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
2020-2021 Formula
Initial U.S. Approval: 23 May 2016

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

Indications and Usage (1)	03/2021
Dosage and Administration (2.1)	03/2021

----------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)

FLUCELVAX QUADRIVALENT is approved for use in persons 2 years of age and older. (1)

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

For intramuscular use only

Age	Dose	Schedule
2 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, 0.5mL	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 0.5 mL). (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----------

- In adults 18 through 64 years of age who received FLUCELVAX QUADRIVALENT, the most commonly reported injection-site adverse reactions were pain (≥ 40%), erythema and induration (≥ 10%). The most common systemic adverse events were headache, fatigue and myalgia (≥ 10%). (6)
- In adults ≥ 65 years of age who received FLUCELVAX QUADRIVALENT, the most commonly reported injection-site adverse reactions were pain (≥ 20%) and erythema (≥ 10%). (6)
- In children 2 through 8 years of age who received FLUCELVAX QUADRIVALENT, the most commonly reported injection-site adverse reactions were tenderness (28.7%), pain (27.9%) and erythema (21.3%), induration (14.9%) and ecchymosis (10.0%). The most common systemic adverse events were sleepiness (14.9%), headache (13.8%), fatigue (13.8%), irritability (13.8%) and loss of appetite (10.6%).
- In children and adolescents 9 through 17 years of age who received FLUCELVAX QUADRIVALENT, the most commonly reported injection-site adverse reactions were injection site pain (21.7%), erythema (17.2%) and induration (10.5%). The most common systemic adverse events were headache (18.1%) and fatigue (17.0%). (6)

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

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

- Geriatric Use: Antibody responses were lower in adults 65 years and older than in younger adults. (8.5)

See 17 for PATIENT COUNSELING INFORMATION. **Revised: 03/2021**

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 2 years of age and older. *[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.

Table 1: Dosage and Schedule

Age	Dose	Schedule
2 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, 0.5mL	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 2° and 8°C (36° and 46°F). 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, preferably in the region of the deltoid muscle of the upper arm. Younger children with insufficient deltoid mass should be vaccinated in the anterolateral aspect of the thigh. Do not inject the vaccine in the gluteal region or areas where there may be a major nerve trunk. 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 QUADRIVALENT. 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

In adults 18 through 64 years of age who received FLUCELVAX QUADRIVALENT, the most commonly reported (≥10%) injection-site adverse reactions were pain (≥ 40%), erythema and induration (≥10%). The most common systemic adverse events were headache, fatigue and myalgia (≥10%).

In adults ≥ 65 years of age who received FLUCELVAX QUADRIVALENT, the most commonly reported injection-site adverse reactions were pain (≥ 20%) and erythema (≥ 10%).

In children 2 through 8 years of age who received FLUCELVAX QUADRIVALENT, the most commonly reported injection-site adverse reactions were tenderness (28.7%), pain (27.9%) and erythema (21.3%), induration (14.9%) and ecchymosis (10.0%). The most common systemic adverse events were sleepiness (14.9%), headache (13.8%), fatigue (13.8%), irritability (13.8%) and loss of appetite (10.6%).

In children and adolescents 9 through 17 years of age who received FLUCELVAX QUADRIVALENT, the most commonly reported injection-site adverse reactions were injection site pain (21.7%), erythema (17.2%) and induration (10.5%). The most common systemic adverse events were headache (18.1%) and fatigue (17.0%). (6)

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 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, adults 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 adults who received FLUCELVAX QUADRIVALENT was 57.4 years of age; 54.8% of adults 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 adults 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 Adult Safety Population[1] Reported Within 7 Days of Vaccination (Study 1)

	Percentage (%)[2] of participants in each Age Cohort Reporting an Event											
	Participants 18 through 64 years						Participants ≥ 65 years					
	FLUCELVAX Quadrivalent N=663		TIV1c N=330		TIV2c N=327		FLUCELVAX Quadrivalent N=656		TIV1c N=340		TIV2c N=336	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
Local Adverse Reactions[3]												
Pain	45.4	0.5	37.0	0.3	40.7	0	21.6	0	18.8	0	18.5	0
Erythema	13.4	0	13.3	0	10.1	0	11.9	0	10.6	0	10.4	0
Induration	11.6	0	9.7	0.3	10.4	0	8.7	0	6.8	0	7.7	0
Ecchymosis	3.8	0	3.3	0.3	5.2	0	4.7	0	4.4	0	5.4	0
Systemic Adverse Reactions[4]												
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
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
Nausea	9.7	0.3	7.3	0.9	8.9	1.2	3.8	0.2	4.1	0	4.2	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
Arthralgia	8.1	0.5	8.2	0	9.5	0.9	5.5	0.5	5.0	0.3	6.8	0.9
Diarrhea	7.4	0.6	7.6	0	7.6	0.6	4.3	0.5	5.0	0.9	5.1	0.3
Chills	6.2	0.2	6.4	0.6	6.4	0	4.4	0.3	4.1	0.3	4.5	0.6
Vomiting	2.6	0	1.5	0.3	0.9	0	0.9	0.2	0.3	0	0.6	0
Fever	0.8	0	0.6	0	0.3	0	0.3	0	0.9	0	0.6	0

Abbreviations: Gr 3, Grade 3.

N = number of participants in the Safety Population for each study vaccine group.

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

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

[3] Local Adverse reactions: Grade 3 pain is that which prevents daily activity; Erythema, induration and ecchymosis: any = ≥ 1mm diameter, Grade 3 = > 100 mm diameter.

[4] Systemic adverse events: Fever: any = ≥ 100.4°F (Oral), Grade 3 = ≥ 102.2°F (Oral); Grade 3 vomiting: requires outpatient hydration; Grade 3 diarrhea: 6 or more stools or requires outpatient IV hydration; Grade 3 for all other adverse events is that which prevents daily activity.

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 adults 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 adults who received FLUCELVAX QUADRIVALENT. None of the SAEs were assessed as being related to study vaccine.

Children and Adolescents 2 through 17 years of age:

The safety of FLUCELVAX QUADRIVALENT was evaluated in children and adolescents in Study 2.

Study 2 was a multi-season, multi-national (Australia, Estonia, Finland, Lithuania, Philippines, Poland, Spain, Thailand), randomized, observer-blind study in children and adolescents 2 through 17 years of age. The solicited safety population included a total of 4509 children and adolescents 2 through 17 years of age who received FLUCELVAX QIV (N=2255) or a non-influenza (meningococcal (Groups A, C, Y, and W-135) oligosaccharide diphtheria CRM197 conjugate) comparator vaccine (N=2254).

Children 2 through 8 years of age received one or two doses (separated by 4 weeks) of FLUCELVAX QUADRIVALENT or comparator vaccine depending on the subject's prior influenza vaccination history. Children in the 2-dose comparator group received non-influenza comparator as the first dose and saline placebo as the second dose. Children and adolescents 9 through 17 years of age received a single dose of FLUCELVAX QUADRIVALENT or non-influenza comparator vaccine.

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

In children 2 through 8 and children and adolescents 9 through 17 years of age, the incidence of local and systemic solicited adverse reactions reported by children and adolescents who received FLUCELVAX QUADRIVALENT and comparator are summarized in Table 3.

Table 3: Incidence of Solicited Adverse Reactions in the Safety Population[1] (2 through 8 and 9 through 17 years of age) Reported Within 7 Days of Any Dose of Vaccination (Study 2)

	Percentage (%)[2] of participants in each Age Cohort Reporting an Event							
	Participants 2 through 8 years				Participants 9 through 17 years			
	FLUCELVAX Quadrivalent N=559-1143		Comparator[3] N=562-1142		FLUCELVAX Quadrivalent N=1096-1109		Comparator[3] N=1100-1108	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
Local Adverse Reactions[4]								
Tenderness[5]	28.7	1.0	25.4	1.4	-	-	-	-
Pain	27.9	1.2	20.3	1.6	21.7	0.5	18.3	1.0
Erythema	21.3	0.4	23.7	1.1	17.2	0	18.7	0.5
Induration	14.9	0.2	15.2	0.4	10.5	0.1	11.0	0.2
Ecchymosis	10.0	0	7.5	0.1	5.0	0	5.2	0
Systemic Adverse Reactions[6]								
Sleepiness[5]	14.9	0.9	17.6	1.8	-	-	-	-
Headache	13.8	0.4	11.8	0.5	18.1	1.4	17.4	0.6
Fatigue	13.8	0.9	12.7	0.7	17.0	1.1	18.2	1.2
Irritability[5]	13.8	0.2	10.8	0.5	-	-	-	-
Loss of Appetite	10.6	0.5	8.0	0.5	8.5	0.5	7.5	0.5
Change of eating habits[5]	9.9	1.0	10.1	0.7	-	-	-	-
Fever	7.6	0.5	6.1	0.2	2.8	0.1	3.0	0.3
Diarrhea	6.5	0.4	6.8	0.6	7.4	0.5	8.1	0.3
Arthralgia	5.2	0.4	6.2	0.3	7.1	0.4	8.4	0.5
Nausea	5.2	0	4.5	0.7	6.0	0.2	6.1	0.6
Vomiting	4.9	0.6	4.1	0.6	3.0	0.3	3.0	0.4
Shivering/Chills	4.7	0.7	3.9	0.4	7.6	0.4	7.6	0.3
Myalgia	2.9	0.2	4.0	0.3	6.1	0.5	5.5	0.5

Abbreviations: Gr 3, Grade 3.

[1] Solicited Safety Population: participants who were vaccinated and provided any solicited local or systemic adverse event safety data, from 6 hours through 7 days after vaccination.

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

N = number of participants in the Safety Population for each study vaccine group.

[3] Non-influenza vaccine comparator: MENVEO, meningococcal (Groups A, C, Y, and W-135) oligosaccharide diphtheria CRM197 conjugate vaccine (GlaxoSmithKline Biologicals SA); children assigned to 2 doses received saline placebo as the second dose.

[4] Local Adverse reactions: Grade 3 pain is that which prevents daily activity; Erythema, induration and ecchymosis: any = ≥ 1mm diameter, Grade 3 = > 50 mm diameter for 2 through 5 years and > 100 mm diameter for 6 through 17 years.

[5] Tenderness, change in eating habits, sleepiness, and irritability were collected for participants 2 through 6 years of age only.

[6] Systemic adverse events: Fever: any = ≥ 100.4°F (Oral), Grade 3 = ≥ 102.2°F (Oral); Grade 3 change of eating habits: Missed more than 2 feeds/meals; Grade 3 sleepiness: Sleeps most of the time and is hard to arouse him/her; Grade 3 vomiting: 6 or more times in 24 hours or requires intravenous hydration; Grade 3 diarrhea: 6 or more loose stools in 24 hours or requires intravenous hydration; Grade 3 irritability: unable to console. Grade 3 for all other adverse events is that which prevents daily activity.

The rates of antipyretic or analgesic use reported on the diary card for prophylaxis or treatment of high temperature or pain were as follows: 2 through 8 years of age FLUCELVAX QUADRIVALENT 11.0%, Comparator 7.7%; 9 through 18 years of age FLUCELVAX QUADRIVALENT 6.7%, Comparator 7.1%.

Study 2: NCT03165617

In children who received a second dose (N=762) of FLUCELVAX QUADRIVALENT, the rates of solicited local and systemic adverse reactions were generally lower after the second dose compared to the first dose.

Serious adverse events (SAEs) were collected throughout the study duration (until 6 months after last vaccination) and were reported by 1.1% of the children and adolescents 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

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).

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 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 2 years of age.

8.5 Geriatric Use

Of the total number of adults who received one dose of FLUCELVAX QUADRIVALENT in clinical studies and included in the safety population (2493), 26% (660) were 65 years of age and older and 8% (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 adults. *[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 β-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 2020-2021 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/Nebraska/14/2019 (an A/Hawaii/70/2019 (H1N1)pdm09-like virus);

A/Delaware/39/2019 (an A/Hong Kong/45/2019 (H3N2)-like virus);

B/Darwin/7/2019 (a B/Washington/02/2019-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), cetyltrimethylammonium bromide (≤ 18 mcg), and β-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 pre-filled 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 adults.[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 (Study 3). A total of 11,404 adults 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 4 and 5, respectively).

Table 4: Vaccine Efficacy against Culture-Confirmed Influenza in Participants aged 18 through 49 years (Study 3)

	Number of participants per protocol	Number of participants 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 3: NCT00630331

Table 5: Efficacy of FLUCELVAX against Culture-Confirmed Influenza by Influenza Viral Subtype in Participants aged 18 through 49 years (Study 3)

	FLUCELVAX (N=3776)		Placebo (N=3843)		Vaccine Efficacy (VE)[2]	
	Attack Rate (%)	Number of Participants with Influenza	Attack Rate (%)	Number of Participants 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 3: NCT00630331.

14.2 Efficacy of FLUCELVAX QUADRIVALENT in Children and Adolescents 2 through 17 Years of Age

Absolute efficacy of FLUCELVAX QUADRIVALENT was evaluated in children and adolescents 2 through 17 years of age in Study 2. This was a multinational, randomized, non-influenza vaccine comparator-controlled efficacy, immunogenicity and safety study conducted in 8 countries during the following 3 influenza seasons: Southern Hemisphere 2017, Northern Hemisphere 2017/2018 and Northern Hemisphere 2018/2019. The study enrolled 4514 children and adolescents. Out of the 4514 enrolled, 4513 received either FLUCELVAX QUADRIVALENT (N=2258) or a non-influenza (meningococcal (Groups A, C, Y, and W-135) oligosaccharide diphtheria CRM197 conjugate) comparator vaccine (N=2255). The full analysis set (FAS) for efficacy consisted of 4509 children and adolescents.

Children 2 through 8 years of age received either one or two doses (separated by 4 weeks) of FLUCELVAX QUADRIVALENT or comparator vaccine depending on the subject's prior influenza vaccination history. Children in the 2-dose comparator group received non-influenza comparator as the first dose and saline placebo as the second dose. Children and adolescents 9 through 17 years of age received a single dose of FLUCELVAX QUADRIVALENT or non-influenza comparator vaccine. Among all enrolled children and adolescents (N=4514), the mean age was 8.8 years, 48% were female, 51% were 2 through 8 years of age, 50% were Caucasian and 49% were Asian. There were no notable differences in the distribution of demographic and baseline characteristics between the two treatment groups.

FLUCELVAX QUADRIVALENT efficacy was assessed by the prevention of confirmed influenza illness caused by any influenza Type A or B strain. Influenza cases were identified by active and passive surveillance of influenza-like illness (ILI) and confirmed by cell culture and/or real-time polymerase chain reaction (RT-PCR). ILI was defined as a fever (oral temperature

≥ 100.0°F / 37.8°C) along with any of the following: cough, sore throat, nasal congestion, or rhinorrhea. The overall vaccine efficacy for the entire study population (2 through 17 years) was 54.6% (95% CI 45.7 – 62.1), which met predefined success criteria. In addition, vaccine efficacy was 50.5% (95% CI 38.4 – 60.2) in children 2 through 8 years of age and 61.9% (95% CI 47.4 – 72.3) in those 9 through 17 years of age. Vaccine efficacy against all influenza viral subtypes and against individual influenza viral subtypes antigenically similar to the subtypes in the vaccine were calculated (Table 6).

Table 6: Efficacy of FLUCELVAX QUADRIVALENT Against First Occurrence RT-PCR Confirmed or Culture Confirmed Influenza in Participants 2 through 17 years of age– FAS Efficacy[1] (Study 2).

	Number of participants per protocol[1]	Number of cases of influenza	Attack Rate (%)	Vaccine Efficacy (VE)[2]	
				VE %	95% Confidence Interval[3]
RT-PCR or Culture Confirmed Influenza					
FLUCELVAX Quadrivalent	2257	175	7.8	54.6	45.7 - 62.1
Non-Influenza Comparator[4]	2252	364	16.2	-	-
Culture Confirmed Influenza					
FLUCELVAX Quadrivalent	2257	115	5.1	60.8	51.3 - 68.5
Non-Influenza Comparator[4]	2252	279	12.4	-	-
Antigenically Matched Culture-Confirmed Influenza					
FLUCELVAX Quadrivalent	2257	90	4.0	63.6	53.6 - 71.5
Non-Influenza Comparator[4]	2252	236	10.5	-	-

[1]Number of participants in the Full-Analysis Set (FAS) – Efficacy, which included all participants randomized, received a study vaccination and provided efficacy data

[2]Efficacy against influenza was evaluated over three influenza seasons, SH 2017, NH 2017-18 and NH 2018-19

[3]FLUCELVAX QUADRIVALENT met the pre-defined success criterion defined as the lower limit of the two-sided 95% CI of absolute vaccine efficacy greater than 20%

[4]Non-Influenza Comparator: (MENVEO, meningococcal (Groups A, C, Y, and W-135) oligosaccharide diphtheria CRM197 conjugate vaccine, GlaxoSmithKline Biologicals SA); children assigned to 2 doses received saline placebo as the second dose.

Study 2: NCT03165617

14.3 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, adults 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 adults who received FLUCELVAX QUADRIVALENT was 57.5 years; 55.1% of adults were female and 76.1% of adults 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 adults 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 FLUCELVAX QUADRIVALENT, as assessed by ratios of GMTs and the differences in the percentages of adults 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[1] (Study 1)

		FLUCELVAX Quadrivalent N = 1250	TIV1c/TIV2c[2] 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[3] (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[3] (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[3] (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[3] (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 participants 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 participants 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

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

Immunogenicity of FLUCELVAX QUADRIVALENT was evaluated in children and adolescents 4 through 17 years of age in a randomized, double-blind, controlled study conducted in the US (Study 4). (See section 6.1) In this study, 1159 children and adolescents received FLUCELVAX QUADRIVALENT. In the per protocol set, the mean age of children and adolescents who received FLUCELVAX QUADRIVALENT was 9.8 years; 47% of children and adolescents were female and 54% of children and adolescents 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 children and adolescents 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 children and adolescents with a post-vaccination HI titer ≥ 1:40.

In children and adolescents receiving FLUCELVAX QUADRIVALENT, for all four influenza strains, the 95% LBCI seroconversion rates were ≥ 40% and the percentage of children and adolescents 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 4)

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

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

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

[1] Seroconversion rate = percentage of participants 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 participants with HI titer ≥ 1:40 is ≥ 70%; and the lower limit of the 95% CI of the percentage of participants with seroconversion is ≥ 40%.

[2] Per protocol set: All participants 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 4: NCT 01992107

15 REFERENCES

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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.
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	70461-320-03	0.5 mL single dose pre-filled syringe, package of 10 syringes per carton [NDC 70461-320-04]
Multi-dose Vial	70461-420-10	5 mL multi-dose vial, individually packaged in a carton [NDC 70461-420-11]

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.

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.

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