PRODUCT MONOGRAPH

FLUZONE® Quadrivalent

Influenza Virus Vaccine Quadrivalent Types A and B (Split Virion)

Suspension for Injection

Active Immunizing Agent for the Prevention of Influenza

ATC Code: J07B B

Manufactured by:

Sanofi Pasteur Limited

Toronto, Ontario, Canada

Fabricated by:

Sanofi Pasteur Inc.

Swiftwater, PA 18370 USA

Control #: 215739 **Date of Approval:** May 01, 2018

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration: Intramuscular injection.

Dosage Form/Strength: Suspension for injection.

Active Ingredients:

Each 0.5 mL dose is formulated to contain: 15 µg of hemagglutinin (HA) for each strain listed below. (See DESCRIPTION.)

Each 0.25 mL dose is formulated to contain: 7.5 µg of hemagglutinin (HA) for each strain listed below. (See DESCRIPTION.)

Clinically Relevant Non-medicinal Ingredients: thimerosal*, formaldehyde, egg protein, Triton® X-100†.

* multidose presentation only

† Triton® X-100 is a registered trademark of Union Carbide, Co.

For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.

DESCRIPTION

FLUZONE® Quadrivalent [Influenza Virus Vaccine Quadrivalent Types A and B (Split Virion)] for intramuscular use, is a sterile suspension containing four strains of influenza viruses propagated in embryonated chicken eggs, inactivated with formaldehyde, concentrated and purified by zonal centrifugation on a sucrose gradient, split with Triton® X-100, further purified and then suspended in sodium phosphate-buffered isotonic sodium chloride solution. The FLUZONE® Quadrivalent process uses an additional concentration factor after the ultrafiltration step in order to obtain a higher hemagglutinin (HA) antigen concentration.

The type and amount of viral antigens contained in FLUZONE® conform to the current requirements of the World Health Organization (WHO). (1) The strains for the 2018-2019 season are: A/Michigan/45/2015 X-275 (H1N1)pdm09-like strain, A/Singapore/INFIMH-16-0019/2016 IVR-186 (H3N2)-like strain, B/Phuket/3073/2013-like strain and B/Colorado/6/2017-like strain (B/Maryland/15/2016 BX-69A).

INDICATIONS AND CLINICAL USE

FLUZONE® Quadrivalent is indicated for active immunization against influenza caused by the specific strains of influenza virus contained in the vaccine in adults and children 6 months of age

and older.

Although the current influenza vaccine can contain one or more of the antigens administered in previous years, annual vaccination using the current vaccine is necessary because immunity declines in the year following vaccination.

The National Advisory Committee on Immunization (NACI) encourages annual influenza vaccination for all Canadians 6 months of age and older who have no contraindications. (2)

The vaccine should be offered to both children and adults up to and even after influenza virus activity is documented in a community. (2)

CONTRAINDICATIONS

FLUZONE® Quadrivalent should not be administered to anyone with a history of severe allergic reaction to egg protein or any component of the vaccine or after previous administration of the vaccine or a vaccine containing the same components or constituents. (See DOSAGE FORMS, COMPOSITION AND PACKAGING.)

WARNINGS AND PRECAUTIONS

General

Before administration of FLUZONE® Quadrivalent, health-care providers should inform the recipient or parent/guardian of the recipient of the benefits and risks of immunization, inquire about the recent health status of the recipient, review the recipient's history concerning possible hypersensitivity to the vaccine or similar vaccines, previous immunization history, the presence of any contraindications to immunization and comply with any local requirements regarding information to be provided to the recipient/guardian before immunization.

As with any vaccine, immunization with influenza vaccine may not protect 100% of individuals.

Influenza virus is remarkably unpredictable in that significant antigenic changes may occur from time to time. It is known that FLUZONE® Quadrivalent, as now constituted, is not effective against all possible strains of influenza virus. Protection is limited to those strains of virus from which the vaccine is prepared or against closely related strains.

Administration Route Related Precautions: Do not administer by intravascular injection: ensure that the needle does not penetrate a blood vessel.

FLUZONE® Quadrivalent should not be administered into the buttocks.

Aseptic technique must be used for withdrawal of each dose from a multidose vial. A maximum of 10 total doses (0.25 mL or 0.5 mL) can be withdrawn from a multidose vial. To prevent disease transmission, use a separate sterile needle and syringe or sterile disposable unit for each individual patient and for each entry into a multidose vial. The same needle and/or syringe must never be used to re-enter a multidose vial to withdraw vaccine even when it is to be used for inoculation of the same patient. This may lead to contamination of the vial contents and nosocomial infection of patients who subsequently receive vaccine from the vial. (3)

F**ebrile or Acute Disease:** Persons with serious acute febrile illness usually should not be vaccinated until their symptoms have abated. Those with mild non-serious febrile illness (such as mild upper respiratory tract infections) may be given influenza vaccine. (2)

Hematologic

Because any intramuscular injection can cause injection site hematoma, in persons with any bleeding disorders, such as hemophilia or thrombocytopenia, or in persons on anticoagulant therapy, intramuscular injections with FLUZONE® Quadrivalent should not be administered to persons unless the potential benefits outweigh the risk of administration. If the decision is made to administer any product by intramuscular injection to such persons, it should be given with caution, with steps taken to avoid the risk of hematoma formation following injection.

NACI has recommendations for giving vaccinations to persons with bleeding disorders. (4)

Immune

As with all products, epinephrine hydrochloride solution (1:1,000) and other appropriate agents should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. (4) Health-care providers should be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings including proper airway management. For instructions on recognition and treatment of anaphylactic reactions see the current edition of the Canadian Immunization Guide or visit the Health Canada website. (4)

As each dose may contain traces of formaldehyde and Triton® X-100 which are used during vaccine production, caution should be exercised when the vaccine is administered to subjects with hypersensitivity to one of these substances. (See CONTRAINDICATIONS.) The multidose vial presentation contains thimerosal as a preservative. Thimerosal has been associated with allergic reactions. (5)

According to NACI, egg-allergic individuals may be vaccinated against influenza without prior influenza vaccine skin test and with the full dose, irrespective of a past severe reaction to egg and without any particular consideration including immunization setting. (2)

Immunocompromised persons (whether from disease or treatment) may not achieve the expected immune response. Nevertheless, as recommended by NACI, the possibility of lower efficacy should not prevent immunization in those at high risk of influenza-associated morbidity, since protection is still likely to occur. (2)

Neurologic

Guillain-Barré syndrome (GBS) has been reported after influenza vaccination. However, it is not known whether influenza vaccination specifically might increase the risk for recurrence of GBS. Therefore, NACI and the US Advisory Committee on Immunization Practices (ACIP) state it is prudent to avoid vaccinating persons who are not at high risk for severe influenza complications and who are known to have experienced GBS within 6 weeks after a previous influenza vaccination. (2) (See ADVERSE REACTIONS.)

Special Populations

Pregnant Women

Animal reproductive studies have not been conducted with FLUZONE® Quadrivalent. It is also not known whether FLUZONE® Quadrivalent can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Data on the use of this vaccine in pregnant women are limited. FLUZONE® Quadrivalent should be given to pregnant women only if clearly needed and following an assessment of the risks and benefits. However, there is no evidence to suggest a risk to the fetus or the pregnancy from maternal immunization with FLUZONE® Quadrivalent. (2)

NACI states that influenza vaccination is recommended for pregnant women. (2)

Pregnancy Registry

Sanofi Pasteur Inc. is conducting a prospective pregnancy exposure registry to collect data on pregnancy outcomes and newborn health status following vaccination with FLUZONE® Quadrivalent during pregnancy. Healthcare providers are encouraged to enroll women who receive FLUZONE® Quadrivalent during pregnancy in Sanofi Pasteur Inc.'s vaccination pregnancy registry by calling 1-888-621-1146.

Nursing Women

It is not known whether FLUZONE® Quadrivalent is excreted in human milk. Caution must be exercised when FLUZONE® Quadrivalent is administered to a nursing mother.

NACI states that influenza vaccination is considered safe for breastfeeding women.

Pediatrics

The use of FLUZONE® Quadrivalent in infants under 6 months of age is not recommended.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse event information is derived from clinical trials with FLUZONE® Quadrivalent and worldwide post-marketing experience with trivalent influenza vaccine (FLUZONE®).

Because FLUZONE® Quadrivalent does not contain infectious viral particles, it cannot cause influenza.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse reactions that appear to be related to vaccine use and for approximating rates of these reactions.

The safety of FLUZONE® Quadrivalent was evaluated in 3,307 study participants in 3 clinical trials in the U.S. (1,223 children 6 through 35 months of age, 1,669 children 3 through 8 years of age, 190 adults ≥18 years of age, and 225 adults ≥65 years of age). (6) (7) (8) For children requiring a second dose as per the U.S. ACIP guidelines, the doses were administered approximately 4 weeks apart. The most common injection-site reaction in children and adults occurring after vaccine administration was pain. The most frequent systemic reaction in infants and toddlers (6 through 35 months) was irritability, while myalgia was the most frequent systemic reaction reported in children (3 through 8 years) and adults.

Within 6 months post-vaccination, there was one serious adverse event thought to be caused by vaccination with FLUZONE® Quadrivalent: a 13-month-old who experienced croup 3 days post-first vaccination; the subject recovered within 18 days without sequelae and continued in the study. There were no deaths considered to be caused from vaccination for any of the subjects.

The frequency of the solicited injection site and systemic reactions reported in the trials are shown in Table 1.

Table 1: Percentage of Solicited Injection-Site Reactions and Systemic Adverse Events in Children and Adults After Vaccination with FLUZONE® Quadrivalent (6) (7) (8)

	Infants & Toddlers 6 through 35 months* N = 1,223	Children 3 through 8 years* N = 1,669	Adults ≥18 years† N = 190	Adults ≥65 years* N = 225
Injection site reactions				
Pain	57.0‡	66.6	47.4	32.6
Tenderness	54.1§	-	-	-
Erythema	37.3	34.1	1.1	2.7
Swelling	21.6	24.8	0.5	1.8
Induration	-	-	0.5	-
Ecchymosis	-	-	0.5	-
Systemic reactions				
Myalgia	26.7‡	38.6	23.7	18.3
Headache	8.9‡	23.1	15.8	13.4
Malaise	38.1‡	31.9	10.5	10.7
Irritability	54.0§	-	-	-
Crying-abnormal	41.2§	-	-	-
Drowsiness	37.7§	-	-	-
Appetite loss	32.3§	-	-	-
Vomiting	14.8§	-	-	-
Shivering	-	-	2.6	-
Fever	14.3	7.0	0.0	1.3

* Injection site and systemic reactions were collected from Day 0 to Day 7 after vaccination

† Injection site and systemic reactions were collected from Day 0 to Day 3 after vaccination

‡ Assessed in children 24 months through 35 months of age

§ Assessed in children 6 months through 23 months of age

Data from Post-marketing Experience

Currently, there are no post-marketing data available for FLUZONE® Quadrivalent.

The following additional events have been reported during the post-approval use of trivalent influenza vaccine (FLUZONE®). 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 vaccine exposure.

Eye Disorders

Ocular hyperemia

Blood and Lymphatic System Disorders

Thrombocytopenia, lymphadenopathy

Immune System Disorders

Anaphylaxis, other allergic/hypersensitivity reactions (including urticaria and angioedema).

Nervous System Disorders

Guillain-Barré syndrome, convulsions, febrile convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), dizziness, paraesthesia

Vascular Disorders

Vasculitis, vasodilatation, flushing

Respiratory, Thoracic and Mediastinal Disorders

Dyspnea, pharyngitis, rhinitis

Skin and Subcutaneous Tissue Disorders

Stevens-Johnson syndrome, rash, cough, wheezing, throat tightness

General Disorders and Administration Site Conditions

Asthenia/fatigue, pain in extremity, chest pain

Gastrointestinal Disorders

Vomiting

Physicians, nurses and pharmacists should report any adverse occurrences temporally related to the administration of the product in accordance with local requirements and to the Pharmacovigilance Department, Sanofi Canada, 2905 Place Louis-R-Renaud, Laval, QC, H7V 0A3, Canada. 1-888-621-1146 (phone) or 1-888-276-1546 (fax).

DRUG INTERACTIONS

Immunosuppressive treatments may interfere with the development of the expected immune response. (See WARNINGS AND PRECAUTIONS.)

Concomitant Vaccine Administration

No studies regarding the concomitant administration of inactivated influenza vaccine and other vaccines have been conducted with FLUZONE® Quadrivalent.

NACI states that influenza vaccine may be given at the same time as other vaccines. The same limb may be used if necessary, but different sites on the limb should be chosen. Different administration sets (needle and syringe) must be used. (2)

FLUZONE® Quadrivalent must not be mixed in the same syringe with other parenterals.

DOSAGE AND ADMINISTRATION

Recommended Dose

Table 2: Recommended Influenza Vaccine Dosage, by Age

Age Group	Dose	No. of Doses
6 through 35 months	0.25 mL* or 0.5 mL**	1 or 2***
3 through 8 years	0.5 mL	1 or 2***
≥9 years	0.5 mL	1

* In clinical studies conducted by Sanofi Pasteur children 6 through 35 months of age received 0.25 mL dose.

** NACI recommends that children 6 through 35 months of age should be given a full dose (0.5 mL) of influenza vaccine. (2)

*** Previously unvaccinated children 6 months to <9 years of age require 2 doses of seasonal influenza vaccine with an interval of 4 weeks. Eligible children <9 years of age who have properly received one or more doses of seasonal influenza vaccine in the past are recommended to receive one dose per season thereafter. (2)

Fractional doses (doses of less volume than indicated for each age group in Table 2 above) should not be given. The effect of fractional doses on the safety and efficacy has not been determined.

Administration

Inspect for extraneous particulate matter and/or discolouration before use. If these conditions exist, the product should not be administered.

Administer the vaccine **intramuscularly**. The preferred site is into the deltoid muscle in adults and children >1 year of age. The preferred site for infants and young children (<1 year of age) is the anterolateral aspect of the mid-thigh (vastus lateralis muscle).

If using a vial, SHAKE THE VIAL WELL to uniformly distribute the suspension before withdrawing each dose. When administering a dose from a stoppered vial, do not remove either the stopper or the metal seal holding it in place. Aseptic technique must be used for withdrawal of each dose. (See WARNINGS AND PRECAUTIONS.)

If using a prefilled syringe, SHAKE THE PREFILLED SYRINGE WELL to uniformly distribute the suspension before administering each dose.

Aseptic technique must be used. Use a separate, sterile syringe and needle, or a sterile disposable unit, for each individual patient to prevent disease transmission. Needles should not be recapped and should be disposed of according to biohazard waste guidelines.

Give the patient a permanent personal immunization record. In addition, it is essential that the physician or nurse record the immunization history in the permanent medical record of each patient. This permanent office record should contain the name of the vaccine, date given, dose, manufacturer and lot number.

OVERDOSAGE

Not applicable.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The inoculation of antigen prepared from inactivated influenza virus stimulates the production of specific antibodies. Protection is afforded only against those strains of virus from which the vaccine is prepared or closely related strains.

Immunity to the surface antigens, particularly the hemagglutinin, reduces the likelihood of infection. Antibody against one influenza virus type or subtype confers limited or no protection against another type or subtype of influenza. Furthermore, antibody to one antigenic type or subtype of influenza virus might not protect against infection with a new antigenic variant of the same type or subtype. Frequent emergence of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and is the reason for annually reassessing the need to change one or more of the recommended strains for influenza vaccines. (9)

Each year's quadrivalent influenza vaccine contains four virus strains (two type A and two type B) representing the influenza viruses that are believed likely to circulate in the coming winter. (2) The selection of these strains conforms to the requirements of the World Health Organization. (1) The antigenic characteristics of current and emerging influenza virus strains provide the basis for selecting the strains included in each year’s vaccine. (2) (1)

Pharmacodynamics

Seroprotection is generally obtained within 2 to 3 weeks.

Pharmacokinetics

No pharmacokinetic studies have been performed.

Duration of Effect

Protection against influenza post-vaccination persists throughout the influenza season for which the vaccine is indicated. (10) (11)

STORAGE AND STABILITY

Store at 2° to 8°C (35° to 46°F). **Do not freeze.** Discard product if exposed to freezing. Protect from light. Do not use vaccine after expiration date.

SPECIAL HANDLING INSTRUCTIONS

A multidose vial of FLUZONE® Quadrivalent which has been entered and stored at 2° to 8°C may be used up to the expiry date indicated on the vial label.

A maximum of 10 total doses (0.25 mL dose or 0.5 mL dose) can be withdrawn from the multidose vial.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

FLUZONE® Quadrivalent is supplied as a clear to slightly opalescent suspension in a vial or prefilled syringe.

Composition

For the 2018-2019 season FLUZONE® Quadrivalent contains the following:

Active Ingredients

0.5 mL dose: 15 µg HA of each strain listed below:

0.25 mL dose: 7.5 µg HA of each strain listed below:

A/Michigan/45/2015 X-275 (H1N1)pdm09-like strain, A/Singapore/INFIMH-16-0019/2016 IVR-186 (H3N2)-like strain, B/Phuket/3073/2013-like strain and B/Colorado/6/2017-like strain (B/Maryland/15/2016 BX-69A).

Other Ingredients

0.5 mL dose: ≤100 µg formaldehyde, up to 0.5 mL sodium phosphate buffered, isotonic sodium chloride solution and ≤250 µg Triton® X-100.

0.25 mL dose: ≤50 µg formaldehyde, up to 0.25 mL sodium phosphate buffered, isotonic sodium chloride solution and ≤125 µg Triton® X-100.

0.01% w/v thimerosal in multidose presentation only (25 µg mercury/0.5 mL dose)

Antibiotics and gelatin are not used in the manufacture of FLUZONE® Quadrivalent.

Packaging

FLUZONE® Quadrivalent is supplied in single dose vials, single dose prefilled syringes, and multidose vials.

The vials and syringes are made of Type 1 glass. The container closure system for all presentations of FLUZONE® Quadrivalent does not contain latex (natural rubber). FLUZONE® Quadrivalent is considered safe for use in persons with latex allergies.

FLUZONE® Quadrivalent is available in packages of:

10 x 0.5 mL (Single Dose) vial

1 x 5 mL (Multidose) vial

10 x 0.25 mL (Single Dose) syringes without attached needle

10 x 0.5 mL (Single Dose) syringes without attached needle

Not all pack sizes may be marketed.

Vaccine Information Service: 1-888-621-1146 or 416-667-2779

Business Hours: 7:30 a.m. to 7:30 p.m. Eastern Time, Monday to Friday.

Full product monograph available on request or visit us at www.sanofipasteur.ca

Product information as of April 2018.

Manufactured by:
Sanofi Pasteur Inc.
Swiftwater, PA 18370 USA

Distributed by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

R2-0418 Canada

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

FLUZONE® Quadrivalent [Influenza Virus Vaccine Quadrivalent Types A and B (Split Virion)]

For the 2018-2019 season FLUZONE® Quadrivalent contains the following strains:

A/Michigan/45/2015 (H1N1)pdm09-like strain [A/Michigan/45/2015 X-275]

A/Singapore/INFIMH-16-0019/2016 (H3N2)-like strain [A/Singapore/INFIMH-16-0019/2016 IVR-186]

B/Phuket/3073/2013-like strain [B/Phuket/3073/2013]

B/Colorado/6/2017-like strain [B/Maryland/15/2016 BX-69A]

Product Characteristics

FLUZONE® Quadrivalent, Influenza Virus Vaccine Quadrivalent Types subtypes A and types B (Split Virion) for intramuscular use, is a sterile suspension prepared from influenza viruses propagated in embryonated chicken eggs. The virus-containing allantoic fluid is harvested and inactivated with formaldehyde. Influenza virus is concentrated and purified on a linear sucrose density gradient solution using a continuous flow centrifuge. The virus is then chemically disrupted using a nonionic surfactant (Triton® X-100 - a registered trademark of Union Carbide, Co.) producing 'split-virus'. The split-virus is then further purified by ultrafiltration and diluted to appropriate sodium phosphate-buffered isotonic sodium chloride solution. The FLUZONE® Quadrivalent process uses an additional concentration factor after the ultrafiltration step in order to obtain a higher hemagglutinin (HA) antigen concentration.

FLUZONE® Quadrivalent has been standardized according to USPHS (US Public Health Service) requirements for the 2018-2019 influenza season and is formulated to contain 60 micrograms (µg) hemagglutinin (HA) per 0.5 mL dose, in the recommended ratio of 15 µg HA of each strain. The multidose presentation of FLUZONE® Quadrivalent contains the preservative thimerosal (mercury derivative; 25 µg mercury/0.5 mL dose).

FLUZONE® Quadrivalent, after shaking well, is clear to slightly opalescent in colour.

CLINICAL TRIALS

Study Demographics and Trial Design

Three clinical trials were conducted in the United States (see Table 3) with FLUZONE® Quadrivalent formulated using the strains A/H1N1, A/H3N2, B/Victoria lineage, and B/Yamagata lineage.

Table 3: Summary of Demographics and Study Design of the Trials with FLUZONE® Quadrivalent (6) (7) (8)

Study	Study Design	Dosage and Route of Administration	Study Participants N = Number		Mean & Age Range	Gender N = number Males/Females
			Randomized	Immuno-genicity*		
QIV04	Randomized, observer-blinded, active-controlled, multicentre comparative trial with FLUZONE® Quadrivalent, 2010-2011 TIV and investigational TIV.	1 Dose at Visit 1; a second dose at Visit 2 if required as per ACIP guidance 0.25 mL I.M (6 through 35 months) 0.5 mL I.M. (3 through 8 years)	N = 4363†	N = 3520	49.8 (6.0, 117.3) (months)	N = 2210/2153
GRC43	Randomized, open-label, active-controlled, multicentre comparative trial with FLUZONE® Quadrivalent, 2009-2010 TIV and 2008-2009 TIV.	1 Dose 0.5 mL I.M.	N = 570	N = 565	55.6 (18.0, 89.7) (years)	N = 187/383
QIV03	Randomized, active-controlled, multicentre comparative trial with FLUZONE® Quadrivalent, 2010-2011 TIV and investigational TIV.	1 Dose 0.5 mL I.M.	N = 675	N = 660	72.7 (65.0, 94.6) (years)	N = 299/376

* Per-protocol population.

† One subject was not included in any age by-age analysis, although she received QIV and was randomized.

IMMUNOGENICITY

Immunogenicity of FLUZONE® Quadrivalent in Children 6 Months Through 8 Years of Age

In a multi-center study (QIV04) conducted in the US, 1419 children 6 months through 35 months of age and 2101 children 3 years through 8 years of age were included in the per-protocol analysis set and given one or two 0.25 mL doses or one or two 0.5 mL doses, respectively of FLUZONE® Quadrivalent, 2010-2011 TIV, or investigational TIV. For participants requiring two doses, the doses were administered approximately 4 weeks apart.

HI antibody geometric mean titers (GMTs) following FLUZONE® Quadrivalent were non-inferior to those following TIV for all four strains (see Table 4). Seroconversion rates following FLUZONE® Quadrivalent were non-inferior to those following TIV for all four strains (see Table 5). At 28 days following vaccination the percentages of FLUZONE® Quadrivalent recipients with a serum HI antibody titer of at least 1:40 were 98.6% for H1N1, 99.7% for H3N2, 78.6% for B/Brisbane, and 71.6% for B/Florida.

Table 4: Non-inferiority* of FLUZONE® Quadrivalent Relative to TIV for Each Strain by HI Antibody GMTs at 28 Days Post-Vaccination, Persons 6 Months Through 8 Years of Age (Per-protocol Analysis Set)† (6)

Antigen Strain	FLUZONE® Quadrivalent N = 2339‡	Pooled TIV§ N = 1181‡		GMT Ratio (95%CI)
	GMT	GMT		
A (H1N1)	1124	1096		1.03 (0.93; 1.14)
A (H3N2)	822	828		0.99 (0.91; 1.08)
	FLUZONE® Quadrivalent N = 2339‡	2010-2011 TIV** N = 582‡	Investigational TIV†† N = 599‡	GMT Ratio (95%CI)
	GMT	GMT	GMT	
B/Brisbane/60/2008	86.1	64.3	-	1.34 (1.20; 1.50)
B/Florida/04/2006	61.5	-	58.3	1.06 (0.94; 1.18)

* Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio of GMTs (FLUZONE® Quadrivalent divided by TIV) was > 0.66

† Per-protocol analysis set includes all persons who had no study protocol deviations

‡ N is the number of subjects in the per-protocol analysis set

§ Pooled TIV group includes subjects vaccinated with either 2010-2011 TIV or investigational TIV

** 2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

†† Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed

Table 5: Non-inferiority* of FLUZONE® Quadrivalent Relative to TIV for Each Strain by Seroconversion Rates at 28 Days Post-Vaccination, Persons 6 Months Through 8 Years of Age (Per-protocol Analysis Set)† (6)

Antigen Strain	FLUZONE® Quadrivalent N = 2339‡	Pooled TIV§ N = 1181‡		Difference of Seroconversion Rates (95% CI)
	Seroconversion** (%)			
A (H1N1)	92.4	91.4		0.9 (-0.9;3.0)
A (H3N2)	88.0	84.2		3.8 (1.4;6.3)
	FLUZONE® Quadrivalent N = 2339‡	2010-2011 TIV†† N = 582‡	Investigational TIV‡‡ N = 599‡	Difference of Seroconversion Rates (95% CI)
	Seroconversion** (%)			
B/Brisbane/60/2008	71.8	61.1	-	10.7 (6.4; 15.1)
B/Florida/04/2006	66.1	-	64.0	2.0 (-2.2; 6.4)

* Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference in seroconversion rates (FLUZONE® Quadrivalent minus TIV) was > -10%

† Per-protocol analysis set included all persons who had no study protocol deviations

‡ N is the number of subjects in the per-protocol analysis set

§ Pooled TIV group includes subjects vaccinated with either 2010-2011 TIV or investigational TIV

** Seroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination titer ≥1:40 or a minimum 4-fold increase for participants with pre-vaccination titer ≥1:10

†† 2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

‡‡ Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed

In addition, HI antibody GMTs and seroconversion rates following FLUZONE® Quadrivalent were statistically superior to those following TIV for the B strain not contained in each respective TIV.

Immunogenicity of FLUZONE® Quadrivalent in Adults 18 years of Age and Older

In a multi-center study (GRC43) conducted in the US, 565 adults 18 years of age and older (281 subjects 18 through 60 years of age; 284 subjects 61 years of age and older) were included in the per-protocol analysis set and given one dose of FLUZONE® Quadrivalent, 2009-2010 TIV, or 2008-2009 TIV.

HI antibody GMTs following FLUZONE® Quadrivalent were non-inferior to those following TIV for all four strains (see Table 6). At 21 days following vaccination, the percentages of FLUZONE® Quadrivalent recipients with a serum HI antibody titer of at least 1:40 were 92.6% for H1N1, 94.7 for H3N2, 85.3% for B/Brisbane, and 92.1% for B/Florida.

Table 6: Non-inferiority* of FLUZONE® Quadrivalent Relative to TIV for Each Strain by HI Antibody GMTs at 21 Days Post-Vaccination, Adults 18 Years of Age and Older (Per-protocol Analysis Set)† (7)

Antigen Strain	FLUZONE® Quadrivalent N = 190‡	Pooled TIV§ N = 375‡		GMT Ratio (95%CI)
	GMT	GMT		
A (H1N1)	161	151		1.06 (0.87, 1.31)
A (H3N2)	304	339		0.90 (0.70, 1.15)
	FLUZONE® Quadrivalent N = 190‡	2009-2010 TIV** N = 187‡	2008-2009 TIV†† N = 188‡	GMT Ratio (95%CI)
	GMT	GMT	GMT	
B/Brisbane/60/2008	101	114	-	0.89 (0.70, 1.12)
B/Florida/04/2006	155	-	135	1.15 (0.93, 1.42)

* Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio of GMTs (FLUZONE® Quadrivalent divided by TIV) was >2/3. Non-inferiority testing for the A strains was performed post-hoc.

† Per-protocol analysis set included all persons who had no study protocol deviations

‡ N is the number of subjects in the per-protocol analysis set

§ Pooled TIV group includes subjects vaccinated with either 2009-2010 TIV or 2008-2009 TIV

** 2009-2010 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

†† 2008-2009 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Florida/04/2006 (Yamagata lineage), licensed

Immunogenicity of FLUZONE® Quadrivalent in Adults 65 Years of Age and Older

In a multi-center study (QIV03) conducted in the US, 660 adults 65 years of age and older were included in the per-protocol analysis set and given one dose of FLUZONE® Quadrivalent, 2010-2011 TIV, or investigational TIV.

HI antibody GMTs following FLUZONE® Quadrivalent were non-inferior to those following TIV for all four strains (see Table 7). Seroconversion rates following FLUZONE® Quadrivalent, 2010-2011 TIV, and Investigational TIV are shown in Table 8.

Table 7: Non-inferiority* of FLUZONE® Quadrivalent Relative to TIV for Each Strain by HI Antibody GMTs at 21 Days Post-Vaccination, Adults 65 Years of Age and Older (Per-protocol Analysis Set)† (8)

Antigen Strain	FLUZONE® Quadrivalent N = 220‡	Pooled TIV§ N = 440‡		GMT Ratio (95%CI)
	GMT	GMT		
A (H1N1)	231	270		0.85 (0.67; 1.09)
A (H3N2)	501	324		1.55 (1.25; 1.92)
	FLUZONE® Quadrivalent N = 220‡	2010-2011 TIV** N = 219‡	Investigational TIV†† N = 221‡	GMT Ratio (95%CI)
	GMT	GMT	GMT	
B/Brisbane/60/2008	73.8	57.9	-	1.27 (1.05; 1.55)
B/Florida/04/2006	61.1	-	54.8	1.11 (0.90; 1.37)

* Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio of GMTs (FLUZONE® Quadrivalent divided by TIV) was >0.66

† Per-protocol analysis set included all persons who had no study protocol deviations

‡ N is the number of subjects in the per-protocol analysis set

§ Pooled TIV group includes subjects vaccinated with either 2010-2011 TIV or investigational TIV

** 2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

†† Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed

Table 8: Seroconversion Rates at 21 Days Post-Vaccination of FLUZONE® Quadrivalent Relative to TIV for Each Strain, Adults 65 Years of Age and Older (Per-protocol Analysis Set)* (8)

Antigen Strain	FLUZONE® Quadrivalent N = 220†	Pooled TIV‡ N = 440†		Difference of Seroconversion Rate (95% CI)
	Seroconversion§ (%)			
A (H1N1)	65.91	69.77		-3.86 (-11.50; 3.56)
A (H3N2)	69.09	59.32		9.77 (1.96; 17.20)
	FLUZONE® Quadrivalent N = 220†	**2010-2011 TIV** N = 219†**	**Investigational TIV†† N = 221†**	**Difference of Seroconversion Rate (95% CI)**
	Seroconversion§ (%)			
B/Brisbane/60/2008	28.64	18.72	-	9.91 (1.96; 17.70)
B/Florida/04/2006	33.18	-	31.22	1.96 (-6.73; 10.60)

* Per-protocol analysis set included all persons who had no study protocol deviations

† N is the number of subjects in the per-protocol analysis set

‡ Pooled TIV group includes subjects vaccinated with either 2010-2011 TIV or investigational TIV

§ Seroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination titer ≥1:40 or a minimum 4-fold increase for participants with pre-vaccination titer ≥1:10

** 2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

†† Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed

FLUZONE® Quadrivalent induced higher HI antibody GMTs and seroconversion rates to B/Florida compared with those induced by 2010-2011 TIV (not containing B/Florida) and higher GMTs and seroconversion rates to B/Brisbane compared with the investigational TIV (not containing B/Brisbane). At 21 days following vaccination, the percentages of FLUZONE® Quadrivalent recipients with a serum HI antibody titer of at least 1:40 were 91.4% for H1N1, 100.0% for H3N2, 77.7% for B/Brisbane, and 73.2% for B/Florida.

SAFETY

Children 6 Months Through 8 Years of Age

In clinical trial QIV04, children 6 months through 35 months of age received one or two 0.25 mL doses of either FLUZONE® Quadrivalent, 2010-2011 TIV, or investigational TIV, and children 3 years through 8 years of age received one or two 0.5 mL doses of either FLUZONE® Quadrivalent, 2010-2011 TIV, or investigational TIV. For participants requiring two doses, the doses were administered approximately 4 weeks apart. The safety analysis set included 1,841 children 6 months through 35 months of age and 2,506 children 3 years through 8 years of age. Table 9 and Table 10 summarize solicited injection-site reactions and systemic adverse events reported within 7 days post-vaccination via diary cards.

Table 9: Percentage of Solicited Injection-Site Reactions and Systemic Adverse Events Within 7 Days After Vaccination with FLUZONE® Quadrivalent, 2010-2011 TIV, and Investigational TIV in Children 6 Months Through 35 Months of Age (Safety Analysis Set)*

	FLUZONE® Quadrivalent N = 1223†			2010-2011 TIV N = 310†			Investigational TIV N = 308†		
	Any (%)	Grade 2‡ (%)	Grade 3§ (%)	Any (%)	Grade 2‡ (%)	Grade 3§ (%)	Any (%)	Grade 2‡ (%)	Grade 3§ (%)
Injection-site reactions									
Pain**	57.0	10.2	1.0	52.3	11.5	0.8	50.3	5.4	2.7
Tenderness††	54.1	11.3	1.9	48.4	8.2	1.9	49.7	10.3	0.0
Erythema	37.3	1.5	0.2	32.9	1.0	0.0	33.3	1.0	0.0
Swelling	21.6	0.8	0.2	19.7	1.0	0.0	17.3	0.0	0.0
Systemic reactions									
Fever‡‡	14.3	5.5	2.1	16.0	6.6	1.7	13.0	4.1	2.0
Malaise**	38.1	14.5	4.6	35.2	14.8	4.7	32.4	12.8	6.8
Myalgia**	26.7	6.6	1.9	26.6	9.4	1.6	25.0	6.8	2.7
Headache**	8.9	2.5	0.6	9.4	3.9	0.0	12.2	4.7	0.0
Irritability††	54.0	26.4	3.2	52.8	20.1	3.1	53.5	22.9	2.8
Crying-abnormal††	41.2	12.3	3.3	36.5	8.2	1.9	29.9	10.4	2.1
Drowsiness††	37.7	8.4	1.3	32.1	3.8	0.6	31.9	5.6	0.7
Appetite loss††	32.3	9.1	1.8	33.3	5.7	1.9	25.0	8.3	0.7
Vomiting††	14.8	6.2	1.0	11.3	4.4	0.6	13.9	6.3	0.0

* The safety analysis set includes all persons who received study vaccine

† N is the number of subjects in the safety analysis set

‡ Grade 2 - Injection-site pain: sufficiently discomforting to interfere with normal behavior or activities; Injection-site tenderness: cries and protests when injection-site is touched; Injection-site erythema, Injection-site swelling: ≥2.5 cm to <5 cm; Fever: ≥38.5°C to ≤39.5°C (>101.3°F to ≤103.1°F) (6 months through 23 months); ≥38.5°C to ≤38.9°C (≥101.2°F to ≤ 102.0°F) (24 months through 35 months); Malaise, Myalgia, and Headache,: some interference with activity; Irritability: requiring increased attention; Crying abnormal: 1 to 3 hours; Drowsiness: not interested in surroundings or did not wake up for a feed/meal; Appetite lost: missed 1 or 2 feeds/meals completely; Vomiting: 2 to 5 episodes per 24 hours

§ Grade 3 - Injection-site pain: incapacitating, unable to perform usual activities; Injection-site tenderness: cries when injected limb is moved, or the movement of the injected limb is reduced; Injection-site erythema, Injection-site swelling,: ≥5 cm; Fever: >39.5°C (>103.1°F) (6 months through 23 months); ≥39.0°C (≥ 102.1ºF) (24 months through 35 months); Malaise, Myalgia, and Headache: Significant; prevents daily activity; Irritability: inconsolable; Crying abnormal: >3 hours; Drowsiness: sleeping most of the time or difficult to wake up; Appetite lost: refuses ≥3 feeds/meals or refuses most feeds/meals; Vomiting: ≥6 episodes per 24 hours or requiring parenteral hydration

** Assessed in children 24 months through 35 months

†† Assessed in children 6 months through 23 months of age

‡‡ Fever - Any Fever: ≥38.0°C (≥100.4°F). The percentage of temperature measurements that were taken by axillary, rectal, or oral routes, or not recorded for the 3 vaccine groups combined were 41.0%, 35.4%, 23.4%, and 0.2%, respectively for Dose 1; and 38.4%, 36.0%, 25.6%, and 0.1%, respectively for Dose 2

Table 10: Percentage of Solicited Injection-Site Reactions and Systemic Adverse Events Within 7 Days After Vaccination with FLUZONE® Quadrivalent, 2010-2011 TIV, and Investigational TIV in Children 3 Years Through 8 Years of Age (Safety Analysis Set)*

	FLUZONE® Quadrivalent N = 1669†			2010-2011 TIV N = 424†			Investigational TIV N = 413†		
	Any (%)	Grade 2‡ (%)	Grade 3§ (%)	Any (%)	Grade 2‡ (%)	Grade 3§ (%)	Any (%)	Grade 2‡ (%)	Grade 3§ (%)
Injection-site reactions									
Pain	66.6	15.8	2.1	64.6	9.5	2.0	63.8	11.6	2.8
Erythema	34.1	2.9	1.8	36.8	3.4	1.2	35.2	2.5	1.8
Swelling	24.8	2.8	1.4	25.4	1.5	1.2	25.9	2.5	1.8
Systemic reactions									
Fever**	7.0	2.1	2.1	7.1	2.2	1.2	7.6	2.8	0.8
Headache	23.1	6.8	2.2	21.2	5.1	2.7	24.4	7.5	2.0
Malaise	31.9	11.2	5.5	32.8	11.4	5.6	33.4	10.8	5.0
Myalgia	38.6	12.2	3.3	34.1	9.0	2.7	38.4	11.1	2.8

* The safety analysis set includes all persons who received study vaccine

† N is the number of subjects in the safety analysis set

‡ Grade 2 - Injection-site pain: sufficiently discomforting to interfere with normal behavior or activities; Injection-site erythema, Injection-site swelling,: ≥2.5 cm to <5 cm; Fever: ≥38.4°C to ≤38.9°C (≥101.2°F to ≤102.0°F); Headache, Malaise, and Myalgia: some interference with activity

§ Grade 3 - Injection-site pain: incapacitating, unable to perform usual activities; Injection-site erythema, Injection-site swelling ≥5 cm; Fever: ≥39.0°C (≥102.1°F); Headache, Malaise, and Myalgia: Significant; prevents daily activity

** Fever - Any Fever indicates≥38.0°C (≥100.4°F). The percentage of temperature measurements that were taken by oral, axillary, or rectal routes, or not recorded for the 3 vaccine groups combined were 85.1%, 14.4%, 0.3%, and 0.2%, respectively for Dose 1; and 86.2%, 13.4%, 0.3%, and 0.1%, respectively for Dose 2

Within 6 months post-vaccination, a total of 41 (1.4%) recipients in the FLUZONE® Quadrivalent group, 7 (1.0%) recipients in the 2010-2011 TIV group, and 14 (1.9%) recipients in the investigational TIV group, experienced at least one SAE. There were three serious adverse events thought to be caused by vaccination: one in the FLUZONE® Quadrivalent group (13-month-old who experienced croup 3 days post-first vaccination), one in the 2010-2011 TIV group (4-year-old who experienced a febrile seizure one day post-first vaccination), and one in the

investigational TIV group (11-month-old who experienced a febrile seizure on the day of second vaccination). There were no deaths considered to be caused by vaccination.

Adults 18 Years of Age and Older

The safety profile of FLUZONE® Quadrivalent was assessed in a total of 190 study participants (≥ 18 years of age) in clinical trial GRC43. The most common solicited injection-site reaction occurring after FLUZONE® Quadrivalent vaccine administration was pain and the most common solicited systemic reaction was myalgia. Solicited reactions usually occurred within the first 2 days after vaccination and typically lasted for 1 to 3 days after onset. The frequency and intensity of the solicited injection-site and systemic reactions reported are presented in Table 11.

In the follow-up period, there were two subjects who experienced serious adverse events; each serious adverse event was considered by the investigator to be unrelated to the study vaccine. No deaths were reported during the trial period.

Table 11: Percentage of Solicited Injection-Site Reactions and Systemic Adverse Events Within 3 Days After Vaccination with FLUZONE® Quadrivalent, 2009-2010 TIV, and 2008-2009 TIV in Adults 18 Years of Age and Older (Safety Analysis Set)*

	FLUZONE® Quadrivalent N = 190†			2009-2010 TIV N = 190†			2008-2009 TIV N =190†		
	Any (%)	Grade 2‡ (%)	Grade 3§ (%)	Any (%)	Grade 2‡ (%)	Grade 3§ (%)	Any (%)	Grade 2‡ (%)	Grade 3§ (%)
Injection-site reactions									
Pain	47.4	6.8	0.5	52.1	7.9	0.5	43.2	6.3	0.0
Erythema	1.1	0.0	0.0	1.6	0.5	0.0	1.6	0.5	0.0
Swelling	0.5	0.0	0.0	3.2	0.5	0.0	1.1	0.0	0.0
Induration	0.5	0.0	0.0	1.6	0.5	0.0	0.5	0.0	0.0
Ecchymosis	0.5	0.0	0.0	0.5	0.0	0.0	0.5	0.0	0.0
Systemic reactions									
Myalgia	23.7	5.8	0.0	25.3	5.8	0.0	16.8	5.8	0.0
Headache	15.8	3.2	0.5	18.4	6.3	0.5	18.0	4.2	0.0
Malaise	10.5	1.6	1.1	14.7	3.2	1.1	12.1	4.7	0.5
Shivering	2.6	0.5	0.0	5.3	1.1	0.0	3.2	0.5	0.0
Fever**	0.0	0.0	0.0	0.5	0.5	0.0	0.5	0.5	0.0

* The safety analysis set includes all persons who received study vaccine

† N is the number of subjects in the safety analysis set

‡ Grade 2 - Injection-site pain: Some interference with activity; Injection-site erythema, Injection-site swelling, Injection-site induration, and Injection-site ecchymosis: ≥5.1 to ≤10 cm; Fever: ≥38.5°C to ≤38.9°C (≥101.2°F to ≤102.0°F); Myalgia, Headache, Malaise, and Shivering: some interference with activity

§ Grade 3 - Injection-site pain: Significant; prevents daily activity; Injection-site erythema, Injection-site swelling, Injection-site induration, and Injection-site ecchymosis: >10 cm; Fever: ≥39.0°C (≥102.1°F); Myalgia, Headache, Malaise, and Shivering: Significant; prevents daily activity

** Fever - Any Fever indicates ≥38.0°C (≥100.4°F). The percentage of temperature measurements that were taken by the oral route was 100.0% in each group

Geriatric Adults 65 Years of Age and Older

A total of 225 study participants (≥ 65 years of age) received FLUZONE® Quadrivalent in clinical trial QIV03. The most common solicited injection-site reaction occurring after FLUZONE® Quadrivalent administration was pain and the most common solicited systemic reaction was myalgia (see Table 12). Solicited reactions usually occurred within 3 days of vaccination and typically resolved within 1 to 3 days.

A total of three subjects experienced a serious adverse event; each serious adverse event was considered by the Investigator to be unrelated to study vaccine. There were no deaths in any vaccine group.

Table 12: Percentage of Solicited Injection-Site Reactions and Systemic Adverse Events Within 7 Days After Vaccination with FLUZONE® Quadrivalent, 2010-2011 TIV, and Investigational TIV in Adults 65 Years of Age and Older (Safety Analysis Set)*

	FLUZONE® Quadrivalent N = 225†			2010-2011 TIV N = 225†			Investigational TIV N = 225†		
	Any (%)	Grade 2‡ (%)	Grade 3§ (%)	Any (%)	Grade 2‡ (%)	Grade 3§ (%)	Any (%)	Grade 2‡ (%)	Grade 3§ (%)
Injection-site reactions									
Pain	32.6	1.3	0.9	28.6	2.7	0.0	23.1	0.9	0.0
Erythema	2.7	0.9	0.0	1.3	0.0	0.0	1.3	0.4	0.0
Swelling	1.8	0.4	0.0	1.3	0.0	0.0	0.0	0.0	0.0
Systemic reactions									
Myalgia	18.3	4.0	0.4	18.3	4.0	0.0	14.2	2.7	0.4
Headache	13.4	1.3	0.4	11.6	1.3	0.0	11.6	1.8	0.4
Malaise	10.7	4.5	0.4	6.3	0.4	0.0	11.6	2.7	0.9
Fever**	1.3	0.0	0.4	0.0	0.0	0.0	0.9	0.4	0.4

* The safety analysis set includes all persons who received study vaccine

† N is the number of subjects in the safety analysis set

‡ Grade 2 - Injection-site pain: some interference with activity; Injection-site erythema and Injection-site swelling: ≥5.1 to ≤10 cm; Fever: ≥38.5°C to ≤38.9°C (≥101.2°F to ≤102.0°F); Myalgia, Headache, and Malaise: some interference with activity

§ Grade 3 - Injection-site pain: Significant; prevents daily activity ; Injection-site erythema and Injection-site swelling: >10 cm; Fever: ≥39.0°C (≥102.1°F); Myalgia, Headache , and Malaise: Significant; prevents daily activity

** Fever - Any Fever indicates≥38.0°C (≥100.4°F). The percentage of temperature measurements that were taken by the oral or axillary routes, or not recorded for the 3 vaccine groups combined were 99.8%, 0.2%, and 0.03%, respectively

TOXICOLOGY

FLUZONE® Quadrivalent has not been evaluated in non-clinical studies.

ADDITIONAL RELEVANT INFORMATION

In Canada approximately 2,000-8,000 deaths can be attributed to influenza and its complications annually. (12) (13) (14) Over 95% of these deaths occur in individuals over 65 years of age. Up to 20,000 hospitalizations can be attributed annually to influenza. (15) The rate of hospitalizations in adults ≥65 years attributable to influenza can be as high as 3.4 per 1,000 individuals. Influenza also has a significant impact on the working-age population: in the 2007-2008 Canadian flu season, 36% of influenza infections occurred in people ranging from 25 to 64 years of age. (16) Furthermore, approximately 12% of employed persons in Canada took time off work as a result of influenza in 2008-2009. (17)

Trivalent influenza vaccines (TIVs) are traditionally composed of one H1N1 strain, one H3N2 strain, and one B strain, each chosen to provide protection against the strains anticipated to circulate in the upcoming influenza season. In recent years, the two distinct lineages of influenza B circulating worldwide, have not provided good cross-protection against the other. (18) Unfortunately, the ability to predict with acceptable accuracy which B lineage will be dominant in an upcoming season has been unsatisfactory, with frequent mismatches. (18) This mismatch was the driver behind developing QIV.

The public health impact of influenza B as well as the potential benefit of QIV becomes increasingly apparent when considering the model that the US Centers for Disease Control and Prevention (CDC) developed. This model assesses what the public health impact of QIV would have been on the number of influenza cases, hospitalizations, and deaths in the US compared with TIV (18). In doing so, the model utilizes US influenza-related health outcomes (illness, hospitalization, and death) data collected over ten consecutive influenza seasons starting in 1999/2000. Further, the model considers the concurrent circulating viruses, vaccine coverage, vaccine effectiveness, as well as, vaccine manufacturing capacity.

The CDC reports that across the 10 influenza seasons, the proportion of all influenza disease identified as type B varied from 0.4% to 46% each season and the proportion of type B isolates of a lineage not in a given year's TIV varied from 0% to 98%. Consequently, the model projects that if QIV were used instead of TIV over these 10 seasons, it would have resulted in a modest reduction in the burden of influenza disease. More specifically, the use of QIV could have reduced annual cases (range: 2200–970,000), hospitalizations (range: 14–8200), and deaths (range: 1–485) in the US.

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Vaccine Information Service: 1-888-621-1146 or 416-667-2779

Business Hours: 7:30 a.m. to 7:30 p.m. Eastern Time, Monday to Friday

Full product monograph available on request or visit us at www.sanofipasteur.ca

Product information as of April 2018.

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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

FLUZONE® Quadrivalent

Influenza Virus Vaccine Quadrivalent Types A and B, Zonal Purified, Subvirion

This leaflet is part III of a three-part "Product Monograph" published when FLUZONE® Quadrivalent was approved for sale in Canada. It provides important information about the product for consumers. This leaflet is a summary and it does not tell you everything about FLUZONE® Quadrivalent. Contact your doctor, nurse or pharmacist if you have any questions about the vaccine.

ABOUT THIS VACCINE

What the vaccine is used for:

FLUZONE® Quadrivalent is a vaccine used to prevent influenza. Influenza (or flu) is an infection caused by the influenza virus.

This vaccine may be given to adults and children 6 months of age and older.

Flu symptoms can include fever, headache, muscle pain, runny nose, sore throat, extreme tiredness and cough. Some people get much sicker.

The influenza virus spreads when a person who has the flu coughs or sneezes into the air. Small droplets of the flu virus stay in the air for a short time then fall onto surfaces nearby. You can get the flu by:

- breathing in these droplets through your nose or mouth.
- the droplets landing directly on your eyes.
- touching the hands of a person who has the flu and then touching your eyes, nose or mouth.
- touching surfaces that have been contaminated with flu virus and then touching your eyes, nose or mouth.

What it does:

FLUZONE® Quadrivalent causes your body to produce its own protection against influenza virus. After you get a flu shot, your immune system produces antibodies against the strains of virus that are in the vaccine. The antibodies are effective for the duration of the flu season. When you are exposed to the virus, the antibodies will help to keep you from getting sick. If you do get the flu, you may not be as sick.

When it should not be used:

FLUZONE® Quadrivalent should not be used in the following situations:

Do not give FLUZONE® Quadrivalent to anyone who has ever had a severe allergic reaction to:

- egg or egg products
- any component of FLUZONE® Quadrivalent

What the medicinal ingredient is:

Each 0.5 mL dose of FLUZONE® Quadrivalent contains killed split viruses from four strains of influenza virus for the 2018-2019 season. The viruses in FLUZONE® Quadrivalent are:

- A/Michigan/45/2015 X-275 (H1N1) pdm09-like strain
- A/Singapore/INFIMH-16-0019/2016 IVR-186 (H3N2)-like strain
- B/Phuket/3073/2013-like strain
- B/Colorado/6/2017-like strain (B/Maryland/15/2016 BX-69A)

What the important nonmedicinal ingredients are:

Sodium phosphate-buffered, isotonic sodium chloride solution, formaldehyde, and Triton® X-100. The multidose vial contains thimerosal.

What dosage forms it comes in:

Individual doses in a vial or a prefilled syringe.

The packaging of FLUZONE® Quadrivalent does not contain any latex.

WARNINGS AND PRECAUTIONS

FLUZONE® Quadrivalent will only protect against the strains of flu virus contained in the vaccine or those that are closely related.

FLUZONE® Quadrivalent will not protect against any other strains of flu virus.

If you have any of the following conditions, talk to your doctor, nurse or pharmacist BEFORE you use FLUZONE® Quadrivalent:

- **Diseases of the immune system or who are having treatment that affects the immune system.** The vaccine may provide you with a lower level of protection than it does for people with healthy immune systems.
- **A bleeding disorder or taking blood-thinning medications.** Tell the person giving you the injection about your condition. There is a risk of excessive bleeding at the injection site if it is not done carefully.
- **Pregnant or breast-feeding women.** It is important that you understand the risks and benefits of vaccination. FLUZONE® should be given to a pregnant or nursing woman only if it is clearly needed. Tell the person giving you the injection if you are pregnant or breast-feeding.
- **Allergy to egg protein or any component of the vaccine.**
- **Fever or serious illness.** Wait until the person is better before giving the flu shot. A person who has a mild illness (such as a mild cold) may have the flu shot. Ask your doctor, nurse or pharmacist for advice.
- **A history of Guillain-Barré syndrome (GBS) within 6 weeks of a previous influenza vaccination.**

The use of FLUZONE® in infants under 6 months of age is not recommended.

As with all vaccines, FLUZONE® does not protect 100% of people immunized.

Pregnancy Registry

Sanofi Pasteur Inc. is collecting information on pregnancy outcomes and the health of newborns following vaccination with Fluzone Quadrivalent during pregnancy. Women who receive Fluzone Quadrivalent during pregnancy are encouraged to contact Sanofi Pasteur Inc. directly or have their healthcare provider contact Sanofi Pasteur Inc. at 1-888-621-1146.

INTERACTIONS WITH THIS VACCINE

FLUZONE® Quadrivalent must not be mixed with other vaccines or medicinal products in the same syringe.

PROPER USE OF THIS VACCINE

Usual dose:

For children 6 through 35 months - recommended dose is 0.25 mL or 0.5 mL. The National Advisory Committee on Immunization (NACI) recommends that children 6 to through 35 months of age should be given a full dose (0.5 mL).

For persons 3 years or older - recommended dose is 0.5 mL.

Children under 9 years of age who have not received a previous vaccination - 2 doses are required 4 weeks apart. The second dose is not needed if the child received one or more doses of influenza vaccine in a previous season.

For adults and children older than 1 year, inject the vaccine into the deltoid (shoulder) muscle.

For infants and children less than 1 year inject the vaccine into the mid-thigh muscle.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If a child's second dose is missed, it can be given at any time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

A vaccine, like any medicine, may cause serious problems, such as severe allergic reactions. The risk of FLUZONE® Quadrivalent causing serious harm is extremely small. The small risks associated with FLUZONE® Quadrivalent are much less than the risks associated with getting the disease against which it protects.

The flu vaccine cannot cause influenza because it does not contain any live virus. The most common side effect is soreness where you got the injection. Children and adults might also notice muscle pain and infants may suffer from irritability.

Severe allergic reactions to the flu shots are very rare. A very rare but possible side effect of influenza vaccination is Guillain-Barré syndrome (GBS). This is an autoimmune disease that attacks the nervous system. GBS causes weakness and abnormal

sensations. Most patients recover fully. This is not a complete list of side effects. Talk to your doctor or nurse before receiving FLUZONE®.

Tell your doctor, nurse or pharmacist as soon as possible if you do not feel well after having FLUZONE® Quadrivalent.

For any unexpected effects after having FLUZONE® Quadrivalent, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

Store in a refrigerator at 2° to 8°C (35° to 46°F). **Do not freeze.** Discard product if it has been exposed to freezing. Protect from light.

Do not use vaccine after expiration date.

Keep FLUZONE® Quadrivalent out of children's reach.

A maximum of 10 total doses (0.25 mL dose or 0.5 mL dose) can be withdrawn from the multidose vial.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects information on serious and unexpected case reports on adverse events following immunization.

For Health Care Professionals:

If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events Following Immunization (AEFI) Form and send it to your local Health Unit in your province/territory.

For the General Public:

Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events Following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact the Vaccine Safety Section at the Public Health Agency of Canada:

By toll-free telephone: 1-866-844-0018
By toll-free fax: 1-866-844-5931
Web: http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php

By regular mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road
Address Locator: 6502A
Ottawa, ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. **The Public Health Agency of Canada does not provide medical advice**.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.sanofipasteur.ca or by contacting the vaccine producer, Sanofi Pasteur Limited, 1755 Steeles Avenue West, Toronto, Ontario, M2R 3T4.

Phone: 1-888-621-1146 or 416-667-2779.
Business Hours: 7:30 a.m. to 7:30 p.m., Eastern Time, Monday to Friday.

This leaflet was prepared by Sanofi Pasteur Limited.
Last revised: April 2018

R2-0418 Canada