

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

FLUCELVAX® QUAD

Influenza Vaccine (surface antigen, inactivated, prepared in cell cultures)

Suspension for Injection

Active Immunizing Agent for the Prevention of Influenza

ATC Code: J07BB02

20XX/20XX strains	
A/<Official strain> (H1N1)-like virus	15 micrograms HA
A/<Official strain> (H3N2)-like virus	15 micrograms HA
B/<Official strain> <Victoria>-like virus	15 micrograms HA
B/<Official strain> <Yamagata>-like virus	15 micrograms HA

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RECENT MAJOR LABEL CHANGES

Not applicable.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

FLUCELVAX® QUAD is a quadrivalent inactivated vaccine indicated for active immunization of adults and children aged 9 years or older for the prevention of influenza disease caused by influenza virus subtypes A and B contained in the vaccine.

The National Advisory Committee on Immunization (NACI) provides additional guidance on the use of the influenza vaccine in Canada. Please refer to the published Statement on Seasonal Influenza Vaccine for the current season.

1.1 Pediatrics

Pediatrics (9 to < 18 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of FLUCELVAX® QUAD in pediatric patients has been established; therefore, Health Canada has authorized an indication for use in the pediatric population 9 years of age and older (see **Error! Reference source not found.** ADVERSE REACTIONS, Clinical Trial Adverse Reactions (Pediatrics); and CLINICAL TRIALS).

2 CONTRAINDICATIONS

FLUCELVAX® QUAD is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 DOSAGE AND ADMINISTRATION

3.1 Recommended Dose

Adults and children from 9 years of age: a single 0.5 mL dose.

3.2 Administration

The vaccine should be administered by intramuscular injection. The preferred site for intramuscular injection is the deltoid muscle of the upper arm.

Shake before use. After shaking, the normal appearance of the vaccine is a clear to slightly opalescent suspension.

Visually inspect the contents of each multi-dose vial or pre-filled syringe for particulate matter and/or variation in appearance prior to administration. If either condition exists, do not administer the vaccine.

FLUCELVAX® QUAD must not be mixed with other products.

Multi-Dose Vial

Between uses, return the multi-dose vial to the recommended storage conditions.

Please refer to the Canadian Immunization Guide, Public Health Agency of Canada, for general

information regarding vaccine administration practices.

4 OVERDOSAGE

There is no experience of overdose with FLUCELVAX® QUAD.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medical Ingredients
Intramuscular Injection	Pre-filled syringe/ Multi-dose vials Each 0.5 mL contains 15 mcg haemagglutinin (HA) of each influenza virus strain listed below	<u>Excipients:</u> Disodium phosphate dihydrate, Magnesium chloride hexahydrate, Potassium chloride, Potassium dihydrogen phosphate, Sodium chloride, Thimerosal*, Water for injections <u>Residuals:</u> beta-propiolactone, cetyltrimethylammonium bromide, polysorbate 80

*Multi-dose vials only.

For the 20XX/20XX Northern Hemisphere Influenza Season, FLUCELVAX® QUAD contains the following strains:

- A/Official strain (H1N1)-like virus (A/actual strain (H1N1))
- A/Official strain (H3N2)-like virus (A/actual strain (H3N2))
- B/Official strain (Victoria)-like virus (B/actual strain)
- B/Official strain (Yamagata)-like virus (B/actual strain)

As recommended annually by the World Health Organization (WHO) and the National Advisory Committee on Immunization (NACI).

Packaging

FLUCELVAX® QUAD suspension for injection is supplied in two presentations:

- 0.5 mL suspension in needle-free pre-filled syringes (type I glass), with a plunger stopper (bromobutyl rubber) (needles not supplied)
- 5.0 mL multi-dose vial (type 1 glass), with rubber (bromobutyl) stopper

FLUCELVAX® QUAD 0.5 mL pre-filled syringes contain no preservative or antibiotics.

FLUCELVAX® QUAD 5 mL multi-dose vial formulation contains thimerosal, a mercury derivative, added as a preservative. Each 0.5 mL dose from the multi-dose vial contains 25 mcg mercury. FLUCELVAX® QUAD 5 mL multi-dose vial formulation contains no antibiotics.

The tip caps and plungers of the pre-filled syringes and the multi-dose vial stopper are not made with natural rubber latex.

Both presentations of FLUCELVAX® QUAD are considered safe for use in persons with latex allergies.

6 DESCRIPTION

FLUCELVAX® QUAD 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 beta-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.

Eggs are not used in the manufacturing process, therefore, FLUCELVAX® QUAD does not contain egg protein.

FLUCELVAX® QUAD is a sterile, slightly opalescent suspension in phosphate buffered saline.

FLUCELVAX® QUAD is standardized according to recommendations from the World Health Organization (WHO) and National Advisory Committee on Immunization (NACI) for the Northern Hemisphere 20XX – 20XX season.

7 WARNINGS AND PRECAUTIONS

General

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Immunization should be postponed in patients with febrile illness until the fever is resolved.

A protective immune response may not be elicited in all vaccine recipients.

Hematologic

As with other intramuscular injections, administration of FLUCELVAX® QUAD requires careful consideration in patients with clinically significant bleeding disorders.

Immune

Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.

Neurologic

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

7.1 Special Populations

7.1.1 Pregnant Women

Healthcare providers should assess the benefit and potential risks of administering the vaccine to pregnant women taking into consideration official recommendations.

The safety of FLUCELVAX® QUAD in pregnancy has not been assessed in clinical trials.

There are no reproductive and developmental toxicology studies with FLUCELVAX® QUAD. Reproductive and developmental toxicology data from trivalent influenza vaccines do not predict an increased risk of developmental abnormalities.

7.1.2 Breast-feeding

FLUCELVAX® QUAD has not been evaluated in nursing mothers.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse event information is derived from clinical trials and worldwide post-marketing experience with FLUCELVAX® QUAD.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of FLUCELVAX® QUAD in adults 18 years and older 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 to less than 65 years of age and 1340 adults 65 years of age and older.

In this study, subjects received FLUCELVAX® QUAD (N=1334) or one of the two formulations of comparator trivalent influenza vaccine (FLUCELVAX, TIVc, TIV1c N=677 or TIV2c N= 669). 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 in the safety population of adults 18 to less than 65 years of age and 65 years of age and older are shown in Table 2. Overall, the most common (≥10%) local and systemic reactions in adults 18 to less than 65 years of age were injection site pain (45%),

headache (19%), fatigue (18%), myalgia (15%), injection site erythema (13%), induration (12%) and nausea (10%). The most common ($\geq 10\%$) local and systemic reactions in adults 65 years of age and older were injection site pain (22%) and injection site erythema (12%).

Table 2: Incidence of Solicited Adverse Reactions¹ in the Adult and Elderly Safety Population² Reported Within 7 Days of Vaccination (Study 1)

	Percentages of Subjects with Any (Severe) Solicited Reactions ³					
	18 to less than 65 years of age			≥ 65 years of age		
	FLUCELVAX [®] QUAD N=663	Trivalent Influenza Vaccine		FLUCELVAX [®] QUAD N=656	Trivalent Influenza Vaccine	
TIV1c N=330		TIV2c N=327	TIV1c N=340		TIV2c N=336	
Local Adverse Reactions						
Injection site pain	45 (<1)	37 (<1)	41 (0)	22 (0)	19 (0)	19 (0)
Injection site erythema	13 (0)	13 (0)	10 (0)	12 (0)	11 (0)	10 (0)
Injection site induration	12 (0)	10 (<1)	10 (0)	9 (0)	7 (0)	8 (0)
Injection site ecchymosis	4 (0)	3 (<1)	5 (0)	5 (0)	4 (0)	5 (0)
Systemic Adverse Reactions						
Headache	19 (<1)	19 (<1)	19 (<1)	9 (<1)	9 (<1)	8 (<1)
Fatigue	18 (<1)	22 (<1)	16 (2)	9 (<1)	11 (<1)	9 (<1)
Myalgia	15 (<1)	15 (<1)	15 (1)	8 (<1)	9 (<1)	8 (<1)
Nausea	10 (<1)	7 (<1)	9 (1)	4 (<1)	4 (0)	4 (<1)
Arthralgia	8 (<1)	8 (0)	10 (<1)	6 (<1)	5 (<1)	7 (<1)
Loss of appetite	8 (<1)	9 (<1)	8 (<1)	4 (<1)	5 (0)	4 (<1)
Diarrhea	7 (<1)	8 (0)	8 (<1)	4 (<1)	5 (<1)	5 (<1)
Chills	6 (<1)	6 (<1)	6 (0)	4 (<1)	4 (<1)	5 (<1)
Vomiting	3 (0)	2 (<1)	<1(0)	<1 (<1)	<1 (0)	<1(0)
Fever: ≥ 38.0 °C (≥ 40.0 °C)	<1 (0)	<1 (0)	<1 (0)	<1 (0)	<1 (0)	<1 (0)

¹ All solicited local and systemic adverse events reported within 7 days of vaccination are included.

² Safety population: all subjects in the exposed population who provided post-vaccination safety data.

³ Percentage of severe adverse reactions are presented in parenthesis.

Definition of severe reactions: Erythema, Induration and Ecchymosis: Severe= >100 mm; Pain and systemic adverse reactions: Severe = unable to perform daily activity.

Unsolicited adverse events (AEs) were collected for 21 days after vaccination. Comparable percentages of unsolicited events were reported in subjects in the FLUCELVAX[®] QUAD, TIV1c and TIV2c groups, (16.1%, 14.7% and 16.5% respectively).

Serious adverse events (SAEs) were collected throughout the study duration (until 6 months after vaccination). Comparable percentages of SAEs were reported in subjects in the FLUCELVAX[®] QUAD, TIV1c and TIV2c groups, (3.9%, 3.3% and 3.2% respectively). No SAE was assessed as being related to study vaccines.

8.3 Clinical Trial Adverse Reactions (Pediatrics)

Children 9 to less than 18 years of age

The safety of FLUCELVAX® QUAD in children 4 to less than 18 years of age 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 to less than 18 years of age; 1161 children 4 to less than 9 years of age and 1171 children 9 to less than 18 years of age.

In this study, subjects 9 to less than 18 years received a single dose of FLUCELVAX® QUAD or one of the two formulations of comparator trivalent influenza vaccine (FLUCELVAX® QUAD N=1159, TIV1c N=593 or TIV2c N= 580). 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 in the safety population of children 9 years to less than 18 years of age are shown in Table 3.

The most common ($\geq 10\%$) local and systemic reactions in children and adolescents 9 to less than 18 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%).

Table 3: Incidence of Solicited Adverse Reactions¹ in the Safety Population² of Children 9 to less than 18 years of age Reported After Any Dose Within 7 Days of Vaccination (Study 2)

	Percentages of Subjects with Any (Severe) Solicited Reactions ³		
	FLUCELVAX® QUAD N=579	Trivalent Influenza Vaccine	
		TIV1c N=294	TIV2c N=281-282 ⁴
Local Adverse Reactions			
Injection site pain	58 (1)	51 (<1)	50 (0)
Injection site erythema	19 (< 1)	17(0)	15 (< 1)
Injection site induration	15 (0)	15 (0)	13 (< 1)
Injection site ecchymosis	4 (0)	5 (0)	5 (0)
Systemic Adverse Reactions			
Headache	22 (1)	23 (2)	18 (1)
Fatigue	18 (< 1)	16 (1)	16 (< 1)
Myalgia	16 (< 1)	17(< 1)	15 (< 1)
Loss of appetite	9 (0)	9 (< 1)	9 (0)
Nausea	9 (< 1)	8 (1)	7 (1)
Fever: ≥ 38.0 °C (≥ 40.0 °C)	1 (< 1)	3 (0)	1 (0)
Arthralgia	6 (0)	6 (0)	8 (< 1)
Vomiting	2 (0)	1 (0)	2 (0)
Diarrhea	4 (0)	4 (0)	3 (< 1)
Chills	7 (0)	6 (1)	4 (1)

¹ All solicited local and systemic adverse events reported within 7 days of vaccination are included.

² Safety population: all subjects in the exposed population who provided post-vaccination safety data.

³ Percentage of severe adverse reactions are presented in parenthesis.

Definition of severe reactions: Erythema, Induration and Ecchymosis: Severe= >100 mm; Pain and systemic adverse reactions: Severe = unable to perform daily activity.

⁴ 281 subjects provided data for Injection site ecchymosis.

Unsolicited adverse events were collected for 21 days after last vaccination. Comparable percentages of unsolicited events were reported in children 9 through 17 years of age in the FLUCELVAX[®] QUAD, TIV1c and TIV2c groups, (37.2%, 36.7% and 39.8% respectively).

Serious adverse events (SAEs) were collected throughout the study duration (until 6 months after last vaccination). Comparable percentages of SAEs were reported in children 9 through 17 years of age in the FLUCELVAX[®] QUAD, TIV1c and TIV2c groups, (0.9%, 1.3% and 0% respectively). No SAE was assessed as being related to study vaccines.

8.4 Post-Market Adverse Reactions

The following events have been identified during post-approval use of FLUCELVAX[®] QUAD:

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

Nervous system disorders: paraesthesia.

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.

9 DRUG INTERACTIONS

9.1 Drug-Drug Interactions

Interactions with other drugs have not been established.

There are no data available on co-administration of FLUCELVAX[®] QUAD with other vaccines.

If FLUCELVAX[®] QUAD is to be given at the same time as another injectable vaccine(s), the vaccine(s) should always be administered to separate limbs. It should be noted that adverse reactions may be intensified.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

FLUCELVAX[®] QUAD provides active immunization against four influenza virus strains (two A subtypes and two B types) contained in the vaccine. FLUCELVAX[®] QUAD induces humoral antibodies against the haemagglutinins. These antibodies neutralize influenza viruses.

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 post-vaccination with inactivated influenza virus 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.

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 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 Canada in the upcoming winter on the basis of the recommendations from the World Health Organization (WHO) and the National Advisory Committee on Immunization (NACI).

10.2 Pharmacodynamics

Seroprotection is generally obtained within 3 weeks following vaccination.

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.

Duration of Effect: Protection against influenza post-vaccination is expected throughout the influenza season for which the vaccine is indicated.

11 STORAGE, STABILITY AND DISPOSAL

Store under refrigeration at 2° to 8°C. Do not freeze. Protect from exposure to light. Do not use after the expiration date. Any unused product or waste material should be disposed of in compliance with local requirements.

The multi-dose vial must be used within 28 days from removal of the first dose, and between uses, should be returned to the recommended storage conditions.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

Drug Substance

For the 20XX-20XX season, FLUCELVAX® QUAD contains:

Influenza virus surface antigens (haemagglutinin and neuraminidase)*, inactivated, of the following strains:

A/<Official strain> (H1N1)-like virus	15 micrograms HA**
A/<Official strain> (H3N2)-like virus	15 micrograms HA**
B/<Official strain> <Victoria>-like virus	15 micrograms HA**
B/<Official strain> <Yamagata>-like virus	15 micrograms HA**

per 0.5 mL dose

* propagated in Madin Darby Canine Kidney (MDCK) cells

** haemagglutinin

Product Characteristics

FLUCELVAX® QUAD is a clear to slightly opalescent liquid.

FLUCELVAX® QUAD 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 beta-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.

Eggs are not used in the manufacturing process, therefore, FLUCELVAX® QUAD does not contain egg protein.

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

Two safety and immunogenicity clinical trials (V130_01 and V130_03) were conducted in the United States with FLUCELVAX® QUAD, one in adults 18 years and older, and one in children 4 to less than 18 years of age. Two trials (V58P12 and V58P13) were conducted with TIVc, one safety and immunogenicity trial in children 3 to less than 18 years and one safety, efficacy and immunogenicity trial in adults 18 years and older. The trial designs and demographics of the clinical trial are presented in Table 4.

Table 4: Summary of Trial Designs and Study Demographics for Clinical Trials with FLUCELVAX® QUAD and TIVc.

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N)*	Mean age (Range)**	Sex**
1 (V130_01)	Randomized, double-blind, controlled study with FLUCELVAX® QUAD and two formulations of comparator trivalent influenza vaccine (TIV1c or TIV2c)	Single dose 0.5 mL IM	FLUCELVAX® QUAD=1335 TIV1c=676 TIV2c=669	57.4 years (18-96)	Male: 603 (45%) Female: 732 (55%)
2 (V130_03)	Randomized, double-blind, controlled study with FLUCELVAX® QUAD and two formulations of comparator trivalent influenza vaccine (TIV1c or TIV2c)	Single dose*** 0.5 mL IM	FLUCELVAX® QUAD=1159 TIV1c=593 TIV2c=581	9.5 years (4-17)	Male: 603 (52%) Female: 556 (48%)
3 (V58P13)	Randomized, observer-blind, placebo-controlled, multicenter study with TIVc and egg-derived comparator influenza vaccine (TIVeA) and placebo	Single dose 0.5 mL IM	TIVc=3828 TIVeA=3676 PLACEBO=3900	32.7 years (18-49)	Male: 1740 (45%) Female: 2088 (55%)
4 (V58P12)	Randomized, observer blind, controlled study with TIVc and egg-derived comparator trivalent influenza vaccine (TIVeF)	Single dose 0.5 mL IM (cohort 1 and 2); two doses of 0.5 mL 4 weeks apart (cohort 3)	TIVc=2264 TIVeF=1340	12.6 years**** (9-17)	Male: 1165 (51%) Female 1099 (49%)

*All randomized subjects.

** Age and gender data are presented only for subjects who received FLUCELVAX® QUAD in studies 1 and 2 and TIVc in studies 3 and 4.

***Previously unvaccinated subjects <9 years of age received a second dose after 4 weeks.

****For 9-17 years of age group (cohort 1)

TIVeA = egg-based trivalent influenza vaccine (Agrimflu); TIVeF = egg-based trivalent influenza vaccine (Fluvirin)

13.2 Study Results

Efficacy against Culture-Confirmed Influenza

The efficacy experience with trivalent influenza vaccine (FLUCELVAX, TIVc) is relevant to FLUCELVAX® QUAD because both vaccines are manufactured using the same process and have overlapping compositions.

A multinational (US, Finland and Poland), randomized, observer-blinded, placebo-controlled trial (Study 3) was performed to assess the clinical efficacy and safety of TIVc during the 2007-2008 influenza season in adults aged 18 to 49 years. A total of 11,404 subjects were enrolled to receive TIVc (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.

Vaccine efficacy was assessed by the prevention of culture-confirmed symptomatic influenza illness caused by viruses antigenically matched to those in the vaccine compared to placebo. Influenza cases were identified by active and passive surveillance of influenza-like illness (ILI). ILI was defined according to Centers for Disease Control and Prevention (CDC) case definition, i.e., a fever (oral temperature $\geq 100.0^{\circ}\text{F}$ / 38°C) and cough or sore throat. After an episode of ILI, nose and throat swab samples were collected for analysis. Vaccine efficacies against vaccine-matched influenza viral strains, against all influenza viral strains, and against individual influenza viral subtypes were calculated (**Error! Reference source not found.** Tables 5 and REF_Ref526345327 \h * MERGEFORMAT **Error! Reference source not found.**6).

Table 5: Vaccine Efficacy against Culture-Confirmed Influenza

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

Abbreviations: CI = confidence interval.

1. Per Protocol (PP) Population, Efficacy: All subjects in the Exposed/MIIT Efficacy population who correctly received the vaccine, provided evaluable swab samples within the 120 hour time window, and had no major protocol violation as defined prior to unblinding. Exposed/Modified Intention-to-Treat (MIIT) Efficacy Population: All subjects in the enrolled population who received a study vaccination. PP population: 52 (1.4%) and 57 (1.5%) of the enrolled subjects were excluded for TIVc and placebo groups, respectively.

2. Simultaneous one-sided 97.5% confidence intervals for the vaccine efficacy of each influenza vaccine relative to placebo based on the Sidak-corrected score confidence intervals for the two relative risks. Vaccine Efficacy = $(1 - \text{Relative Risk}) \times 100\%$.

3. Vaccine Efficacy: Each vaccine was considered statistically compliant with the May 2007 CBER guidance for industry criteria for estimating VE against placebo if the lower limit of the one-sided simultaneous 97.5% Confidence Interval (CI) for the estimate of VE relative to placebo was greater than 40%.

Table 6: Vaccine Efficacy of Trivalent Influenza Vaccine versus Placebo against Culture-Confirmed Influenza by Influenza Viral Subtype (Per Protocol Analysis Set¹)

	TIVc (N=3776)		Placebo (N=3843)		Vaccine Efficacy ^{2, 4}	
	Attack Rate (%)	Number of Subjects with Influenza	Attack Rate (%)	Number of Subjects with Influenza	%	Lower Limit of One-Sided 97.5% CI
Antigenically Matched Strains						
A/H3N2³	0.05	2	0	0	--	--
A/H1N1	0.13	5	1.12	43	88.2	67.4
B³	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

Abbreviations: CI = confidence interval.

1. Per Protocol (PP) Population, Efficacy: All subjects in the Exposed/MITT Efficacy population who correctly received the vaccine, provided evaluable swab samples within the 120 hour time window, and had no major protocol violation as defined prior to unblinding. Exposed/Modified Intention-to-Treat (MITT) Efficacy Population: All subjects in the enrolled population who received a study vaccination. PP population: 52 and 57 of the enrolled subjects were excluded for TIVc and placebo groups, respectively.

2. Simultaneous one-sided 97.5% confidence intervals for the vaccine efficacy of each influenza vaccine relative to placebo based on the Sidak-corrected score confidence intervals for the two relative risks. 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. Vaccine efficacy criterion were not pre-specified in the protocol for individual virus subtypes.

4. Vaccine efficacy criterion were not pre-specified in the protocol for individual virus subtypes.

There are no efficacy data demonstrating prevention of influenza disease after vaccination with FLUCELVAX or FLUCELVAX[®] QUAD in the pediatric age group.

Immunogenicity of FLUCELVAX[®] QUAD in Adults 18 years of age and above

Immunogenicity of FLUCELVAX[®] QUAD 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[®] QUAD or one of the two formulations of comparator trivalent influenza vaccine (FLUCELVAX[®] QUAD N=1334, TIV1c N=677 or TIV2c N= 669), each containing an influenza type B virus that corresponded to one of the two B viruses in QIV (a type B virus of the Massachusetts lineage (TIV1c) or a type B virus of the Brisbane lineage (TIV2c)), respectively and the same influenza A subtype viruses. The treatment randomization ratio was 2:1:1 (FLUCELVAX[®] QUAD:TIV1c:TIV2c). In the per protocol set, the mean age of subjects who received FLUCELVAX[®] QUAD 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 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 with a prevaccination HI titer of ≥10 and a minimum 4-fold increase in serum HI antibody titer. Noninferiority criteria for GMT was defined as the upper bound of the 2-sided 95% confidence interval (CI) for the ratio of GMTs (GMT TIV1c or TIV2c /GMT QIVc) for HI antibody should not exceed the noninferiority

margin of 1.5. Noninferiority criteria for seroconversion was defined as the upper bound of the 2-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV1c or TIV2c – % seroconversion QIVc) for HI antibody should not exceed the margin of 10%.

FLUCELVAX® QUAD was noninferior to trivalent influenza vaccine. Noninferiority was established for all 4 influenza strains included in FLUCELVAX® QUAD, as assessed by ratios of GMTs and the differences in the percentages of subjects achieving seroconversion at 3 weeks following vaccination (Table 7).

Table 7: Noninferiority of FLUCELVAX® QUAD Relative to Trivalent Influenza Vaccine in Adults 18 Years of Age and Above, Per Protocol Analysis Set^c

		FLUCELVAX® QUAD N = 1250	TIV1c/TIV2c ^a 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 ^b (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 ^b (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 ^b (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 ^b (95% CI)	39.8% (37.0-42.5)	35.4% (31.7-39.2)	-	-4.4% (-8.9-0.2)

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

^a The comparator vaccine for noninferiority comparisons for A/H1N1, A/H3N2 and B1 is TIV1c, for B2 it is TIV2c.

^b Seroconversion rate = percentage of subjects with either a prevaccination HI titer < 1:10 and postvaccination HI titer ≥ 1:40 or with a prevaccination HI titer ≥ 1:10 and a minimum 4-fold increase in postvaccination HI antibody titer.

^c The per protocol (PP) analysis set is defined as all subjects in the FAS Immunogenicity who correctly received the vaccine (i.e., receive the vaccine to which the subjects is randomized and at the scheduled time points), had 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. PP population: 85 (6.4%), 41 (6.1%) and 31 (4.5%) enrolled subjects were excluded for QIVc, TIV1c and TIV2c groups, respectively.

Immunogenicity in Children and Adolescents 9 to less than 18 years of age

Immunogenicity of FLUCELVAX® QUAD was evaluated in children 9 to less than 18 years of age as part of a randomized, double-blind, controlled study conducted in the pediatric population 4 to less than 18 years of age in the US (Study 2). In this study, subjects received FLUCELVAX® QUAD or one of the two formulations of comparator trivalent influenza vaccine (FLUCELVAX® QUAD N=1159, TIV1c N=593 or TIV2c N= 580). Subjects were randomized at an approximately 2:1:1 ratio to receive QIVc, TIV1c, or TIV2c vaccine. Enrolled subjects were first split into age cohorts based on age at time of enrollment (at least 4 to less than 9 years of age and at least 9 to less than 18 years of age). In the per protocol set, the mean age 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 GMTs of 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 \geq 1:40 or with a prevaccination HI titer \geq 1:10 and a minimum 4-fold increase in serum HI antibody titer. The definition of noninferiority criteria for GMT and seroconversion was the same as for Study 1.

FLUCELVAX[®] QUAD was noninferior to trivalent influenza vaccine. Noninferiority was established for all 4 influenza strains included in the FLUCELVAX[®] QUAD, as assessed by ratios of GMTs and the differences in the percentages of subjects achieving seroconversion at 3 weeks following vaccination (Table 8).

Table 8: Noninferiority^a of FLUCELVAX[®] QUAD Relative to Trivalent Influenza Vaccine in Children and Adolescents 4 to less than 18 Years of Age, Per Protocol Analysis Set

		FLUCELVAX [®] QUAD	TIV1c/TIV2c ^b	Vaccine Group Ratio	Vaccine Group Difference
A/H1N1		N = 1014	N = 510		
	GMT (95% CI)	1090 (1027-1157)	1125 (1034-1224)	1.03 (0.93-1.14)	-
	Seroconversion Rate ^c (95% CI)	72% (69-75)	75% (70-78)	-	2% (-2.5- 6.9)
A/H3N2		N = 1013	N = 510		
	GMT (95% CI)	738 (703-774)	776 (725-831)	1.05 (0.97-1.14)	-
	Seroconversion Rate ^c (95% CI)	47% (44-50)	51% (46-55)	-	4% (-1.4- 9.2)
B1		N = 1013	N = 510		
	GMT (95% CI)	155 (146-165)	154 (141-168)	0.99 (0.89-1.1)	-
	Seroconversion Rate ^c (95% CI)	66% (63-69)	66% (62-70)	-	0% (-5.5- 4.5)
B2		N = 1009	N = 501		
	GMT (95% CI)	185 (171-200)	185 (166-207)	1 (0.87-1.14)	-
	Seroconversion Rate ^c (95% CI)	73% (70-76)	71% (67-75)	-	-2% (-6.5- 3.2)

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

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

^b The comparator vaccine for noninferiority comparisons for A/H1N1, A/H3N2 and B1 is TIV1c, for the B2 strain the comparator vaccine is TIV2c.

^c Seroconversion rate = percentage of subjects with either a prevaccination HI titer < 1:10 and postvaccination HI titer \geq 1:40 or with a prevaccination HI titer \geq 1:10 and a minimum 4-fold increase in postvaccination HI antibody titer. The definition of the PP analysis set in study V130_03 is the same as in V130_01, see Table 7 above. PP population: 145 (12.5%), 83 (14.0%) and 79 (13.6%) enrolled subjects were excluded for QIVc, TIV1c and TIV2c groups, respectively.

The immunogenicity data with TIVc are relevant to the use of FLUCELVAX® QUAD because both vaccines are manufactured using the same process and have overlapping compositions. Immunogenicity of TIVc in children 9 to less than 18 years of age was evaluated as part of a randomised, double-blind, controlled study (Study 4) that was performed in the pediatric population 3 to less than 18 years of age in the 2007-2008 northern hemisphere influenza season. In the 9 to < 18 year age group, CBER criteria for TIVc for seroconversion and seroprotection were achieved for all three strains (Table 9).

Table 9: Seroprotection and Seroconversion Rates in Pediatric Subjects Vaccinated with TIVc, Per Protocol Analysis Set^a

		V58P12 (Subjects 9 to <18 years)	
		TIVc	TIVeF
		N=142	N=144
A/H1N1	Seroprotection Rate ^b	99% (96-100)	98% (94-100)
	Seroconversion Rate ^c	74% (66-81)	74% (66-81)
A/H3N2	Seroprotection Rate	100% (97-100)	100% (97-100)
	Seroconversion Rate	52% (44-61)	78% (70-84)
B	Seroprotection Rate	95% (90-98)	94% (89-98)
	Seroconversion Rate	63% (55-71)	69% (61-76)

HI data, cell-derived assay

TIVc = cell-based trivalent influenza vaccine; TIVeF = egg-based trivalent influenza vaccine (Fluvirin)

^a PP population: 9 (6.0%) and 10 (6.5%) enrolled subjects were excluded for TIVc and TIVeF, respectively.

^b Seroprotection rate equals percentage of subjects with HI titers greater or equal than 1:40. CBER criteria for seroprotection: The lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody titer \geq 1:40 should meet or exceed 70%.

^c Seroconversion rate equals percentage of subjects with either a prevaccination HI titre <1:10 and postvaccination HI titre \geq 1:40 or with a prevaccination HI titre \geq 1:10 and a minimum 4-fold increase in postvaccination HI antibody titre. CBER criteria for seroconversion: The lower bound of the two-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 40%.

14 NON-CLINICAL TOXICOLOGY

Non-clinical data reveal no special hazard for humans based on a repeat dose toxicity study and a reproductive and developmental toxicity study with FLUCELVAX (trivalent formulation).

In a repeat-dose toxicity study, male and female rabbits received 2 intramuscular doses of trivalent vaccine (45 mcg HA/dose) 1 week apart. There was no evidence of systemic toxicity and trivalent vaccine was locally well tolerated.

In a reproductive and developmental toxicity study, the effect of cell culture-derived antigens on embryo-foetal and postnatal development was evaluated in pregnant rabbits. Female rabbits were administered vaccine (45 mcg HA/dose) 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 11-fold excess relative to the projected adult human dose (60 mcg) on a body weight basis). No adverse effects on mating, female fertility, pregnancy, embryo-foetal development, or post-natal development were observed. There were no vaccine-related foetal malformations or other evidence of teratogenesis.

Genotoxicity and carcinogenic potential were not assessed.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

FLUCELVAX® QUAD
Influenza Vaccine, suspension for injection

Read this carefully before you are given **FLUCELVAX® QUAD**. This leaflet is a summary and will not tell you everything about this vaccine. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **FLUCELVAX® QUAD**.

What is FLUCELVAX® QUAD used for?

FLUCELVAX® QUAD is used in adults and children 9 years and older to prevent influenza, often called “the flu.”

Influenza is caused by infection with specific influenza viruses. New types of influenza viruses can appear each year. FLUCELVAX® QUAD vaccine contains fragments of four different types of influenza virus. Each year the World Health Organization decides which four types of viruses are most suitable to include in the vaccine.

For this season (20XX – 20XX) the viruses are A[Official strain] (H1N1) – like strain, A[Official Strain] (H3N2) – like strain, B[Official Strain] (Victoria) – like strain and B[Official strain] (Yamagata) – like strain.

You cannot catch influenza from the vaccine, as the virus in the vaccine has been killed and split into small non-infectious particles.

The National Advisory Committee on Immunization (NACI) encourages annual influenza vaccination for all Canadians who are able to have the vaccine.

Vaccination against influenza is recommended every year, for anyone wanting to lower their chance of catching influenza. FLUCELVAX® QUAD has been used by many people to lower their risk of catching the flu.

How does FLUCELVAX® QUAD work?

FLUCELVAX® QUAD vaccine works by helping your body to protect itself against infection by the types of influenza viruses that are in the vaccine. The vaccine stimulates the body to make substances called antibodies. Antibodies fight the influenza virus. If you have been vaccinated, when you come into contact with the influenza viruses in the vaccine, your body is usually able quickly to destroy the virus, which may prevent you from getting influenza.

Your body takes a few weeks after vaccination to fully develop effective protection against the influenza virus.

Protection against influenza requires one dose of FLUCELVAX® QUAD vaccine.

As with all vaccines, 100% protection cannot be guaranteed.

What are the ingredients in FLUCELVAX® QUAD?

Medicinal ingredients:

Each 0.5 mL dose of the vaccine contains 15 mcg haemagglutinin (HA) from each influenza strain:

- A/Official strain (H1N1)-like virus (A/actual strain (H1N1))
- A/Official strain (H3N2)-like virus (A/actual strain (H3N2))
- B/Official strain (Victoria)-like virus (B/actual strain)
- B/Official strain (Yamagata)-like virus (B/actual strain)

Non-medicinal ingredients:

- Beta-propiolactone**,
- Cetyltrimethylammonium bromide**,
- Disodium phosphate dihydrate,
- Magnesium chloride hexahydrate,
- Polysorbate 80**,
- Potassium chloride,
- Potassium dihydrogen phosphate,
- Sodium chloride,
- Thimerosal,
- Water for injections

*Thimerosal is included in multi-dose vials only.

**Residuals

FLUCELVAX® QUAD is not made using eggs, therefore, there are no egg proteins in the vaccine.

The syringe and vial components do not contain latex. FLUCELVAX® QUAD is considered safe for use in persons with latex allergies.

FLUCELVAX® QUAD pre-filled syringes contain no preservative or antibiotics. FLUCELVAX® QUAD multi-dose vial formulation contains a preservative, but does not contain any antibiotics.

FLUCELVAX® QUAD comes in the following dosage forms:

FLUCELVAX® QUAD is supplied as a suspension for intramuscular injection in either a 0.5 mL single-dose, pre-filled syringe or a 5 mL multi-dose vial.

Do not use FLUCELVAX® QUAD if:

- Your child is under 9 years of age. FLUCELVAX® QUAD vaccine is only approved for use in children aged 9 years and older.
- You or your child have or previously have had an allergy to FLUCELVAX® QUAD or any ingredient listed in this leaflet.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take FLUCELVAX® QUAD. Talk about any health conditions or problems you may have, including if you or your child:

- **have or have had a reaction to vaccination with any of the following:**
 - severe allergic reaction

- difficulty breathing
 - swelling of the throat
 - fainting or collapse
 - fits or convulsions
 - high temperature (greater than 38.5°C)
 - severe skin reaction at the injection site, including severe bruising
- **have an infection or temperature higher than 38.5°C.** Your doctor may decide to delay vaccination until the illness has passed. A minor illness such as a cold is not usually a reason to delay vaccination.
 - **have low immunity due to treatment with certain medicines**
 - **have or have had Guillain-Barré Syndrome (GBS),** an illness which affects the nervous system and causes paralysis.
 - **have allergies to other medicines or substances**
 - **are pregnant or breastfeeding.** Your healthcare professional will be able to discuss the potential risks and benefits of having FLUCELVAX® QUAD while you are pregnant or breastfeeding.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How FLUCELVAX® QUAD is given:

FLUCELVAX® QUAD is given as an injection into a muscle, usually in the upper arm.

Usual dose:

FLUCELVAX® QUAD is given once every year as follows:

- Adults and children 9 years and over: one injection of 0.5 mL.

Overdose:

If you think you have been given too many doses of FLUCELVAX® QUAD or have been given it by mistake, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using FLUCELVAX® QUAD?

These are not all the possible side effects you may experience when taking FLUCELVAX® QUAD. If you experience any side effects not listed here, contact your healthcare professional.

The following are common or very common side effects of FLUCELVAX® QUAD. Most of these side effects are mild and do not last long. Tell your doctor if you or your child have side effects that bother you:

- Injection site pain, reddening, hardening or swelling
- Headache
- Muscle or joint pain
- Tiredness
- Nausea, vomiting, diarrhea
- Loss of appetite
- Bruising
- Shivering

Children may also experience the following common side effect:

- Fever

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Anaphylaxis Difficulty breathing, dizziness, a weak and rapid pulse, skin rash		✓	
Allergic reaction Rash, itching or hives on the skin, swelling of the face, lips, tongue, or other parts of the body		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

<p>Reporting Suspected Side Effects</p> <p>For the general public: Should you experience a side effect following immunization, please report it to your doctor, nurse, or pharmacist.</p> <p>Should you require information related to the management of the side effect, please contact your healthcare provider. The Public Health Agency of Canada, Health Canada and Seqirus cannot provide medical advice.</p> <p>For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (http://www.phac-aspc.gc.ca/im/ae-fi-essi-form-eng.php) and send it to your local Health Unit.</p>

Storage:

Store in a refrigerator between 2° to 8°C. Do not freeze. Protect from light. Do not use after the expiration date. The multi-dose vial must be used within 28 days from the initial removal of the first dose and between uses, return the multi-dose vial to the recommended storage conditions.

Keep out of reach and sight of children.

If you want more information about FLUCELVAX® QUAD:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#); the manufacturer’s website www.seqirus.ca, or by calling 1-855-358-8966.

This leaflet was prepared by Seqirus UK Limited, 29 Market Street, Level 3, Maidenhead, Berkshire, SL6 8AA, UK.

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