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

FLUCELVAX (Influenza Vaccine)
Suspension for Intramuscular Injection
2015-2016 Formula
Initial U.S. Approval: 2012

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

INDICATIONS AND USAGE (1)	4/2016
DOSAGE AND ADMINISTRATION (2)	4/2016

----------INDICATIONS AND USAGE----------
FLUCELVAX 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 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. Data demonstrating a decrease in influenza disease after vaccination of children and adolescents 4 through 17 years of age with FLUCELVAX 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 1 month 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 0.5-mL single-dose pre-filled syringes. (3)

----------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 should be based on careful consideration of the potential benefits and risks. (5.1)
- The tip caps of the pre-filled syringes may contain natural rubber latex which may cause allergic reactions in latex-sensitive individuals. (5.2)

----------ADVERSE REACTIONS----------
- The most common (≥10%) local and systemic reactions in adults 18-64 years of age were injection site pain (28%), injection site erythema (13%), headache (16%), fatigue (12%), myalgia (11%) and malaise (10%). (6)
- The most common (≥10%) local and systemic reactions in adults 65 years of age and older were injection site erythema (10%), fatigue (11%), headache (10%) and malaise (10%). (6)
- The most common (≥10%) local and systemic reactions in children 4 through 8 years of age were pain at the injection site (29%), erythema at the injection site (11%) and fatigue (10%). (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 (34%), myalgia (15%), headache (14%) and erythema at the injection site (14%). (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.

----------USE IN SPECIFIC POPULATIONS----------
- Safety and effectiveness of FLUCELVAX have not been established in pregnant women or nursing mothers. (8.1)
- Geriatric Use: Antibody responses were lower in adults 65 years of age and older than in younger adults. (8.5)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FLUCELVAX 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 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. Data demonstrating a decrease in influenza disease after vaccination of this age group with FLUCELVAX are not available [*see Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Dosage and Schedule

Administer FLUCELVAX 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.

Age	Dose	Schedule
4 through 8 years of age	One or two doses[a], 0.5 mL each	If 2 doses, administer at least 1 month 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.

2.2 Administration

Shake the syringe vigorously before administering. FLUCELVAX 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. Do not use the vaccine if the contents have been frozen.

Attach a sterile needle to the pre-filled syringe and administer intramuscularly.

FLUCELVAX should not be administered intravascularly, intradermally or subcutaneously.

3 DOSAGE FORMS AND STRENGTHS

FLUCELVAX is a suspension for injection supplied in a 0.5 mL single-dose pre-filled Luer Lock syringe.

4 CONTRAINDICATIONS

Do not administer FLUCELVAX 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] [*see References (15)*]. If GBS has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLUCELVAX should be based on careful consideration of the potential benefits and risks.

5.2 Latex

The tip caps of the pre-filled syringes may contain natural rubber latex which may cause allergic reactions in latex-sensitive individuals [*see Description (11)*].

5.3 Preventing and Managing Allergic Reactions

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

5.4 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.

5.5 Altered Immunocompetence

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

5.6 Limitations of Vaccine Effectiveness

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

6 ADVERSE REACTIONS

Overall, the most common (≥10 %) solicited adverse reactions occurring in adults 18 to 64 years of age within 7 days of vaccination with FLUCELVAX were pain at the injection site (28%), erythema at the injection site (13%), headache (16%), fatigue (12%), myalgia (11%) and malaise (10%). The most common (≥10%) solicited adverse reactions occurring in adults 65 years of age and older within 7 days of vaccination were erythema at the injection site (10%), fatigue (11%), headache (10%) and malaise (10%).

Overall, the most common (≥10%) solicited adverse events occurring in children 4 through 8 years of age within 7 days of any vaccination with FLUCELVAX were pain at the injection site (29%), erythema at the injection site (11%) and fatigue (10%). The most common (≥10%)

solicited adverse events occurring in children and adolescents 9 through 17 years of age within 7 days of any vaccination with FLUCELVAX were pain at the injection site (34%), myalgia (15%), headache (14%) and erythema at the injection site (14%).

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 was evaluated in seven randomized, controlled studies conducted in the US, Europe and New Zealand. The safety population includes 5709 adults 18 through 64 years of age and 572 adults 65 years of age and older administered FLUCELVAX.

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

One of the 7 clinical trials, study 1 was a randomized, double-blind, placebo-controlled study that evaluated three vaccines including: FLUCELVAX (N=3813), placebo (N=3894) and another influenza vaccine. The population was 18 through 49 years of age (mean 32.8 years), 55% were female and 84% were Caucasian. Solicited adverse reactions for FLUCELVAX and placebo are summarized in Table 1.

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

	Adults 18 through 49 Years	
	Percentages (%)	
	FLUCELVAX N=3813	**Placebo[3] N=3894**
Local adverse reactions		
Injection site pain	30	10
Erythema	13	10
Induration	6	3
Swelling	6	3
Ecchymosis	4	4
Systemic adverse reactions		
Headache	15	15
Fatigue	10	10
Myalgia	12	7
Malaise	8	6

Chills	6	6
Arthralgia	3	3
Sweating	3	3
Fever (≥38° C)	1	<1

[1] NCT 00630331
[2] Safety population: all subjects in the exposed population who provided post vaccination safety data
[3] Placebo: 0.5 mL Phosphate Buffered Saline

Study 2 was a randomized, double-blind study comparing FLUCELVAX (N=1330) to AGRIFLU, a US-licensed trivalent inactivated influenza vaccine (N=1324) in adults 18 years of age or older. The mean age was 43.7 years of age for adults 18 through 64 years of age and 71.3 years of age for adults 65 years of age and older; 57% of subjects were female and 100% were Caucasian. The safety data observed are summarized in Table 2.

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

	Adults 18 through 64 Years		**Adults 65 Years of Age and Older**	
	Percentages (%)			
	FLUCELVAX N=821	**Comparator[3] N=841**	**FLUCELVAX N=509**	**Comparator[3] N=483**
Local adverse reactions				
Injection site pain	20	15	8	4
Erythema	14	15	10	11
Induration	6	6	5	4
Swelling	4	4	4	2
Ecchymosis	3	3	4	4
Systemic adverse reactions				
Headache	12	11	10	11
Fatigue	11	11	11	13
Myalgia	7	8	6	8
Malaise	11	11	10	11
Chills	4	4	3	4

Arthralgia	5	5	6	7
Sweating	5	4	7	8
Fever (≥38° C)	1	1	<1	1

[1] Safety population: all subjects in the exposed population who provided post-vaccination safety data
[2] NCT 00492063
[3] AGRIFLU (Influenza Virus Vaccine)

Unsolicited adverse events, including serious adverse events (SAEs), were collected for 21 days after vaccination in five studies. In adults 18 through 64 years of age (N=4038), 13% (284 out of 2266) of subjects who received FLUCELVAX and 13% (224 out of 1772) of subjects who received the comparator trivalent influenza vaccine (AGRIFLU) reported at least one unsolicited adverse event within 21 days after vaccination. The most commonly reported unsolicited adverse events after FLUCELVAX vaccination were rhinitis (3%), headache (2%) and oropharyngeal pain (2%). In adults 65 years of age and older (N=2013), 11% (110 out of 997) of subjects who received FLUCELVAX and 9% (95 out of 1016) of subjects who received the comparator trivalent influenza vaccine (AGRIFLU) reported at least one unsolicited adverse event within 21 days after vaccination. Within this age group, the most commonly reported unsolicited adverse events after FLUCELVAX vaccination were rhinitis (3%) and cough (2%). In both age groups, all other unsolicited adverse events were reported in 1% or fewer subjects.

In the seven controlled studies of FLUCELVAX, serious adverse events were collected for a duration of 21 days in two studies and for a duration of 6 to 9 months in five studies. The rates (in all seven controlled studies) of serious adverse events among adults 18 through 64 years of age were 1% (84 out of 6388) in groups that received FLUCELVAX, 1% (55 out of 5745) in groups that received the comparator trivalent influenza vaccine (AGRIFLU) and 1% (37 out of 3894) in groups that received placebo. The rates of serious adverse events among adults 65 years of age and older were 4% (36 out of 997) in groups that received FLUCELVAX and 4% (44 out of 1016) in groups that received the comparator trivalent influenza vaccine (AGRIFLU).

Children and Adolescents 4 through 17 Years of Age
Information on the safety of FLUCELVAX administered to 3346 children and adolescents 4 through 17 years of age is available from two multinational, randomized, controlled clinical studies (study 4- NCT00645411 and study 5- NCT01857206). In both studies, children 9 through 17 years of age received a single dose of FLUCELVAX or a US-licensed trivalent inactivated influenza vaccine (FLUVIRIN). In study 4, all children 4 through 8 years of age received two doses of study vaccine separated by 4 weeks. In study 5, children 4 through 8 years of age received one or two doses (separated by 4 weeks) of study vaccine based on determination of the subject's prior influenza vaccination history. Among subjects enrolled in these two studies, the mean age was 8.5 years, 49% were female, and 59% were Caucasian.

Solicited adverse reactions for FLUCELVAX and the comparator trivalent influenza vaccine (FLUVIRIN) for study 4 are summarized in Table 3. In children who received a second dose of FLUCELVAX or the comparator trivalent influenza vaccine (FLUVIRIN), the incidence of

adverse reactions following the second dose of vaccine were similar to those observed with the first dose.

Table 3: Solicited Adverse Reactions in the Safety Population[1] Reported Within 7 Days of Vaccination with FLUCELVAX (Study 4[2])

	Children 4 through 8 Years					
	Percentages (%)[3]					
	FLUCELVAX N=1324			**Comparator[4] N=831**		
Adverse Reaction	**Any**	**Moderate[5]**	**Severe[5]**	**Any**	**Moderate[5]**	**Severe[5]**
Local adverse reactions						
Injection site pain	29	4	<1	26	3	1
Erythema	11	<1	0	14	0	0
Induration	6	<1	0	4	0	0
Swelling	4	0	0	5	<1	0
Ecchymosis	6	0	0	6	0	0
Systemic adverse reactions						
Headache	9	2	1	11	3	<1
Fatigue	10	2	<1	12	2	1
Myalgia	9	2	<1	8	2	<1
Malaise	7	2	1	8	2	1
Chills	3	<1	<1	5	1	<1
Arthralgia	3	<1	0	1	<1	0
Sweating	2	<1	<1	2	1	<1
Fever ≥38°C	2	1	<1	4	1	0
	Children and Adolescents 9 through 17 Years					
	FLUCELVAX N=652			**Comparator[4] N=316**		
	Any	**Moderate[5]**	**Severe[5]**	**Any**	**Moderate[5]**	**Severe[5]**
Local adverse reactions						
Injection site pain	34	5	<1	38	9	1
Erythema	14	0	0	14	<1	0
Induration	7	<1	0	9	0	0
Swelling	5	<1	0	5	<1	0
Ecchymosis	5	0	0	3	0	0
Systemic adverse reactions						
Headache	14	3	<1	14	5	1

Fatigue	9	2	1	13	3	1
Myalgia	15	3	<1	19	4	1
Malaise	9	2	1	11	3	1
Chills	4	1	<1	4	<1	<1
Arthralgia	4	<1	<1	5	1	0
Sweating	2	0	0	1	0	<1
Fever ≥38°C	1	<1	0	1	0	0

[1] Safety population: all subjects in the exposed population who provided post-vaccination safety data.
[2] NCT 00645411
[3] For children 4 through 8 years of age, data shown are after first dose of vaccination
[4] FLUVIRIN (Influenza Virus Vaccine)
[5] Severity gradings: For erythema, induration, ecchymosis and swelling: Moderate=51-≤100 mm; Severe= >100 mm; For pain and systemic adverse reactions: Moderate = some limitation to perform daily activity; Severe = unable to perform daily activity; For fever: Moderate = 39-<40°C; Severe = ≥40°C

In studies 4 and 5 combined, the frequencies of unsolicited non-serious adverse events occurring within 28 days of vaccination were present in 32% of subjects who received FLUCELVAX and in 35% of subjects who received a comparator trivalent inactivated influenza vaccine.

One case of erythema multiforme considered related to vaccination with FLUCELVAX occurred in a 5 year old male.

In the two controlled studies in children and adolescents 4 through 17 years of age, serious adverse events were monitored for 6 months after last vaccination. Serious adverse events occurring within 28 days of any vaccination were reported in <1% of subjects (8 of 3345) who received FLUCELVAX, and in <1% of subjects (5 of 1828) who received a comparator trivalent influenza vaccine . No serious adverse events occurring within 6 months post-vaccination were considered related to the study vaccine.

6.2 Postmarketing Experience

The following additional adverse events have been identified during post-approval use of FLUCELVAX. 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: Anaphylactic reaction, angioedema

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

Nervous systems disorders: Syncope, presyncope, paresthesia

General disorders and administration site conditions: Extensive swelling of the injected limbs

7 DRUG INTERACTIONS

7.1 Concomitant use with Other Vaccines

No data are available to assess the concomitant administration of FLUCELVAX with other vaccines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: A reproductive and developmental toxicity study has been performed in rabbits with a dose level that was approximately 15 times the human dose based on body weight. The study revealed no evidence of impaired female fertility or harm to the fetus due to FLUCELVAX. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this vaccine should be used during pregnancy only if clearly needed.

In a reproductive and developmental toxicity study, the effect of FLUCELVAX on embryo-fetal and post-natal development was evaluated in pregnant rabbits. Animals were administered FLUCELVAX by intramuscular injection 3 times prior to gestation, during the period of organogenesis (gestation day 7) and later in pregnancy (gestation day 20), 0.5 mL/rabbit/occasion (approximately 15-fold excess relative to the projected human dose on a body weight basis). No adverse effects on mating, female fertility, pregnancy, embryo-fetal development, or post-natal development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis.

8.3 Nursing Mothers

FLUCELVAX has not been evaluated in nursing mothers. It is not known whether FLUCELVAX is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FLUCELVAX is administered to a nursing woman.

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 in clinical studies and included in the safety population (6281), 9% (572) were 65 years of age and older and 2% (140) were 75 years of age or older.

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

11 DESCRIPTION

FLUCELVAX (Influenza Vaccine), a vaccine for intramuscular injection, is a subunit influenza vaccine prepared from virus 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 3 virus strains is produced and purified separately then pooled to formulate the trivalent vaccine.

FLUCELVAX is a sterile, slightly opalescent suspension in phosphate buffered saline. FLUCELVAX is standardized according to United States Public Health Service requirements for the 2015-2016 influenza season and is formulated to contain a total of 45 micrograms (mcg) hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 mcg HA of each of the following three influenza strains: A/Brisbane/10/2010 (wild type) (an A/California/7/2009 (H1N1)pdm09-like virus);
A/South Australia/55/2014 (wild type) (an A/Switzerland/9715293/2013 (H3N2)-like virus);
B/Utah/9/2014 (a B/Phuket/3073/2013-like virus). Each dose of FLUCELVAX may contain residual amounts of MDCK cell protein (≤8.4 mcg), protein other than HA (≤ 120 mcg), MDCK cell DNA (≤ 10 ng), polysorbate 80 (≤ 1125 mcg), cetyltrimethlyammonium bromide (≤ 13.5 mcg), and β-propiolactone (<0.5 mcg), which are used in the manufacturing process.

FLUCELVAX contains no preservative or antibiotics.

The tip caps of the pre-filled syringes may contain 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] [*see References (15)*].

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][*see References (15)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

FLUCELVAX did not affect female fertility in a rabbit reproductive and developmental toxicity study.

14 CLINICAL STUDIES

14.1 Efficacy against Culture-Confirmed Influenza in Adults

A multinational (US, Finland, and Poland), randomized, observer-blind, placebo-controlled trial (study 1) 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 4 and 5, respectively).

Table 4: Vaccine Efficacy against Culture-Confirmed Influenza (Study 1[1])

	Number of subjects per protocol	Number of subjects with influenza	Attack Rate (%)	Vaccine Efficacy[2,3]	
				%	Lower Limit of One-Sided 97.5% CI of VE[3,4]
Antigenically Matched Strains					
FLUCELVAX	3776	7	0.19	83.8	61.0
Placebo[5]	3843	44	1.14	--	--
All Culture-Confirmed Influenza					
FLUCELVAX	3776	42	1.11	69.5	55.0
Placebo[5]	3843	140	3.64	--	--

[1] NCT 00630331

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

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

Table 5: Efficacy of FLUCELVAX against Culture-Confirmed Influenza by Influenza Viral Subtype (Study 1[1])

	FLUCELVAX (N=3776)		Placebo (N=3843)		Vaccine Efficacy[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[2,3]
Antigenically Matched Strains						
A/H3N2[4]	0. 05	2	0	0	--	--
A/H1N1	0.13	5	1.12	43	88.2	67.4
B[4]	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] NCT 00630331
[2] No vaccine efficacy (VE) success criterion was pre-specified in the protocol for each individual influenza virus subtype.
[3] Simultaneous one-sided 97.5% confidence intervals for the 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 %
[4] There were too few cases of influenza due to vaccine-matched influenza A/H3N2 or B to adequately assess vaccine efficacy.

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

14.2 Immunogenicity in Adults 18 through 64 Years of Age

Immunogenicity data in adults 18 through 64 years of age were derived from 3 clinical studies including 1353 subjects that received FLUCELVAX. Immune responses measured by hemagglutination inhibition (HI) antibody titers to each virus strain in the vaccine were evaluated in sera obtained 21 days after administration of FLUCELVAX or comparator vaccine.

These studies included clinical study 1 performed in 2007-2008 in the US, Finland and Poland, in which immunogenicity was evaluated in a subset of 978 subjects enrolled at US sites (228, 695, and 55 for FLUCELVAX, AGRIFLU, and placebo, respectively). Among the overall study population enrolled, 58% were female; 67% were Caucasian, 20% Hispanic, 11% Black, 1% Asian and 1% of other ethnic origin; and the mean age was 33 years.

In clinical study 2 conducted in Poland in 2004-2005, immunogenicity data were obtained for 1655 subjects (818 and 837 for FLUCELVAX and AGRIFLU, respectively). Among the overall study population enrolled, 59% were female, 100% of subjects were Caucasian, and the mean age was 43.6 years.

In clinical study 3 conducted in the US in 2005-2006, immunogenicity data were obtained for 610 subjects (307 and 303 for FLUCELVAX and FLUVIRIN, respectively). Among the overall study population enrolled, 64% were female, 96% were Caucasian, and the mean age was 33.9 years. Immunogenicity results are shown separately for the age cohorts 18 through 49 years of age (for which clinical endpoint efficacy data are available, Table 4 and Table 5) and 50 through 64 years of age in Tables 6 and 7.

For all studies outlined in Table 6, antibody responses after vaccination were evaluated according to percentages of subjects with HI antibody titers ≥ 1:40 and seroconversion. For subjects 18 through 64 years of age, success was defined as 1) the lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 70% and 2) the lower bound of the two-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 40% (Table 6).

Table 6: Percentage (%) of subjects with Post-Vaccination HI Titers[1] ≥ 1:40 and Seroconversion in Adult FLUCELVAX Recipients 18 through 49 Years and 50 through 64 Years of Age

		18 through 49 Years		50 through 64 Years	
Study	Vaccine strain	% HI Titer ≥1:40 (95% CI)	% Seroconversion[2] (95% CI)	% HI Titer ≥1:40 (95% CI)	% Seroconversion[2] (95% CI)
		N=228	N=228		
Study 1[3] US, Finland, Poland 2007–2008 N=228	A/H1N1	99 (97-100)	78 (72-83)		
	A/H3N2	99 (98-100)	59 (53-66)		
	B	78 (72-83)	51 (45-58)		
		N=478	N=478	N=340	N=340

Study 2[4] Poland 2004–2005 N=818	A/H1N1	94 (91-96)	73 (69-77)	84 (79-88)	57 (52-63)
	A/H3N2	99 (98-100)	63 (59-68)	99 (97-100)	66 (61-71)
	B	93 (90-95)	88 (84-90)	87 (83-90)	77 (70-79)
		N=307	N=307		
Study 3[5] US 2005–2006 N=307	A/H1N1	96 (94-98)	62 (57-68)		
	A/H3N2	91 (87-94)	85 (81-89)		
	B	94 (91-96)	77 (72-81)		

[1] Egg derived antigen hemagglutination inhibition (HI) assay results
[2] Rates of seroconversion = percentage of subjects with either a pre-vaccination HI titer < 1:10 and a post-vaccination HI titer ≥ 1:40 or a pre-vaccination HI titer ≥ 1:10 and at least a four-fold rise in post-vaccination HI antibody titer
[3] NCT 00630331
[4] NCT 00492063
[5] NCT 00264576

Non-inferiority in Adults 18 through 64 Years of Age

In study 2, non-inferiority of FLUCELVAX to AGRIFLU was demonstrated for HI antibody responses to all three strains for both post-vaccination geometric mean titer (GMT) ratios and seroconversion rates. Success for non-inferiority of the GMT ratio was defined as the lower limit of the two-sided 95% CI for GMT ratio (FLUCELVAX / AGRIFLU) was >0.67; and success for non-inferiority of seroconversion rate was defined as the lower limit of the two-sided 95% CI for the difference between the seroconversion rates (FLUCELVAX – AGRIFLU) was >-10%) (Table 7).

Table 7: Non-inferiority Analysis of FLUCELVAX to a US-Licensed Comparator in Adults 18 through 49 Years and 50 through 64 Years of Age (Study 2[1])

	Ratio or Difference (95% CI) FLUCELVAX Versus Comparator[2]		
	A/H1N1	A/H3N2	B
Subjects 18 through 49 Years: N FLUCELVAX=478; N comparator=472			
GMTs ratio[3,4] (FLUCELVAX / AGRIFLU)	0.96 (0.81, 1.13)	0.98 (0.87, 1.11)	1.07 (0.93, 1.23)

Difference in Seroconversion Rates[4,5,6] (FLUCELVAX – AGRIFLU)	2% (-4, 8)	2% (-5, 8)	5% (1, 10)
Subjects 50 through 64 Years: N FLUCELVAX=340; N comparator=365			
GMTs ratio[3,4] (FLUCELVAX / AGRIFLU)	0.96 (0.79, 1.16)	0.87 (0.74, 1.02)	1.23 (1.02, 1.48)
Difference in Seroconversion Rates[4,5,6] (FLUCELVAX – AGRIFLU)	1% (-6, 8)	-2% (-9, 5)	3% (-4, 9)

[1] NCT00492063
[2] AGRIFLU (Influenza Virus Vaccine)
[3] Non inferiority was demonstrated if the lower limit of the two-sided 95% confidence interval (CI) for geometric mean titer (GMT) ratio (FLUCELVAX/AGRIFLU) was >0.67.
[4] Egg derived antigen hemagglutination inhibition (HI) assay results
[5] Rates of seroconversion = percentage of subjects with either a pre-vaccination HI titer < 1:10 and a post-vaccination HI titer ≥ 1:40 or a pre-vaccination HI titer ≥ 1:10 and at least a four-fold rise in post-vaccination HI antibody titer
[6] Non inferiority was demonstrated if the lower limit of two-sided 95% confidence interval (CI) for difference in percentages of subjects with seroconversion (FLUCELVAX – AGRIFLU) was >-10%.

14.3 Immunogenicity in Adults 65 Years of Age and Older

In clinical study 2, a post-hoc analysis of immune response to FLUCELVAX among adults 65 years of age and older was performed. In this study, 985 subjects 65 years of age or older (504 and 481 for FLUCELVAX and AGRIFLU, respectively) were evaluated. Of these subjects, 56% were female, 100% were Causacian, and the mean age was 71.3 years.

Antibody responses to FLUCELVAX in this older population were evaluated according to percentages of subjects with seroconversion and HI Titer ≥ 1:40 (Table 8) and were compared to antibody responses for non-inferiority to the comparator trivalent influenza vaccine (AGRIFLU, Table 9).

For subjects 65 years of age and older, success was defined as 1) the lower bound of the two-sided 95% CI for the percent of subjects achieving HI an antibody titer ≥ 1:40 should meet or exceed 60% and 2) the lower bound of the two-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 30%.

Table 8: Percentage (%) of subjects with Post-Vaccination HI Titers[1] ≥ 1:40, Seroconversion Rate in Adult FLUCELVAX Recipients 65 Years of Age and Older (Study 2[2])

	Vaccine strain	% of Subjects with HI Titer ≥1:40 [1] (95% CI)	% of Subjects with Seroconversion[1,3] (95% CI)
N=504	A/H1N1	86 (83-89)	55 (50-59)
	A/H3N2	97 (95-98)	68 (64-72)
	B	90 (87-93)	80 (76-84)

[1] Egg derived antigen hemagglutination inhibition (HI) assay results
[2] NCT 00492063
[3] Rates of seroconversion = percentage of subjects with either a pre-vaccination HI titer < 1:10 and a post-vaccination HI titer ≥ 1:40 or a pre-vaccination HI titer ≥ 1:10 and at least a four-fold rise in post-vaccination HI antibody titer

Non-inferiority in Adults 65 Years of Age and Older
Non-inferiority of FLUCELVAX to AGRIFLU was demonstrated for HI antibody responses to all three strains for both post-vaccination GMT ratios and seroconversion rates. Success for non-inferiority of the GMT ratio was defined as the lower limit of the two-sided 95% CI for the GMT ratio (FLUCELVAX / AGRIFLU) >0.67; and success for non-inferiority of seroconversion rate was defined as the lower limit of the two-sided 95% CI for the difference between the seroconversion rates (FLUCELVAX – AGRIFLU) >-10%) (Table 9).

Table 9: Non-inferiority Analysis of FLUCELVAX to a US-Licensed Comparator in Adults 65 Years of Age and Older (Study 2[1])

	Ratio or Difference (95% CI) FLUCELVAX Versus Comparator[2] (N FLUCELVAX=504; N comparator=481)		
	A/H1N1	**A/H3N2**	**B**
GMTs ratio[3,4] (FLUCELVAX / AGRIFLU)	1.06 (0.92, 1.22)	0.97 (0.84, 1.12)	1.28 (1.1, 1.48)
Difference in Seroconversion Rates[4,5,6] (FLUCELVAX – AGRIFLU)	-1% (-7, 6)	3% (-2, 9)	7% (1, 12)

[1] NCT 00492063
[2] AGRIFLU (Influenza Virus Vaccine)
[3] Non inferiority was demonstrated if the lower limit of the two-sided 95% confidence interval (CI) for geometric mean titer (GMT) ratio (FLUCELVAX/AGRIFLU) was >0.67.

[4] Egg derived antigen hemagglutination inhibition (HI) assay results
[5] Rates of seroconversion = percentage of subjects with either a pre-vaccination HI titer < 1:10 and a post-vaccination HI titer ≥ 1:40 or a pre-vaccination HI titer ≥ 1:10 and at least a four-fold rise in post-vaccination HI antibody titer
[6] Non inferiority was demonstrated if the lower limit of the two-sided 95% confidence interval (CI) for difference in percentages of subjects with seroconversion (FLUCELVAX – AGRIFLU) was >-10%.

14.4 Immunogenicity in Children and Adolescents 4 through 17 Years of Age
A randomized, observer blind, active-controlled clinical trial conducted in the US and Europe evaluated the immunogenicity of FLUCELVAX compared to a US-licensed trivalent inactivated influenza vaccine (FLUVIRIN) in healthy children and adolescents 4 through 17 years of age (study 4). In study 4, all children 4 through 8 years of age received 2 doses of vaccine (administered 4 weeks apart) and children and adolescents 8 through 17 years of age received one dose of vaccine. The population analyzed for immunogenicity included 583 subjects who received FLUCELVAX and 574 subjects who received FLUVIRIN. Serum HI antibody titers to each virus strain contained in the vaccine were evaluated 3 to 4 weeks after last vaccination (day 29 in children and adolescents 9 through 17 years of age, and day 50 in children 4 through 8 years of age).

For children and adolescents 9 through 17 years, pre-specified, non-comparative immunogenicity success criteria for FLUCELVAX were met following vaccination for all influenza vaccine strains. For children 4 through 8 years, pre-specified, non-comparative immunogenicity success criteria were met for A/H1N1 and A/H3N2 influenza strains, but not for the influenza B strain (Table 10).

Table 10: Percentage (%) of Subjects with Post-Vaccination HI Titers[1] ≥ 1:40, and Seroconversion Rate in FLUCELVAX Recipients 4 through 17 Years of Age (Study 4[2])

Children 4 through 8 years of age (N=441)			
Strain-specific anti-hemagglutinin antibody	% (95% CI)		
	A/H1N1	A/H3N2	B
% of subjects with HI ≥1:40[4]	99% (97%-99%)	99% (97%-100%)	64% (60%-69%)
% of subjects with seroconversion[3,4]	96% (94%-98%)	80% (76%-84%)	62% (57%-66%)
Children and Adolescents 9 through 17 years of age (N= 142)			
% of subjects with HI ≥1:40[4] (N=142)	99% (96%-100%)	100% (97%-100%)	95% (90%-98%)
% of subjects with seroconversion[3,4] (N=141)	74% (66%-81%)	52% (44%-61%)	63% (55%-71%)

[1] Cell-derived antigen hemagglutination inhibition (HI) assay results
[2] NCT 00645411
[3] % of subjects with seroconversion = percentage of subjects with either a pre-vaccination HI titer < 1:10 and a post-vaccination HI titer ≥ 1:40 or a pre-vaccination HI titer ≥ 1:10 and at least a four-fold rise in post-vaccination HI antibody titer
[4] Immunogenicity success criteria were met if the lower limit of the two-sided 95% confidence interval (CI) of the percentage of subjects with HI titer ≥1:40 was ≥70% and the lower limit of the two-sided 95% CI of the percentage of subjects with seroconversion was ≥40%.

Non-inferiority of FLUCELVAX compared to the comparator trivalent influenza vaccine (FLUVIRIN) was evaluated in children 4 through 8 years of age. Non-inferiority was demonstrated in this age group with respect to the A/H1N1 and B influenza strains but not the A/H3N2 influenza strain (Table 11).

Table 11: Non-inferiority Analysis of FLUCELVAX to a US-Licensed Comparator[1] in Children 4 through 8 Years of Age (Study 4[2])

	Ratio or Difference (95% CI) FLUCELVAX (N=441)[3]; Comparator[1] (N=430)[3]		
	A/H1N1	A/H3N2	B
GMT ratio[4,5] (FLUCELVAX / comparator)	0.89 (0.76-1.04)	0.56 (0.47-0.67)	0.85 (0.68-1.06)
Difference in Seroconversion Rates[4,6] (FLUCELVAX - comparator)	0% (-3% to 2%)	-7% (-12% to -2%)	0% (-6% to 7%)

[1] FLUVIRIN (Influenza Virus Vaccine)
[2] NCT 00645411
[3] Per protocol population
[4] Cell-derived antigen hemagglutination inhibition (HI) assay results
[5] Non-inferiority was demonstrated if the lower limit of the two-sided 95% confidence interval (CI) for geometric mean titer (GMT) ratio (FLUCELVAX/comparator) was >0.67.
[6] Non-inferiority was demonstrated if the lower limit of the two-sided 95% CI for difference in percentages of subjects with seroconversion (FLUCELVAX-comparator) was >-10%.

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, 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 is supplied in a carton containing ten 0.5 mL single-dose syringes without needles:

- Carton NDC number: 70461-614-01
- Pre-filled syringe NDC number: 70461-614-11

The tip caps of the pre-filled syringes may contain natural rubber latex. The syringe and syringe plunger stopper are manufactured without natural rubber latex.

Store this product refrigerated at 2°C to 8°C (36ºF to 46ºF). 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.

Educate vaccine recipients regarding the potential side effects; clinicians should emphasize that (1) FLUCELVAX contains non-infectious particles and cannot cause influenza and (2) FLUCELVAX 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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