PRODUCT MONOGRAPH

FLUZONE®

Influenza Virus Vaccine Trivalent 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 Inc.

Swiftwater, PA 18370 USA

Distributed by:

Sanofi Pasteur Limited

Toronto, Ontario, Canada

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FLUZONE®

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

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*, gelatin, formaldehyde, egg protein, Triton® X-100†, sucrose.

* 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® [Influenza Virus Vaccine Trivalent Types A and B (Split Virion)] for intramuscular use, is a sterile suspension containing 3 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. FLUZONE® has been standardized according to United States Public Health Service (USPHS) requirements for the 2014-2015 influenza season. The strains for the 2014-2015 season are: A/California/7/2009 (H1N1)pdm09-like strain, A/Texas/50/2012 (H3N2)-like strain and B/Massachusetts/2/2012-like strain.

INDICATIONS AND CLINICAL USE

FLUZONE® 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 who have no contraindications. (1)

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® 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®, 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®, 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® should not be administered into the buttocks.

Aseptic technique must be used for withdrawal of each dose from a multidose vial. Use a separate, sterile needle and syringe or a sterile disposable unit for each individual patient and for each entry into a multidose vial, to prevent disease transmission. In particular, 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 infection of patients who subsequently receive vaccine from the vial. (4)

Febrile 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. (1) (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® 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. (1)

NACI has recommendations for giving vaccinations to persons with bleeding disorders. (1)

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. (1) 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. (1)

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

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)

According to NACI, egg-allergic individuals may be vaccinated against influenza, without a prior influenza skin test, based on an assessment of risk for a severe allergic reaction to guide the method of vaccination. (2)

Neurologic

Immunization should be delayed in a patient with an active neurologic disorder, but should be considered when the disease process has been stabilized.

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. (1) (2) (See ADVERSE REACTIONS.)

Respiratory

According to NACI, persons who have experienced oculo-respiratory syndrome (ORS) symptoms including severe ORS consisting of non-lower respiratory symptoms (bilateral red eyes, cough, sore throat, hoarseness, facial swelling) may be safely reimmunized with influenza vaccine. Please refer to the most current NACI recommendations regarding revaccination of subjects who experienced more severe ORS. (1) (2)

Special Populations

Pregnant Women

Animal reproductive studies have not been conducted with FLUZONE®. It is also not known whether FLUZONE® 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® 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®. (1)

NACI states that influenza vaccination is recommended for pregnant women. (1)

Nursing Women

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

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

Pediatrics

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse event information is derived from clinical trials and worldwide post-marketing experience.

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

The most common adverse reactions were at the injection site, mainly pain and induration; the most common systemic reactions were headache and myalgia. Most of the adverse reactions were of mild to moderate intensity and did not interfere with daily activity.

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 strain composition of the influenza virus vaccines is subject to annual changes and respective clinical studies, including at least 50 adults 18 - 60 years of age and at least 50 older adults aged 60 years or older, are conducted to assess the safety and immunogenicity of FLUZONE®. (6)

For the purpose of the cumulative analysis, five years of annual clinical safety data are presented below. (7) (8) (9) (10) (11) In this data set, a total of 601 vaccinees received an intramuscular injection of FLUZONE®. Table 1 summarizes the frequencies (range across individual trials) of the solicited adverse reactions that were recorded within 3 days following vaccination.

Data are categorized by age group and by MedDRA system organ class.

Table 1: Frequencies (%) of Solicited Adverse Reactions Within 3 Days After Vaccination with FLUZONE®

Adverse Event	Adults 18 - 59 Years of Age (n = 59 - 61)*	Adults ≥60 Years of Age (n = 56 - 64)*
General Disorders and Administration Site Conditions		
Injection Site Reactions		
Pain	60.0 to 78.0	8.3 to 30.4
Erythema	6.8 to 13.1	3.2 to 10.0
Induration†	6.7 to 23.0	0.0 to 5.0
Swelling†	3.4 to 12.1	0.0 to 5.5
Bruising†	1.7 to 8.2	0.0 to 3.3
Systemic Reactions		
Fever (>38°C)	0.0 to 3.4	0.0 to 3.3
Chills†	0.0 to 4.9	1.6 to 1.7
Malaise	6.6 to 25.4	1.7 to 9.1
Gastrointestinal Disorders		
Nausea, vomiting or diarrhea†	8.2 to 13.3	0.0 to 6.7
Nervous System Disorders		
Headache	14.8 to 39.0	5.0 to 10.9
Musculoskeletal, Connective Tissue and Bone Disorders		
Arthralgia†	3.3 to 6.7	1.7 to 3.3
Myalgia	9.8 to 36.2	3.3 to 21.4
Respiratory Disorders, Thoracic and Mediastinal Disorders		
Cough, runny nose†	1.7 to 15.0	1.7 to 6.7

* safety population analyzed per study

† specific adverse reactions were not reported or solicited in all studies

The 2003 - 2004 formulation of FLUZONE® was studied in 19 children 6 - 23 months of age and in 12 children 24 - 36 months of age given in 2 doses one month apart. Safety was monitored for 3 days by the parents. (12)

Table 2: Solicited Adverse Reactions Among 31 Infants Within 3 Days After Dose 1 and 2 with the 2003 - 2004 Formulation of Trivalent Inactivated Influenza Vaccine Stratified by Age 6 - 23 Months and 24 - 36 Months

Adverse Reactions	6 - 23 Months of Age (n = 19)		24 - 36 Months of Age (n = 12)	
	Dose 1	Dose 2	Dose 1	Dose 2
Injection Site Reactions				
Pain	3 (15%)	3 (16%)	4 (33%)	6 (50%)
Induration	0	0	2 (17%)	5 (42%)
Erythema	2 (10%)	2 (11%)	4 (33%)	4 (33%)
Systemic Reactions				
Fever (>38°C)	2 (10%)	0	4 (33%)	2 (17%)
Irritability	6 (30%)	7 (37%)	4 (33%)	5 (42%)
Crying	6 (30%)	3 (16%)	5 (42%)	4 (33%)
Lethargy	4 (20%)	3 (16%)	5 (42%)	4 (33%)
Decrease appetite	3 (15%)	4 (21%)	8 (67%)	4 (33%)
Diarrhea	3 (15%)	2 (11%)	3 (25%)	2 (17%)
Vomiting	1 (5%)	2 (11%)	2 (17%)	1 (8%)

Data from Post-Marketing Experience

The following additional adverse events have been spontaneously reported following the post-marketing use of 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, cough, wheezing, throat tightness

Skin and Subcutaneous Tissue Disorders

Stevens-Johnson syndrome, rash

General Disorders and Administration Site Conditions

Pruritus, asthenia/fatigue, pain in extremity, chest pain

Gastrointestinal Disorders

Vomiting

Additional Adverse Reactions

The following adverse events not listed above have been reported with influenza vaccines:

During the 2000 - 2001 influenza season, the Public Health Agency of Canada (PHAC) received an increased number of reports of influenza vaccine-associated symptoms and signs that were subsequently described as oculorespiratory syndrome (ORS). The pathophysiologic mechanism underlying ORS remains unknown, but it is considered distinct from IgE-mediated allergy. (1) Since the 2000 - 2001 influenza season fewer ORS cases have been reported to PHAC.

Neurological disorders temporally associated with influenza vaccination such as encephalopathy (with or without permanent neurological, motor and/or sensory, deficit and/or intellectual

impairment), labyrinthitis, have been reported. However, no cause-and-effect relationships have been established. (13)

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 Global Pharmacovigilance Department, Sanofi Pasteur Limited, 1755 Steeles Avenue West, Toronto, ON, M2R 3T4, Canada. 1-888-621-1146 (phone) or 416-667-2435 (fax).

DRUG INTERACTIONS

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

Concomitant Vaccine Administration

Clinical studies show that influenza vaccine may be administered with pneumococcal polysaccharide vaccine using separate syringes at different sites. (14) (15)

No studies regarding the concomitant administration of inactivated influenza vaccine and other childhood vaccines have been conducted.

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. (1)

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

DOSAGE AND ADMINISTRATION

Recommended Dose

Table 3: Recommended Influenza Vaccine Dosage, by Age

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

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

** NACI recommends that children 6 to 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 3 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. (16)

Each year's influenza vaccine contains three virus strains (usually two type A and one type B) representing the influenza viruses that are believed likely to circulate in the coming winter. (1)The antigenic characteristics of current and emerging influenza virus strains provide the basis for selecting the strains included in each year's vaccine. (1) (17)

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. (18) (19)

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® which has been entered must be stored at 2° to 8°C and used within 28 days. Twenty-eight days after first entry, it must be discarded.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

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

Composition

For the 2014-2015 season FLUZONE® 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/California/7/2009 (H1N1) pdm09-like strain, A/Texas/50/2012 (H3N2)-like strain and B/Massachusetts/2/2012-like strain.

Other Ingredients

0.5 mL dose: 0.05% w/v gelatin, ≤100 µg formaldehyde, up to 0.5 mL sodium phosphate-buffered, isotonic sodium chloride solution, ≤1 µg ovalbumin, ≤0.02% Triton® X-100 and ≤2% sucrose.

0.25 mL dose: 0.05% w/v gelatin, ≤50 µg formaldehyde, up to 0.25 mL sodium phosphate-buffered, isotonic sodium chloride solution, ≤0.5 µg ovalbumin, ≤0.02% Triton® X-100 and ≤2% sucrose.

0.01% w/v thimerosal in multidose presentation only

Packaging

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

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

FLUZONE® 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: 8 a.m. to 5 p.m. Eastern Time, Monday to Friday.

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

Product information as of September 2014.

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

Distributed by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

R26-0914 Canada

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

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

For the 2014-2015 season FLUZONE® contains the following strains:

A/California/7/2009 (H1N1) pdm09-like strain [A/California/7/2009 (NYMC X-179A)]

A/Texas/50/2012 (H3N2)-like strain[A/Texas/50/2012 (NYMC X-223A)]

B/Massachusetts/2/2012-like strain [B/Massachusetts/2/2012].

Product Characteristics

FLUZONE®, Influenza Virus Vaccine Trivalent Types A and 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. FLUZONE® has been standardized according to USPHS (US Public Health Service) requirements for the 2014-2015 influenza season and is formulated to contain 45 micrograms (µg) hemagglutinin (HA) per 0.5 mL dose, in the recommended ratio of 15 µg HA of each strain. Gelatin 0.05% is added as a stabilizer. The multidose presentation of FLUZONE® contains the preservative thimerosal [(mercury derivative), (25 µg mercury/dose)].

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

CLINICAL TRIALS

Study Demographics and Trial Design

Strain-specific virus-neutralizing antibody directed against the hemagglutinin [hemagglutination inhibition (HI)] is the primary immune mediator of protection against infection and clinical illness. (20) Consistent with immunogenicity criteria defined by the US FDA and the European EMEA, the proportion (%) of participants achieving seroprotection (i.e. HI antibody titres ≥1:40) is the principal immunogenicity endpoint in yearly studies of FLUZONE®.

Overview of Results from Clinical Trials

Annual release studies of FLUZONE® have been conducted for years in both adults and children. The results of these studies have consistently shown low rates of adverse reactions in all age

groups. FLUZONE® has demonstrated consistent immune responses to all 3 strains contained in the vaccine, and its efficacy against influenza disease has been demonstrated in randomized, blinded, controlled trials in adults and children. Results of typical studies that have assessed the immunogenicity or efficacy of FLUZONE® in adults and children are presented below.

Immunogenicity in Adults

In an observational study of the 2007 - 2008 strain formulation of FLUZONE®, 53 adults 18 - 59 years of age and 59 adults ≥60 years of age achieved the following immunogenicity results. (11)

Table 4: Geometric Mean Titre (GMT) and Percentage (%) Achieving Seroprotection (HI Titre of ≥1:40) in Adults

Antigen	18 - 59 Years of Age n = 53 GMT (% Titre ≥1:40)	≥60 Years of Age n = 59 GMT (% Titre ≥1:40)
A/Wisconsin/67/2005 (H3N2)	447 (100)	278 (96.6)
A/Solomon Islands/3/2006 (H1N1)	400 (92.5)	145 (86.4)
B/Malaysia/2506/2004	50.3 (60.4)	26.5 (40.7)

Efficacy in Adults

A randomized, double-blind, placebo-controlled trial was conducted in 1,952 healthy adults 18 - 49 years of age, during the 2007 - 2008 influenza season. 814 participants received FLUZONE®. The overall mean age was 23.2 ± 7.4 years, stratified in 35.5% 18 - 19 years of age, 43.6% 20 - 24 years of age, 11.1% 25 - 34 years of age and 9.8% 35 - 49 years of age, 60.7% of participants were women and 14.4% were non-white, 37.7% had previously received influenza vaccination. All eligible participants were healthy and none had health conditions for which influenza vaccination was specifically recommended. Influenza activity began in January 2008 with predominant H3N2 strains identical or antigenically related to the strain present in the 2007 - 2008 vaccine, as well as with a recent antigenic variant of the 2007 - 2008 H1N1 vaccine strain. The predominating B strain was not represented in the 2007 - 2008 vaccine components. The absolute efficacy of FLUZONE®, as measured by virus culture, polymerase chain reaction or both, was 72% (95% CI, 49% to 84%) against influenza A and 40% (95% CI, -189% to 86%) against influenza B. The absolute efficacy of FLUZONE® against all strains was 68% (95% CI, 46% to 81%). (21)

Immunogenicity in Children

In an observational study of the immunogenicity of FLUZONE® in a pediatric population (6 - 23 months of age and 24 - 36 months of age) the following results were obtained using the recommended 0.25 mL 2-dose schedule of the year 2003 - 2004 formulation of FLUZONE®. (12)

Table 5: Post-Vaccination Geometric Mean Titre (GMT) and Percentage (%) Achieving Seroprotection (HI Titre of ≥1:40) in Children

Antigen	6 - 23 Months of Age n = 19 GMT (% Titre ≥40)	24 - 36 Months of Age n = 12 GMT (% Titre ≥40)
A/Panama/2007/99 (H3N2)	44.6 (84)	69.2 (75)
A/New Caledonia/20/99 (H1N1)	58.7 (84)	44.9 (67)
B/Hong Kong 1434/2002	31.0 (53)	22.4 (42)

A subsequent observational study of the immunogenicity of the 2008 - 2009 strain formulation of FLUZONE® was conducted in pediatric populations 8 - 56 months of age grouped by status of previous influenza vaccination. In this study, 7 children 8 - 35 months of age, who had never received influenza vaccination (naïve) or had not been adequately primed in a previous season (less than 2 doses of 0.25 mL of influenza vaccine) received two 0.25 mL doses of FLUZONE® 4 weeks apart and were included in immunogenicity analyses. In addition, 23 children 16 - 56 months of age who had been previously primed with adequate doses of influenza vaccine received a single 0.25 mL dose of FLUZONE® and were included in immunogenicity analyses. The following results were obtained in HI assay following vaccination. (22)

Table 6: Post-Vaccination Geometric Mean Titre (GMT) and Percentage (%) Achieving Seroprotection (HI Titre of ≥1:40) in Children

Antigen	Naïve or inadequately primed n = 7 GMT (% Titre ≥40)	Primed n = 23 GMT (% Titre ≥40)
A/Uruguay/716/2007 (H3N2)	226.3 (85.7)	510.5 (100)
A/Brisbane/59/2007 (H1N1)	168.1 (100)	320.0 (100)
B/Florida/04/2006	31.2 (71.4)	26.2 (43.5)

Efficacy in Children

In a randomized, blinded and controlled study among 791 children 1 - 15 years of age, FLUZONE® was 77.3% (95% CI 20.3% to 93.5%) effective against H3N2 and 91% (95% CI 63.8% to 98.0%) effective against H1N1 respiratory illness. (23)

A randomized, double-blind, placebo-controlled study of the efficacy of 2 doses of FLUZONE® given one month apart against culture positive influenza in healthy children of diverse ethnicity 6 - 24 months of age was conducted over two seasons. During the 1999 - 2000 influenza season, the efficacy of the vaccine against culture-proven influenza in the first cohort was 66% (95% CI 34% to 82%). In this season, culture-proven influenza was identified in 15 (5.5%) of 273 children in the vaccine group and 22 (15.9%) of 138 children in the placebo group. During the 2000 - 2001 season, the efficacy in the second cohort was -7% (95% CI -247% to 67%), however the overall

attack rate was 3% and there were only 9 cases in the FLUZONE® group and 4 cases in the placebo group, making the second year insufficiently powered to assess efficacy. (24) (25)

ADDITIONAL RELEVANT INFORMATION

Influenza A and B are the two types of influenza viruses that cause epidemic human disease. Influenza A viruses are further categorized into subtypes on the basis of two surface antigens: hemagglutinin (H) and neuraminidase (N). Influenza B viruses are not categorized into subtypes. Since 1977, influenza A (H1N1) viruses, influenza A (H3N2) viruses and influenza B viruses have been in global circulation. (1) Influenza A (H1N2) has been circulating widely since 2001. (1) Because circulating influenza A (H1N2) viruses are a reassortant of influenza A (H1N1) and (H3N2) viruses, antibody directed against influenza A (H1N1) and (H3N2) vaccine strains will provide protection against circulating influenza A (H1N2) viruses. (1)

In the tropics, influenza can occur throughout the year. In the southern hemisphere, peak activity occurs from April through September.

Uncomplicated influenza illness is characterized by the abrupt onset of constitutional and respiratory signs and symptoms (e.g. fever, myalgia, headache, malaise, non-productive cough, sore throat and rhinitis). Illness typically resolves after a limited number of days for the majority of persons, although cough and malaise can persist for two or more weeks. Among certain persons, influenza can exacerbate underlying medical conditions (e.g. pulmonary or cardiac disease), lead to secondary bacterial pneumonia or primary influenza viral pneumonia or occur as part of a coinfection with other viral or bacterial pathogens. The spectrum of influenza in children ranges from asymptomatic infection to influenza illness with or without complications. In addition to febrile upper respiratory tract infection, common clinical presentations of influenza in children include lower respiratory tract infection (croup, bronchiolitis, primary viral or secondary bacterial pneumonia), otitis media, diarrheal illness and febrile seizures. Influenza infection has also been associated with encephalopathy, transverse myelitis, Reye syndrome, myositis, myocarditis, and pericarditis. The risks of complications, hospitalizations and deaths from influenza are higher among persons 65 years of age or older, young children and persons of any age with some underlying health conditions than among healthy older children and younger adults.

In Canada approximately 4,000 deaths can be attributed to influenza annually. (26) Over 95% of these deaths occur in individuals over 65 years of age. Up to 17,000 hospitalizations can be attributed annually to influenza. (27) The rate of hospitalizations in adults ≥65 years attributable to influenza can be as high as 3.4 per 1,000 individuals.

Vaccination is recognized as the single most effective way of preventing or attenuating influenza for those at high risk of serious illness or death from influenza infection and related complications. (1) The national goal of influenza immunization programs is to prevent serious illness caused by influenza and its complications, including death. NACI therefore recommends that immunization programs target vaccine delivery as a priority to those persons at high risk of complications and those who provide essential community services. However, NACI encourages annual vaccination for all Canadians.

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 to 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 virus. Furthermore, antibody to one antigenic variant of influenza virus might not protect against 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. (16)

Each year's influenza vaccine contains three virus strains (usually two type A and one type B) representing the influenza viruses that are believed likely to circulate in the coming winter. (1) (17) The antigenic characteristics of current and emerging influenza virus strains provide the basis for selecting the strains included in each year’s vaccine. (1) (17) The WHO reviews the world epidemiological situation annually and if necessary recommends new strains based on the current epidemiological evidence.

The majority of vaccinated children and young adults develop high post-vaccination hemagglutination inhibition antibody titres. These antibody titres are protective against illness caused by strains similar to those in the vaccine. Older persons and persons with certain chronic diseases might develop lower post-vaccination antibody titres than healthy young adults and thus can remain susceptible to influenza-related upper respiratory tract infection. The vaccine can also be effective in preventing secondary complications and reducing the risk for influenza-related hospitalization and death among adults 65 years and older with and without high-risk medical conditions (e.g. heart disease and diabetes). (16)

The effectiveness of influenza vaccine varies depending upon the age and immunocompetence of the vaccine recipient, the degree of similarity between the virus strain included and the characteristics of the strain of circulating virus during the influenza season. With a good match, influenza vaccination has been shown to prevent laboratory-confirmed influenza illness in approximately 70% or more of healthy individuals. (28) In older adults, vaccination against influenza is associated with reductions in the risk of hospitalization for heart disease, cerebrovascular disease and pneumonia or influenza as well as the risk of death from all causes during influenza season. (29) In older persons living in residential facilities influenza vaccine prevents pneumonia, hospital admission, death from pneumonia (vaccine effectiveness 42% to 46%) and all-cause mortality (vaccine effectiveness 60%). (29)

Children aged as young as 6 months can develop protective levels of antibody after influenza vaccination, although the antibody response among children at high risk of influenza-related complications might be lower than among healthy children. In a randomized study among children aged 1 - 15 years, inactivated influenza vaccine was 77% - 91% effective against influenza respiratory illness. (16) Vaccination of health-care workers has been associated with reduced work absenteeism (16) (30) and decreased deaths among nursing home patients. (16) (31)

Vaccination is associated with reductions in influenza-related respiratory illness and physician visits among all age groups, hospitalization and death among persons at high risk, otitis media among children and work absenteeism among adults. (16) (32)

Although influenza vaccines may contain one or more antigens administered in previous years, annual vaccination is necessary because antigenic drift of circulating strains requires incorporation of one or more new antigens each season.

TOXICOLOGY

Data in animals revealed no unexpected findings and no target organ toxicity.

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

Business Hours: 8 a.m. to 5 p.m. Eastern Time, Monday to Friday

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

Product information as of September 2014.

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

Distributed by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

R26-0914 Canada

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

FLUZONE®

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

This leaflet is part III of a three-part "Product Monograph" published when FLUZONE® 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®. Contact your doctor, nurse or pharmacist if you have any questions about the vaccine.

ABOUT THIS VACCINE

What the vaccine is used for:

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

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

- egg or egg products
- any component of FLUZONE® or its container.

What the medicinal ingredient is:

Each 0.5 mL dose of FLUZONE® contains killed split viruses from three strains of influenza virus for the 2014-2015 season. The viruses in FLUZONE® are:

- A/California/7/2009 (H1N1) pdm09-like strain
- A/Texas/50/2012 (H3N2)-like strain
- B/Massachusetts/2/2012-like strain.

What the important nonmedicinal ingredients are:

Thimerosal (only in the multidose vial), sodium phosphate-buffered, isotonic sodium chloride solution, formaldehyde, Triton® X-100, sucrose and gelatin.

What dosage forms it comes in:

Individual doses in a vial or a prefilled syringe, or a vial that contains enough vaccine for many doses.

WARNINGS AND PRECAUTIONS

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

FLUZONE® 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®:

- **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 or the container.**
- **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.

INTERACTIONS WITH THIS VACCINE

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

PROPER USE OF THIS VACCINE

Usual dose:

For children 6 - 35 months - recommended dose is 0.25 mL or 0.5 mL. The National Advisory Committee on Immunization (NACI) recommends that children 6 to 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® causing serious harm is extremely small. The small risks associated with FLUZONE® 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. It may last a couple of days. You might also notice fever, fatigue and muscle aches within 6 to 12 hours after your shot. These side effects may last a day or two.

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®.

For any unexpected effects after having FLUZONE®, 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.

Discard the multidose vials of FLUZONE® 28 days after first use.

Keep FLUZONE® out of children's reach.

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: 8 a.m. to 5 p.m., Eastern Time, Monday to Friday.

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