culture-Confirmed Influenza					
FLUCELVAX	3776	42	1.11	69.5	55.0
Placebo	3843	140	3.64	--	--

[1]Efficacy against influenza was evaluated over a 9-month period in 2007/2008

[2]Simultaneous one-sided 97.5% confidence intervals for the vaccine efficacy (VE) of FLUCELVAX relative to placebo based on the Sidak-corrected score confidence intervals for the relative risk. Vaccine Efficacy = (1 - Relative Risk) x 100 %

[3]VE success criterion: the lower limit of the one-sided 97.5% CI for the estimate of the VE relative to placebo is >40%

Study: NCT00630331

Table 6: Efficacy of FLUCELVAX against Culture-Confirmed Influenza by Influenza Viral Subtype

	FLUCELVAX (N=3776)		Placebo (N=3843)		Vaccine Efficacy (VE)[2]	
	Attack Rate (%)	Number of Subjects with Influenza	Attack Rate (%)	Number of Subjects with Influenza	%	Lower Limit of One-Sided 97.5% CI of VE[1,2]
Antigenically Matched Strains						
A/H3N2[3]	0. 05	2	0	0	--	--
A/H1N1	0.13	5	1.12	43	88.2	67.4
B[3]	0	0	0.03	1	--	--
All Culture-Confirmed Influenza						
A/H3N2	0.16	6	0.65	25	75.6	35.1
A/H1N1	0.16	6	1.48	57	89.3	73.0
B	0.79	30	1.59	61	49.9	18.2

[1]No VE success criterion was prespecified in the protocol for each individual influenza virus subtype.

[2]Simultaneous one-sided 97.5% confidence intervals for the vaccine efficacy (VE) of FLUCELVAX relative to placebo based on the Sidak-corrected score confidence intervals for the relative risk. Vaccine Efficacy = (1 - Relative Risk) x 100 %;

[3]There were too few cases of influenza due to vaccine-matched influenza A/H3N2 or B to adequately assess vaccine efficacy.

Study: NCT00630331

There are no data demonstrating prevention of influenza disease after vaccination with FLUCELVAX in the pediatric age group.

14.2 Immunogenicity of FLUCELVAX QUADRIVALENT in Adults 18 years of age and above

Immunogenicity of FLUCELVAX QUADRIVALENT was evaluated in adults 18 years of age and older in a randomized, double-blind, controlled study conducted in the US (Study 1). In this study, subjects received FLUCELVAX QUADRIVALENT or one of the two formulations of comparator trivalent influenza vaccine (FLUCELVAX QUADRIVALENT (N=1334), TIV1c, N=677 or TIV2c, N= 669). In the per protocol set, the mean age of subjects who received FLUCELVAX QUADRIVALENT was 57.5 years; 55.1% of subjects were female and 76.1% of subjects were Caucasian, 13% were black and 9% were Hispanics. The immune response to each of the vaccine antigens was assessed, 21 days after vaccination.

The immunogenicity endpoints were geometric mean antibody titers (GMTs) of hemagglutination inhibition (HI) antibodies response and percentage of subjects who achieved seroconversions, defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥1:40 or a pre-vaccination HI titer >1:10 and at least 4-fold increase in serum HI antibody titer.

FLUCELVAX QUADRIVALENT was noninferior to TIVc. Noninferiority was established for all 4 influenza strains included in the QIVc, as assessed by ratios of GMTs and the differences in the percentages of subjects achieving seroconversion at 3 weeks following vaccination. The antibody response to influenza B strains contained in FLUCELVAX QUADRIVALENT was superior to the antibody response after vaccination with TIVc containing an influenza B strain from the alternate lineage. There was no evidence that the addition of the second influenza B strain resulted in immune interference to other strains included in the vaccine. (See Table 7)

Table 7: Noninferiority of FLUCELVAX QUADRIVALENT relative to TIVc in adults 18 Years of Age and Above– Per Protocol Analysis Set [Study 1]

		FLUCELVAX QUADRIVALENT N = 1250	TIV1c/TIV2c[1] N = 635/N =639	Vaccine Group Ratio (95% CI)	Vaccine Group Difference (95% CI)
A/H1N1	GMT (95% CI)	302.8 (281.8-325.5)	298.9 (270.3-330.5)	1.0 (0.9-**1.1**)	-
	Seroconversion Rate[2] (95% CI)	49.2% (46.4-52.0)	48.7% (44.7-52.6)	-	-0.5% (-5.3-**4.2**)
A/H3N2	GMT (95% CI)	372.3 (349.2-396.9)	378.4 (345.1-414.8)	1.0 (0.9-**1.1**)	-
	Seroconversion Rate[2] (95% CI)	38.3% (35.6-41.1)	35.6% (31.9-39.5)	-	-2.7% (-7.2-**1.9**)
B1	GMT (95% CI)	133.2 (125.3-141.7)	115.6 (106.4-125.6)	0.9 (0.8-**1.0**)	-
	Seroconversion Rate[2] (95% CI)	36.6% (33.9-39.3)	34.8% (31.1-38.7)	-	-1.8% (-6.2-**2.8**)
B2	GMT (95% CI)	177.2 (167.6-187.5)	164.0 (151.4-177.7)	0.9 (0.9-**1.0**)	-
	Seroconversion Rate[2] (95% CI)	39.8% (37.0-42.5)	35.4% (31.7-39.2)	-	-4.4% (-8.9-**0.2**)

Abbreviations: HI = hemagglutination inhibition. PPS = per protocol set. GMT = geometric mean titer. CI = confidence interval.

[1]Per protocol set: All subjects in Full Analysis Set, immunogenicity population, who has correctly received the assigned vaccine, have no major protocol deviations leading to exclusion as defined prior to unblinding/ analysis and are not excluded due to other reasons defined prior to unblinding or analysis.

[2]The comparator vaccine for noninferiority comparisons for A/H1N1, A/H3N2 and B1 is TIV1c, for B2 it is TIV2c.

[3]Seroconversion rate = percentage of subjects with either a pre-vaccination HI titer < 1:10 and post-vaccination HI titer ≥ 1:40 or with a pre-vaccination HI titer ≥ 1:10 and a minimum 4-fold increase in post-vaccination HI antibody titer

Study 1: NCT01992094

14.3 Immunogenicity in Children and Adolescents 4 through 17 years of age

Immunogenicity of FLUCELVAX QUADRIVALENT was evaluated in children 4 through 17 years of age in a randomized, double-blind, controlled study conducted in the US (Study 2). (See section 6.1) In this study, 1159 subjects received FLUCELVAX QUADRIVALENT.

In the per protocol set, the mean age of subjects who received FLUCELVAX QUADRIVALENT was 9.8 years; 47% of subjects were female and 54% of subjects were Caucasian, 22% were black and 19% were Hispanics. The immune response to each of the vaccine antigens was assessed, 21 days after vaccination.

The immunogenicity endpoints were the percentage of subjects who achieved seroconversion, defined as a pre-vaccination hemagglutination inhibition (HI) titer of <1:10 with a post-vaccination HI titer ≥1:40 or at least a 4-fold increase in serum HI titer; and percentage of subjects with a post-vaccination HI titer ≥1:40.

In subjects receiving FLUCELVAX QUADRIVALENT, for all four influenza strains, the 95% LBCI seroconversion rates were ≥40% and the percentage of subjects who achieved HI titer ≥1:40 post vaccination were ≥70% (95% LBCI). (See Table 8)

Table 8: The Percentage of Children and Adolescents 4 through 17 years of Age with Seroconversion[1] and HI Titers ≥ 1:40 post vaccination with FLUCELVAX QUADRIVALENT– Per-Protocol Analysis Set[2] [Study 2]

		FLUCELVAX QUADRIVALENT
A/H1N1		N = 1014
	Seroconversion Rate[1] (95% CI)	72% (69-75)
	HI titer≥1:40	99% (98-100)
A/H3N2		N = 1013
	Seroconversion Rate[1] (95% CI)	47% (44-50)
	HI titer≥1:40	100% (99-100)
B1		N = 1013
	Seroconversion Rate[1] (95% CI)	66% (63-69)
	HI titer≥1:40	92% (91-94)
B2		N = 1009
	Seroconversion Rate[1] (95% CI)	73% (70-76)
	HI titer≥1:40	91% (89-93)

Abbreviations: HI = hemagglutinin inhibition. CI = confidence interval.

Analyses are performed on data for day 22 for previously vaccinated subjects and day 50 for not previously vaccinated subjects.

[1] Seroconversion rate = percentage of subjects with either a pre-vaccination HI titer < 1:10 and post-vaccination HI titer ≥ 1:40 or with a pre-vaccination HI titer ≥ 1:10 and a minimum 4-fold increase in post-vaccination HI titer. Immunogenicity success criteria were met if the lower limit of the 95% confidence interval (CI) of the percentage of subjects with HI titer ≥1:40 is ≥70%; and the lower limit of the 95% CI of the percentage of subjects with seroconversion is ≥40%.

[2]Per protocol set: All subjects in Full Analysis Set, immunogenicity population, who has correctly received the assigned vaccine, have no major protocol deviations leading to exclusion as defined prior to unblinding/ analysis and are not excluded due to other reasons defined prior to unblinding or analysis.

Study 2: NCT 01992107

15 REFERENCES

1. Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barré syndrome and the 1992-1993 and 1993-1994 influenza vaccines. *N Engl J Med* 1998; 339(25):1797-1802.
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 A, etal. The role of serum hemagglutinin-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. *J Hyg Camb* 1972; 767-777.
4. Centers for Disease Control and Prevention. Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011; 60(33): 1128-1132.

16 HOW SUPPLIED / STORAGE AND HANDLING

FLUCELVAX QUADRIVALENT product presentations are listed in Table 9 below:

Table 9: Flucelvax Product Presentations

Presentation	Carton NDC Number	Components
Pre-filled Syringe	70461-319-03	0.5 mL single dose pre-filled syringe, package of 10 syringes per carton [NDC 70461-319-04]
Multi-dose Vial	70461-419-10	5 mL multi-dose vial, individually packaged in a carton [NDC 70461-419-11]

Store this product refrigerated at 2°C to 8°C (36°F to 46°F). Between uses, return the multi-dose vial to the recommended storage conditions. Do not freeze. Protect from light. Do not use after the expiration date.

17 PATIENT COUNSELING INFORMATION

Inform vaccine recipients of the potential benefits and risks of immunization with FLUCELVAX QUADRIVALENT.

Educate vaccine recipients regarding the potential side effects; clinicians should emphasize that (1) FLUCELVAX QUADRIVALENT contains non-infectious particles and cannot cause influenza and (2) FLUCELVAX QUADRIVALENT is intended to provide protection against illness due to influenza viruses only, and cannot provide protection against other respiratory illnesses.

Instruct vaccine recipients to report adverse reactions to their healthcare provider.

Encourage women who receive FLUCELVAX QUADRIVALENT while pregnant to enroll in the pregnancy registry. Pregnant women can enroll in the pregnancy registry by calling 1-855-358-8966 or sending an email to Seqirus at us.medicalinformation@seqirus.com.

Provide vaccine recipients with the Vaccine Information Statements which are required by the National Childhood Vaccine Injury Act of 1986. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

Inform vaccine recipients that annual vaccination is recommended.

FLUCELVAX QUADRIVALENT is a registered trademark of Seqirus UK Limited or its affiliates.

Seqirus™
A CSL COMPANY

Manufactured by: **Seqirus Inc.**
Holly Springs, NC 27540, USA
US License No. 2049
Distributed by: **Seqirus USA Inc.** 25 Deforest Avenue, Summit, NJ 07901, USA
1-855-358-8966

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
2019-2020 Formula
Initial U.S. Approval (AFLURIA QUADRIVALENT): 2016

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	10/2018
Dosage and Administration (2)	10/2018

----------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 6 months of age and older. (1)

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

For intramuscular injection only, by needle and syringe (6 months and older) or by PharmaJet®Stratis® Needle-Free Injection System (18 through 64 years). (2)

Age	Dose	Schedule
6 months through 35 months	One or two doses[a], 0.25 mL each	If 2 doses, administer at least 1 month apart
36 months through 8 years	One or two doses[a], 0.5 mL each	If 2 doses, administer at least 1 month apart
9 years and older	One dose, 0.5 mL	Not Applicable

[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 QUADRIVALENT is a suspension for injection supplied in three presentations:

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

AFLURIA QUADRIVALENT administered by needle and syringe:

- In adults 18 through 64 years, the most commonly reported injection-site adverse reaction 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 was pain (≥ 20%). The most common systemic adverse event was myalgia (≥ 10%). (6.1)
- In children 5 through 8 years, the most commonly reported injection-site adverse reactions were pain (≥ 50%), redness and swelling (≥ 10%). The most common systemic adverse event was headache (≥ 10%). (6.1)
- In children 9 through 17 years, the most commonly reported injection-site adverse reactions were pain (≥ 50%), redness and swelling (≥ 10%). The most common systemic adverse events were headache, myalgia, and malaise and fatigue (≥ 10%). (6.1)
- In children 6 months through 35 months of age, the most commonly reported injection-site reactions were pain and redness (≥ 20%).The most common systemic adverse events were irritability (≥ 30%), diarrhea and loss of appetite (≥ 20%). (6.1)
- In children 36 through 59 months of age, the most commonly reported injection site reactions were pain (≥ 30%) and redness (≥ 20%). The most commonly reported systemic adverse events were malaise and fatigue, and diarrhea (≥ 10%). (6.1)

AFLURIA (trivalent formulation) administered by the PharmaJet Stratis Needle-Free Injection System:

- In adults 18 through 64 years of age, the most commonly reported injection-site adverse reactions 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 USA Inc. at 1-855-358-8966 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

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

- The safety and effectiveness of AFLURIA QUADRIVALENT in persons less than 6 months of age have not been established. (8.4)
- Antibody responses were lower in geriatric subjects than in younger adults. (8.5)
- Pregnancy: There is a pregnancy exposure registry that monitors outcomes in women exposed to AFLURIA QUADRIVALENT during pregnancy. Enroll in the pregnancy registry by calling 1-855-358-8966 or sending an email to us.medicalinformation@seqirus.com. (8.1).

See 17 for PATIENT COUNSELING INFORMATION **Revised: 03/2019**

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 6 months of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular (IM) use only.

- By needle and syringe (6 months of age and older)
- By PharmaJet® Stratis® Needle-Free Injection System (18 through 64 years of age)

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

Table 1: AFLURIA QUADRIVALENT Dosage and Schedule

Age	Dose	Schedule
6 months through 35 months	One or two doses[a], 0.25 mL each	If 2 doses, administer at least 1 month apart
36 months through 8 years	One or two doses[a], 0.5 mL each	If 2 doses, administer at least 1 month apart
9 years and older	One dose, 0.5 mL	Not Applicable

[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.

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.

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. No more than 10 doses (0.25 mL or 0.5 mL) should be withdrawn from the multi-dose vial.

- 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 sites for intramuscular injection are the anterolateral aspect of the thigh in infants 6 months through 11 months of age, the anterolateral aspect of the thigh (or the deltoid muscle of the upper arm if muscle mass is adequate) in persons 12 months through 35 months of age, or the deltoid muscle of the upper arm in persons ≥ 36 months of age.

3 DOSAGE FORMS AND STRENGTHS

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

AFLURIA QUADRIVALENT is supplied in three presentations:

- 0.25 mL pre-filled syringe (single dose, for persons 6 months through 35 months of age)
- 0.5 mL pre-filled syringe (single dose, for persons 36 months of age and older).
- 5 mL multi-dose vial (for persons 6 months of age and older).

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%).

In children 5 through 8 years, the most commonly reported injection-site adverse reactions when AFLURIA QUADRIVALENT was administered by needle and syringe were pain (≥ 50%) and redness and swelling (≥ 10%). The most common systemic adverse event was headache (≥ 10%).

In children 9 through 17 years, the most commonly reported injection-site adverse reactions when AFLURIA QUADRIVALENT was administered by needle and syringe were pain (≥ 50%) and redness and swelling (≥ 10%). The most common systemic adverse events were headache, myalgia, and malaise and fatigue (≥ 10%).

In children 6 months through 35 months of age, the most frequently reported injection site reactions in the clinical study with AFLURIA QUADRIVALENT administered by needle and syringe were pain and redness (≥ 20%). The most common systemic adverse events were irritability (≥ 30%), diarrhea and loss of appetite (≥ 20%).

In children 36 through 59 months of age, the most commonly reported injection site reactions were pain (≥ 30%) and redness (≥ 20%). The most commonly reported systemic adverse events were malaise and fatigue, and diarrhea (≥ 10%).

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.

Adults

Clinical safety data for AFLURIA QUADRIVALENT in adults have been collected in one clinical trial, Study 1, a randomized, double-blind, active-controlled trial conducted in the U.S. 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 2). 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 2: 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
Head-ache	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 (Oral), Grade 3 = ≥ 102.2°F (Oral); 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 2.

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 3).

Table 3: 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			
	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 (Oral), Grade 3 = ≥ 102.2°F (Oral); 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 by 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%).

Children 5 Years Through 17 Years of Age

Clinical safety data for AFLURIA QUADRIVALENT in older children and adolescents have been collected in one clinical trial, Study 3, a randomized, observer-blinded, comparator-controlled trial conducted in the U.S. in 2278 subjects aged 5 through 17 years. Subjects were stratified into one of two age cohorts of 5 through 8 years or 9 through 17 years (51.2% and 48.8% of the study population, respectively). The mean age of the population was 9.5 years, 52.1% were male, and racial groups consisted of 73.3% White, 20.7% Black, 0.8% Asian, 0.3% American Indian/Native American, and 0.7% Native Hawaiian/Pacific Islander; 23.8% of subjects were Hispanic/Latino. The mean ages of subjects 5 through 8 years and 9 through 17 years were 6.7 years and 12.5 years, respectively. Subjects in the safety population (N=2252) received either AFLURIA QUADRIVALENT (N=1692) or a U.S.-licensed comparator quadrivalent influenza vaccine (N=560). Study subjects were scheduled to receive either a single vaccination or two vaccinations 28 days apart based on their previous vaccination history. In this study, AFLURIA QUADRIVALENT and comparator vaccine 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. Cellulitis-like reactions (defined as concurrent Grade 3 pain, redness, and swelling/lump) at the injection site were monitored for 28 days post-vaccination. Subjects were instructed to report and return to clinic within 24 hours in the event of a cellulitis-like reaction. Unsolicited adverse events were collected for 28 days post-vaccination. All solicited local adverse reactions and systemic adverse events following any vaccination (first or second dose) are presented in Table 4.

Table 4: 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 Comparator (Study 3)[a]

	Percentage (%) [b] of Subjects in each Age Cohort Reporting an Event							
	Subjects 5 through 8 years				Subjects 9 through 17 years			
	AFLURIA Quadrivalent N= 828-829 [c]		Comparator N= 273-274 [c]		AFLURIA Quadrivalent N= 790-792 [c]		Comparator N= 261 [c]	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
Local Adverse Reactions [d]								
Pain	51.3	0.8	49.6	0.7	51.5	0.3	45.2	0.4
Redness	19.4	3.5	18.6	1.8	14.8	1.9	16.1	1.9
Swelling/Lump	15.3	3.4	12.4	2.2	12.2	2.0	10.7	1.9
Systemic Adverse Events [e]								
Headache	12.3	0.1	10.6	0.4	18.8	0.4	14.6	0.4
Myalgia	9.8	0.1	11.3	0.4	16.7	0.3	11.1	0.4
Malaise and Fatigue	8.8	0.4	5.8	0	10.0	0.4	7.7	0
Nausea	7.1	0.1	8.4	0	7.7	0	8.0	0
Diarrhea	5.2	0	3.6	0	5.4	0	4.2	0
Fever	4.5	1.2	3.6	0.7	2.1	0.5	0.8	0
Vomiting	2.4	0.2	4.4	0	1.8	0	2.3	0

Abbreviations: Gr 3, Grade 3 (severe); Comparator, Comparator quadrivalent influenza vaccine [Fluarix® Quadrivalent (GlaxoSmithKline Biologicals)]

[a] NCT02545543

[b] Percent (%) is derived from the number of subjects that reported the event divided by the number of subjects in the Solicited Safety Population with non-missing data for each age cohort, treatment group, and each solicited parameter.

[c] N = number of subjects in the Solicited Safety Population (subjects who were vaccinated and provided any solicited safety data) for each study vaccine group.

[d] Local adverse reactions: Grade 3 pain is that which prevents daily activity; swelling/lump and redness: any = > 0mm diameter, Grade 3 = > 30mm diameter.

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

In subjects 5 through 8 years of age, all solicited local adverse reactions and systemic adverse events were reported at lower frequencies after the second vaccination than after the first vaccination with AFLURIA QUADRIVALENT with the exception of vomiting (which occurred at the same rate of 2.2% after each vaccination).

One subject, 8 years of age, experienced a cellulitis-like reaction at the injection site after vaccination with AFLURIA QUADRIVALENT.

The most commonly reported unsolicited adverse events in the 28 days following the first or second dose of AFLURIA QUADRIVALENT in subjects 5 through 8 years of age were cough (2.4%), pyrexia (1.8%), rhinorrhea (1.2%), and headache (1.0%), and were similar to the comparator.

For subjects ages 9 through 17 years who received AFLURIA QUADRIVALENT, the most commonly reported unsolicited adverse events in the 28 days following vaccination were oropharyngeal pain (1.6%), cough (1.3%), and upper respiratory tract infection (1.0%), and were similar to the comparator.

No deaths were reported in Study 3. In the 180 days following vaccinations, AFLURIA QUADRIVALENT and comparator vaccine recipients experienced similar rates of serious adverse events (SAEs). None of the SAEs appeared related to the study vaccines except for one case of influenza B infection (considered a vaccine failure) in an AFLURIA QUADRIVALENT recipient.

Children 6 Months Through 59 Months of Age

Clinical safety data for AFLURIA QUADRIVALENT in infants and young children have been collected in one clinical trial, Study 4, a randomized, observer-blind, comparator-controlled trial conducted in the U.S. in 2247 subjects aged 6 through 59 months. Subjects were stratified into one of two age cohorts of 6 through 35 months or 36 through 59 months (41.6% and 58.4% of the study population, respectively). The mean age of the population was 36.6 months, 51.6% were male, and racial groups consisted of 71.0% White, 21.5% Black, 1.1% Asian, 0.7% Native Hawaiian/Pacific Islander, and 0.3% American Indian/Native American; 26.4% of subjects were Hispanic/Latino. The mean ages of subjects 6 through 35 months and 36 through 59 months were 21.7 months and 47.1 months, respectively. Subjects in the safety population (N=2232) received either AFLURIA QUADRIVALENT (N=1673) or a U.S.-licensed comparator quadrivalent influenza vaccine (N=559). Study subjects were scheduled to receive either a single vaccination or two vaccinations 28 days apart based on their previous vaccination history. In this study, AFLURIA QUADRIVALENT and comparator vaccine 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. Cellulitis-like reactions (defined as concurrent Grade 3 pain, redness, and swelling/lump) at the injection site were monitored for 28 days post-vaccination. Subjects were instructed to report and return to clinic within 24 hours in the event of a cellulitis-like reaction. Unsolicited adverse events were collected for 28 days post-vaccination, and SAEs for 6 months following the last vaccination. All solicited local adverse reactions and systemic adverse events following any vaccination (first or second dose) are presented in Table 5.

Table 5: 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 Comparator QIV (Study 4)[a]

	Percentage (%) [b] of Subjects in each Age Cohort Reporting an Event							
	6 through 35 months				36 through 59 months			
	AFLURIA Quadrivalent N= 668-669 [c]		Comparator N= 226-227 [c]		AFLURIA Quadrivalent N= 947-949 [c]		Comparator N= 317-318 [c]	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
Local Adverse Reactions [d]								
Pain	20.8	0.1	25.6	0.4	35.5	0	31.4	0.6
Redness	20.8	0.6	17.6	1.8	22.4	2.3	20.8	5.3
Swelling/Lump	6.1	0.4	6.2	0.9	10.1	1.7	12.9	2.5
Systemic Adverse Events [e]								
Irritability	32.9	0.7	28.2	0.4	-	-	-	-
Diarrhea	24.2	0.1	25.6	0.4	12.1	0.1	8.8	0.6
Loss of Appetite	20.0	0.3	19.4	0.4	-	-	-	-
Malaise and Fatigue	-	-	-	-	14.3	0.5	13.2	0.3
Myalgia	-	-	-	-	9.9	0.1	9.4	0
Nausea and/or vomiting	9.4	0.7	11.0	0	9.2	0.4	6.6	0.3
Headache	-	-	-	-	6.2	0.4	5.0	0
Fever [f]	7.2	2.5	11.9	2.6	4.8	1.2	6.0	0.9

Abbreviations: Gr 3, Grade 3 (severe); Comparator, Comparator quadrivalent influenza vaccine [Fluzone® Quadrivalent (Sanofi Pasteur)]

[a] NCT02914275

[b] Percent (%) is derived from the number of subjects that reported the event divided by the number of subjects in the Solicited Safety Population with non-missing data for each age cohort, treatment group, and each solicited parameter.

[c] N = number of subjects in the Solicited Safety Population (subjects who were vaccinated and provided any solicited safety data) for each study vaccine group.

[d] Local adverse reactions: Grade 3 pain is that which prevents daily activity (36 through 59 month subjects); or cried when limb was moved or spontaneously painful (6 through 35 month subjects); Swelling/Lump and redness: any = ≥ 0mm diameter, Grade 3 = ≥ 30mm diameter.

[e] Systemic adverse events: Fever: any = ≥ 99.5°F (Axillary), Grade 3 = ≥ 101.3°F (Axillary); Grade 3 for all other adverse events is that which prevents daily activity; Irritability, Loss of Appetite, Malaise and Fatigue, Myalgia and Headache are age specific systemic adverse events, where "-" denotes event was not applicable to that age cohort.

[f] Prophylactic antipyretics (acetaminophen or ibuprophen-containing medications) were not permitted. Antipyretics used to treat fever were permitted and rates of use were as follows: 6 through 35 months (Afluria QIV 5.9%, Comparator QIV 9.0%); 36 through 59 months (Afluria QIV 3.7%, Comparator QIV 2.5%).

In subjects 6 through 35 months of age, all solicited local adverse reactions and systemic adverse events were reported at lower frequencies after the second vaccination than after the first vaccination with AFLURIA QUADRIVALENT.

In subjects 36 through 59 months of age, all solicited local adverse reactions and systemic adverse events were reported at lower frequencies after the second vaccination than after the first vaccination with AFLURIA QUADRIVALENT.

The most commonly reported unsolicited adverse events in the 28 days following the first or second dose of AFLURIA QUADRIVALENT in subjects 6 through 35 months of age were rhinorrhea (11.2%), cough (10.4%), pyrexia (6.3%), upper respiratory tract infection (4.8%), diarrhea (3.7%), otitis media (2.4%), vomiting (2.4%), nasal congestion (2.4%), nasopharyngitis (1.9%), irritability (1.7%), ear infection (1.6%), croup infectious (1.4%), teething (1.3%), rash (1.2%), influenza like illness (1.0%) and fatigue (1.0%), and were similar to comparator.

The most commonly reported unsolicited adverse events in the 28 days following the first or second dose of AFLURIA QUADRIVALENT in subjects 36 through 59 months of age were cough (7.7%), rhinorrhea (4.9%), pyrexia (3.7%), upper respiratory tract infection (2.5%), vomiting (2.1%), nasal congestion (1.6%), nasopharyngitis (1.7%), ororpharyngeal pain (1.2%) diarrhea (1.1%) and fatigue (1.1%), and were similar to the comparator.

No deaths were reported in Study 4. In the 180 days following vaccinations, AFLURIA QUADRIVALENT and comparator vaccine recipients experienced similar rates of serious adverse events (SAEs), none of which were related to study vaccines. No vaccine-related febrile seizures occurred in Study 4. Unrelated SAEs of febrile seizures occurred in two AFLURIA QUADRIVALENT recipients (6 through 35 months age group) at 43 and 104 days post-vaccinations.

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 limited 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 U.S. 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

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to AFLURIA QUADRIVALENT during pregnancy. Women who are vaccinated with AFLURIA QUADRIVALENT during pregnancy are encouraged to enroll in the registry by calling 1-855-358-8966 or sending an email to Seqirus at us.medicalinformation@seqirus.com.

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. Data for AFLURIA (trivalent formulation) administered to pregnant women are relevant to AFLURIA QUADRIVALENT because both vaccines are manufactured using the same process and have overlapping compositions (*see Description [11]*). There are limited data for AFLURIA QUADRIVALENT administered to pregnant women, and available data for 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. A developmental toxicity study of AFLURIA (trivalent formulation) has been performed in female rats administered a single human dose [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 a single human dose [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.

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.

8.4 Pediatric Use

The safety and effectiveness of AFLURIA QUADRIVALENT in persons less than 6 months of age have not been established.

The PharmaJet Stratis Needle-Free Injection System is not approved as a method of administering AFLURIA QUADRIVALENT 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 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 2019-2020 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 2019-2020 Northern Hemisphere influenza season: A/Brisbane/02/2018 (IVR-190) (an A/Brisbane/02/2018 (H1N1)pdm09 – like virus), A/Kansas/14/2017 (X-327) (an A/Kansas/14/2017 (H3N2) – like virus), B/Maryland/15/2016 (a B/Colorado/06/2017 – like virus) and B/Phuket/3073/2013 BVR-1B (a B/Phuket/3073/2013 – like virus). A 0.25 mL dose contains 7.5 mcg HA of each of the same four influenza strains.

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 and each 0.25 mL dose contains 12.25 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). A single 0.25 mL dose of AFLURIA QUADRIVALENT contains half of these quantities.

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 U.S. 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 5, 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 CI of 41% (Table 6).

Table 6: AFLURIA (trivalent formulation): Laboratory-Confirmed Influenza Infection Rate and Vaccine Efficacy in Adults 18 through 64 Years of Age (Study 5)[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 in Adults and Older Adults Administered by Needle and Syringe

Study 1 was a randomized, double-blind, active-controlled trial conducted in the U.S. 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 7). 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 7: 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	Met both pre-defined non-inferiority criteria? [d]
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)	
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] Non-inferiority (NI) criterion for the GMT ratio: upper bound of 2-sided 95% CI on the GMT ratio of Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria)/AFLURIA Quadrivalent should not exceed 1.5. NI criterion 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 8, 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 8: 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) criterion for the GMT ratio: upper bound of 2-sided 95% CI on the GMT ratio of Needle and Syringe/PharmaJet Stratis Needle-Free Injection System should not exceed 1.5. NI criterion 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%.

14.4 Immunogenicity of AFLURIA QUADRIVALENT in Children 5 through 17 Years Administered via Needle and Syringe

Study 3 was a randomized, observer-blinded, comparator-controlled trial conducted in the U.S. in children 5 through 17 years of age. A total of 2278 subjects were randomized 3:1 to receive one or two doses of AFLURIA QUADRIVALENT (N=1709) or a U.S.-licensed comparator quadrivalent influenza vaccine (N=569). Subjects 5 through 8 years of age were eligible to receive a second dose at least 28 days after the first dose depending on their influenza vaccination history, consistent with the 2015-2016 recommendations of the Advisory Committee on Immunization Practices (ACIP) for Prevention and Control of Seasonal Influenza with Vaccines. Approximately 25% of subjects in each treatment group in the 5 through 8 years of age sub-group received two vaccine doses.

Baseline serology for HI assessment was collected prior to vaccination. Post-vaccination immunogenicity was evaluated by HI assay on sera obtained 28 days after the last vaccination dose.

The primary objective was to demonstrate that vaccination with AFLURIA QUADRIVALENT elicits an immune response that is not inferior to that of a comparator vaccine containing the same recommended virus strains. The Per Protocol Population (AFLURIA QUADRIVALENT n=1605, Comparator n=528) was used for the primary endpoint analyses. The co-primary endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted for baseline HI titers and other covariates) and seroconversion rates for each vaccine strain, 28 days after the last vaccination. Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the GMT ratio (Comparator/AFLURIA QUADRIVALENT) did not exceed 1.5 and the upper bound of the 2-sided 95% CI of the seroconversion rate difference (Comparator minus AFLURIA QUADRIVALENT) did not exceed 10.0% for each strain. Serum HI antibody responses to AFLURIA QUADRIVALENT were non-inferior for both GMT ratio and seroconversion rates relative to the comparator vaccine for all influenza strains (Table 9). 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 among races or ethnicities.

Table 9: Post-Vaccination HI Antibody GMTs, SCRs, and Analyses of Non-Inferiority of AFLURIA QUADRIVALENT Relative to a U.S.-Licensed Comparator Quadrivalent Influenza Vaccine for each Strain 28 Days after Last Vaccination Among a Pediatric Population 5 through 17 Years of Age (Per Protocol Population) (Study 3)[a,b]

	Post-vaccination GMT		GMT Ratio [c]	Seroconversion % [d]		SCR Difference [e]	
Strain	AFLURIA Quadrivalent N=1605	Comparator N=528	Comparator over AFLURIA Quadrivalent (95% CI)	AFLURIA Quadrivalent N=1605 (95% CI)	Comparator N=528 (95% CI)	Comparator minus AFLURIA Quadrivalent (95% CI)	Met both pre-defined non-inferiority criteria? [f]
A(H1N1)	952.6 (n=1604 [g])	958.8	1.01 (0.93, 1.09)	66.4 (64.0, 68.7)	63.3 (59.0, 67.4)	-3.1 (-8.0, 1.8)	Yes
A(H3N2)	886.4 (n=1604 [g])	930.6	1.05 (0.96, 1.15)	82.9 (81.0, 84.7)	83.3 (79.9, 86.4)	0.4 (-4.5, 5.3)	Yes
B/Phuket/3073/2013 (B Yamagata)	60.9 (n=1604 [g])	54.3	0.89 (0.81, 0.98)	58.5 (56.0, 60.9)	55.1 (50.8, 59.4)	-3.4 (-8.3, 1.5)	Yes
B/Brisbane/60/2008 (B Victoria)	145.0 (n=1604 [g])	133.4	0.92 (0.83, 1.02)	72.1 (69.8, 74.3)	70.1 (66.0, 74.0)	-2.0 (-6.9, 2.9)	Yes

Abbreviations: CI, confidence interval; Comparator, Comparator quadrivalent influenza vaccine (Fluarix® Quadrivalent [GlaxoSmithKline Biologicals]); GMT (adjusted), geometric mean titer; SCR, seroconversion rate.
[a] NCT02545543
[b] The Per-Protocol Population comprised all subjects in the Evaluable Population who did not have any protocol deviations that were medically assessed as potentially impacting on immunogenicity results.
[c] GMT Ratio = Comparator /AFLURIA QUADRIVALENT. Adjusted analysis model: Log-transformed Post-Vaccination HI Titer=Vaccine + Age Strata [5-8, 9-17] + Gender + Vaccination History [y/n] + Log-transformed Pre-Vaccination HI Titer + Site + Number of Doses (1 vs 2) + Age Strata*Vaccine. The Age Strata*Vaccine interaction term was excluded from the model fit for the strains B/Yamagata and B/Victoria as the interaction result was non-significant (p>0.05). Least square means were back transformed.
[d] Seroconversion rate was defined as the percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer ≥ 1:40 or a prevaccination HI titer ≥ 1:10 and a 4-fold increase in postvaccination HI titer.
[e] Seroconversion rate difference = Comparator SCR percentage minus AFLURIA QUADRIVALENT SCR percentage.
[f] Non-inferiority (NI) criterion for the GMT ratio: upper bound of two-sided 95% CI on the GMT ratio of Comparator / AFLURIA QUADRIVALENT should not exceed 1.5. NI criterion for the SCR difference: upper bound of two sided 95% CI on the difference between SCR Comparator – AFLURIA QUADRIVALENT should not exceed 10%.
[g] Subject 8400394-0046 was excluded from the Per-Protocol Population for the adjusted GMT analysis for the GMT ratio since the subject did not have information on all covariates (unknown prevaccination history).

14.5 Immunogenicity of AFLURIA QUADRIVALENT in Children 6 Months through 59 Months Administered by Needle and Syringe

Study 4 was a randomized, observer-blind, comparator-controlled trial conducted in the U.S. in children 6 months through 59 months of age. A total of 2247 subjects were randomized 3:1 to receive AFLURIA QUADRIVALENT (N=1684) or a U.S.-licensed comparator quadrivalent influenza vaccine (N=563). Children 6 months through 35 months received one or two 0.25 mL doses and children 36 months through 59 months received one or two 0.5 mL doses. Subjects were eligible to receive a second dose at least 28 days after the first dose depending on their influenza vaccination history, consistent with the 2016-2017 recommendations of the Advisory Committee on Immunization Practices (ACIP) for Prevention and Control of Seasonal Influenza with Vaccines. Approximately 40% of subjects in each treatment group received two vaccine doses. Baseline serology for HI assessment was collected prior to vaccination. Postvaccination immunogenicity was evaluated by HI assay on sera obtained 28 days after the last vaccination dose.

The primary objective was to demonstrate that vaccination with AFLURIA QUADRIVALENT elicits an immune response that is not inferior to that of a comparator vaccine containing the same recommended virus strains. The Per Protocol Population (AFLURIA QUADRIVALENT n=1456, Comparator QIV n=484) was used for the primary endpoint analyses. The co-primary endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted for baseline HI titers and other covariates) and seroconversion rates for each vaccine strain, 28 days after the last vaccination. Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the GMT ratio (Comparator QIV/AFLURIA QUADRIVALENT) did not exceed 1.5 and the upper bound of the 2-sided 95% CI of the seroconversion rate difference (Comparator QIV minus AFLURIA QUADRIVALENT) did not exceed 10.0% for each strain. Serum HI antibody responses to AFLURIA QUADRIVALENT were non-inferior for both GMT ratio and seroconversion rates relative to the comparator vaccine for all influenza strains (Table 10). 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 among races or ethnicities.

Table 10: Post-Vaccination HI Antibody GMTs, SCRs, and Analyses of Non-Inferiority of AFLURIA QUADRIVALENT Relative to a U.S.-Licensed Comparator Quadrivalent Influenza Vaccine for each Strain 28 Days after Last Vaccination Among a Pediatric Population 6 through 59 Months of Age (Per Protocol Population) (Study 4)[a,b]

	Post-vaccination GMT		GMT Ratio [c]	Seroconversion % [d]		SCR Difference [e]	Met both pre-defined non-inferiority criteria? [f]
Strain	AFLURIA Quadrivalent N=1456	Comparator N=484	Comparator over AFLURIA Quadrivalent (95% CI)	AFLURIA Quadrivalent N=1456 (95% CI)	Comparator N=484 (95% CI)	Comparator minus AFLURIA Quadrivalent (95% CI)	
A(H1N1)	353.5 (n=1455 [g])	281.0 (n=484)	0.79 (0.72, 0.88)	79.1 (76.9, 81.1) (n=1456)	68.8 (64.5, 72.9) (n=484)	-10.3 (-15.4, -5.1)	Yes
A(H3N2)	393.0 (n=1454 [gi])	500.5 (n=484)	1.27 (1.15, 1.42)	82.3 (80.2, 84.2) (n=1455[i])	84.9 (81.4, 88.0) (n=484)	2.6 (-2.5, 7.8)	Yes
B/Phuket/3073/2013 (B Yamagata)	23.7 (n=1455 [g])	26.5 (n=484)	1.12 (1.01, 1.24)	38.9 (36.4, 41.4) (n=1456)	41.9 (37.5, 46.5) (n=484)	3.1 (-2.1, 8.2)	Yes
B/Brisbane/60/2008 (B Victoria)	54.6 (n=1455 [g])	52.9 (n=483[h])	0.97 (0.86, 1.09)	60.2 (57.6, 62.7) (n=1456)	61.1 (56.6, 65.4) (n=483[h])	0.9 (-4.2, 6.1)	Yes

Abbreviations: CI, confidence interval; Comparator, Comparator quadrivalent influenza vaccine (Fluzone Quadrivalent [Sanofi Aventis]); GMT (adjusted), geometric mean titer; SCR, seroconversion rate.

[a] NCT02914275

[b] The Per-Protocol Population comprised all subjects (6 through 35 months of age receiving one or two 0.25 mL doses and 36 through 59 months of age receiving one or two 0.5 mL doses) in the Evaluable Population who did not have any protocol deviations that were medically assessed as potentially impacting on immunogenicity results.

[c] GMT Ratio = Comparator / AFLURIA QUADRIVALENT. Adjusted analysis model: Log-transformed Post-Vaccination HI Titer=Vaccine + Age Cohort [6 through 35 months or 36 through 59 months] + Gender + Vaccination History [y/n] + Log-transformed Pre-Vaccination HI Titer + Site + Number of Doses (1 vs 2) + Age Cohort*Vaccine. The Age Cohort*Vaccine interaction term was excluded from the model fit for the strains A(H1N1), A(H3N2) and B/Yamagata as the interaction result was non-significant (p>0.05). Least square means were back transformed.

[d] Seroconversion rate was defined as the percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer ≥ 1:40 or a prevaccination HI titer ≥ 1:10 and a 4-fold increase in postvaccination HI titer.

[e] Seroconversion rate difference = Comparator SCR percentage minus AFLURIA QUADRIVALENT SCR percentage.

[f] Noninferiority (NI) criterion for the GMT ratio: upper bound of two-sided 95% CI on the GMT ratio of Comparator / AFLURIA QUADRIVALENT should not exceed 1.5. NI criterion for the SCR difference: upper bound of two sided 95% CI on the difference between SCR Comparator – AFLURIA QUADRIVALENT should not exceed 10%.

[g] Subject 8400402-0073 was excluded from the Per-Protocol Population for the adjusted GMT analysis for the GMT ratio because the subject did not have information on all covariates (unknown prevaccination history).

[h] Subject 8400427-0070 had missing B/Victoria Antigen pre-vaccination titer.

[i] Subject 8400402-0074 had missing A/H3N2 post-vaccination titer.

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	33332-219-20	• Ten 0.25 mL single-dose syringes fitted with a Luer-Lok™ attachment without needles [NDC 33332-219-21]
Pre-Filled Syringe	33332-319-01	• Ten 0.5 mL single-dose syringes fitted with a Luer-Lok™ attachment without needles [NDC 33332-319-02]
Multi-Dose Vial	33332-419-10	• One 5 mL vial [NDC 33332-419-11]

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.
- No more than 10 doses (0.25 mL or 0.5 mL) should be withdrawn from the multi-dose vial.

17 PATIENT COUNSELING INFORMATION

- Inform the vaccine recipient or guardian of the potential benefits and risks of immunization with AFLURIA QUADRIVALENT.
- Inform the vaccine recipient or guardian 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 or guardian to report any severe or unusual adverse reactions to their healthcare provider.
- Encourage women who receive AFLURIA QUADRIVALENT while pregnant to enroll in the pregnancy registry. Pregnant women can enroll in the pregnancy registry by calling 1-855-358-8966 or sending an email to Seqirus at us.medicalinformation@seqirus.com.
- 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.

Seqirus™
A CSL COMPANY

Manufactured by:
Seqirus Pty Ltd. Parkville, Victoria, 3052, Australia
U.S. License No. 2044

Distributed by:
Seqirus USA Inc. 25 Deforest Avenue, Summit, NJ 07901, USA
1-855-358-8966

AFLURIA is a registered trademark of Seqirus UK Limited or its affiliates.
PharmaJet® and STRATIS® are registered trademarks of PharmaJet.
Luer-Lok™ is a trademark of Becton, Dickinson and Company Corporation.