

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**FLUZONE®**

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

Each 0.5 mL dose contains 15 mcg haemagglutinin of each  
Influenza Virus Type A (H1N1), Type A (H3N2), Type B/strain

Each 0.25 mL dose contains 7.5 mcg haemagglutinin of each  
Influenza Virus Type A (H1N1), Type A (H3N2), Type B/strain

Suspension for Injection

Active Immunizing Agent for the Prevention of Influenza

ATC Code: J07B BB02

**Sanofi Pasteur Limited**  
Toronto, Ontario, Canada

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**RECENT MAJOR LABEL CHANGES**

1 Indications, 1.1 Pediatrics and 1.2 Geriatrics	[MM/YYYY]
Section 7 Warnings and Precautions	[MM/YYYY]
Section 7, Warnings and Precautions, 7.1 Special Populations, 7.1.2 Breast-feeding	[MM/YYYY]

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**PART I: HEALTH PROFESSIONAL INFORMATION****1 INDICATIONS**

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

The National Advisory Committee on Immunization (NACI) encourages annual influenza vaccination for all Canadians who have no contraindications.

**1.1 Pediatrics**

- **Pediatrics (6 months – 18 years of age):** Based on the data submitted and reviewed by Health Canada, the safety and efficacy of FLUZONE® in pediatric patients have been established. Therefore, Health Canada has authorized an indication for pediatric use.

Safety and efficacy of FLUZONE® administration in children less than 6 months of age have not been established.

**1.2 Geriatrics**

- **Geriatrics:** Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

**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 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

**4 DOSAGE AND ADMINISTRATION****4.2 Recommended Dose and Dosage Adjustment****Table 1: 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.

\*\*\* 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.

Fractional doses (doses of less volume than indicated for each age group in Table 1 above) should not be given. The effect of fractional doses on the safety and efficacy has not been determined.

#### 4.4 Administration

**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.

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.

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

Needles should not be recapped and should be disposed of according to biohazard waste guidelines.

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.

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.

#### 4.5 Missed Dose

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

### 5 OVERDOSAGE

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

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

**Table 2: Dosage Forms, Strengths, Composition and Packaging**

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular injection	<p><b>Dosage Form:</b> Suspension for injection.</p> <p><b>Active Ingredients:</b> Each 0.5 mL dose is formulated to contain 15 mcg of hemagglutinin (HA) of each strain listed below: Each 0.25 mL dose is formulated to contain 7.5 mcg of hemagglutinin (HA) of each strain listed below: A (H3N2), A (H1N1), B/strain</p>	<p>0.5 mL dose: 0.05% w/v gelatin, ≤100 mcg formaldehyde, up to 0.5 mL sodium phosphate buffered, isotonic sodium chloride solution, ≤1 mcg ovalbumin, ≤0.02% Triton® X-100† and ≤2% sucrose.</p> <p>0.25 mL dose: 0.05% w/v gelatin, ≤50 mcg formaldehyde, up to 0.25 mL sodium phosphate buffered, isotonic sodium chloride solution, ≤0.5 mcg ovalbumin, ≤0.02% Triton® X-100† and ≤2% sucrose.</p> <p>0.01% w/v thimerosal is present in the multi-dose presentation only.</p> <p>†Triton®X-100 is a registered trademark of Union Carbide, Co</p>

### Description

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

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 YYYY-YYYY influenza season.

This vaccine complies with the World Health Organization (WHO) recommendation (Northern Hemisphere) for the YYYY - YYYY season and contains the following:

**Packaging**

FLUZONE® is supplied in 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:

1 x 5 mL (Multidose) vial.

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

Not all pack sizes may be marketed.

**7 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.

**Febrile or Acute Disease:**

Vaccination should be postponed in case of a moderate or severe acute disease with or without fever: however in case of mild disease with low-grade fever, vaccine could be administered.

**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.

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

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**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. 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.

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 2 CONTRAINDICATIONS.) The multidose vial of this vaccine contains thimerosal as a preservative. Thimerosal has been associated with allergic reactions.

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.

For additional information on FLUZONE® vaccination, please refer to NACI recommendations<sup>1</sup>.

**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. (See 8 ADVERSE REACTIONS).

**Syncope related precautions**

Syncope can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent falling and injury and to manage syncope.

**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.

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<sup>1</sup> The National Advisory Committee on Immunization (NACI) provides additional guidance on vaccines in Canada. Please refer to the published chapter on influenza vaccines.



## 7.1 Special Populations

### 7.1.1 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®.

NACI states that influenza vaccination is recommended for pregnant women.

### 7.1.2 Breast-feeding

There are no available data on the presence of FLUZONE® in human milk, effects on milk production or the effects on the breastfed infant. No conclusions can be drawn regarding whether or not FLUZONE® is safe for use during breastfeeding. FLUZONE® should be used during breastfeeding only if the potential benefits to the mother outweigh the potential risks including those to the breastfed child.

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

### 7.1.3 Pediatrics

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

## 8 ADVERSE REACTIONS

### 8.1 Adverse 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.

### 8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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®.

For the purpose of the cumulative analysis, five years of annual clinical safety data are presented below. In this data set, a total of 601 vaccinees received an intramuscular injection of FLUZONE®.

Table 3 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 3: 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) *
<b>General Disorders and Administration Site Conditions</b>		
<b>Injection Site Reactions</b>		
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
<b>Systemic Reactions</b>		
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
<b>Gastrointestinal Disorders</b>		
Nausea, vomiting or diarrhea†	8.2 to 13.3	0.0 to 6.7
<b>Nervous System Disorders</b>		
Headache	14.8 to 39.0	5.0 to 10.9
<b>Musculoskeletal, Connective Tissue and Bone Disorders</b>		
Arthralgia†	3.3 to 6.7	1.7 to 3.3
Myalgia	9.8 to 36.2	3.3 to 21.4
<b>Respiratory Disorders, Thoracic and Mediastinal Disorders</b>		
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.

### 8.2.1 Clinical Trial Adverse Reactions – Pediatrics

**Table 4: 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
<b>Injection Site Reactions</b>				
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%)
<b>Systemic Reactions</b>				
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%)

### 8.5 Post-Market Adverse Reactions

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

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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. Since the 2000 - 2001 influenza season fewer ORS cases have been reported to PHAC.

Cases of demyelinating disorders (e.g. incident multiple sclerosis in adults, acute disseminated encephalomyelitis, transverse myelitis), have been reported following influenza virus vaccines, although the Institute Of Medicine (IOM) concluded that the evidence is inadequate to accept or reject a causal relationship.

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.

Healthcare professionals should report any adverse occurrences temporally related to the administration of the product in accordance with local requirements (See [PATIENT MEDICATION INFORMATION](#) , Reporting Side Effects for Vaccines).

## 9 DRUG INTERACTIONS

### 9.2 Drug Interactions Overview

Immunosuppressive treatments may interfere with the development of the expected immune response. (See 7 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.

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.

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

**9.4 Drug-Drug Interactions**

Interaction with laboratory tests have not been established.

**10 CLINICAL PHARMACOLOGY****10.1 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.

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. The antigenic characteristics of current and emerging influenza virus strains provide the basis for selecting the strains included in each year's vaccine.

**10.2 Pharmacodynamics**

Seroprotection is generally obtained within 2 to 3 weeks.

**10.3 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.

**11 STORAGE, STABILITY AND DISPOSAL**

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

**12 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.

## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

#### Drug Substance

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

For the YYYY-YYYY season FLUZONE® contains three split influenza virus of the following inactivated strains:

A (H3N2)

A (H1N1)

B/strain

#### 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 YYYY-YYYY influenza season and is formulated to contain 45 micrograms (mcg) hemagglutinin (HA) per 0.5 mL dose, in the recommended ratio of 15 mcg HA of each strain. Gelatin 0.05% is added as a stabilizer. The multidose presentation of FLUZONE® contains the preservative thimerosal [(mercury derivative), (25 mcg mercury/dose)].

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

**14 CLINICAL TRIALS****14.1 Clinical Trials by Indication**

## Influenza In Adults And Children 6 Months Of Age And Older

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

**Table 4: Summary of patient demographics for clinical trials in individuals 6 months of age and older**

Study #	Study Design	Dosage and Route of Administration	Study Subjects	Mean Age (Range)	Male/Female %
<b>GRC17</b>	A single-center, open-label, single-arm study to collect sera for immunogenicity testing in healthy children given FLUZONE® vaccine	0.25 mL Intramuscular Injection	N=33	6 months to > 6 months of age	51.5%/48.5%
<b>GRC37</b>	Multi-center, open label, noncontrolled trial to determine the safety and immunogenicity of the Northern Hemisphere 2007-2008 Formulation of FLUZONE® vaccine in two groups of adults	0.5 mL Intramuscular injection	Adults: N= 60  Elderly: N=64	Adults: 43 (18 to 59)  Elderly: $\geq 60$ years of age 75 (60-89)	Adults: 33.3%/66.7%  Elderly: 37.5%/62.5%
<b>GRC40</b>	Immunogenicity study in children previously primed with adequate doses of influenza vaccine	0.25 mL Intramuscular injection	N= 24	32.8 months (16 to 56 months of age)	45.8%/54.2%
<b>GRC70</b>	Randomized double blind placebo-controlled efficacy trial in healthy adults	0.5 mL Intramuscular injection	N=1952	23 (23 to 49 years of age)	36.7%/63.3%
<b>593-04</b>	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	0.25 mL Intramuscular injection	N=793	13.7 (5.9 to 26.0 months of age)  14.1 (6.0 to 24.8 months of age)	50.8%/49.2%  55.7%/44.3%



## 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.

### Study Results:

#### Efficacy in Adults (GRC70 study)

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  $23.2 \pm 7.4$  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, -18% to 86%) against influenza B. The absolute efficacy of FLUZONE® against all strains was 68% (95% CI, 46% to 81%).

#### Efficacy in Children (593-04 study)

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.

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 -24.7% 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.

**14.3 Immunogenicity****Immunogenicity in Adults (GRC37 study)**

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.

**Table 5: 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)

**Immunogenicity in Children (GRC17 study)**

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®.

**Table 6: 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.

**Table 7: Post-Vaccination Geometric Mean Titre (GMT) and Percentage (%) Achieving Seroprotection (HI Titre of  $\geq 1:40$ ) in Children (GRC40 study)**

Antigen	Naïve or inadequately primed n = 7 GMT (% Titre $\geq 40$ )	Primed n = 23 GMT (% Titre $\geq 40$ )
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)

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

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

A FLUZONE® QIV formulation revealed no evidence of impaired female fertility and did not induce any maternal toxicity or adverse effects on embryo-fetal development (including an evaluation of teratogenicity) or early post-natal development in the rabbit.

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**PATIENT MEDICATION INFORMATION****READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE****FLUZONE®****Influenza Virus Vaccine Trivalent Types A and B, Zonal Purified, Subvirion**

Read this carefully before you start taking FLUZONE® and each time you get a dose. This leaflet is a summary and will not tell you everything about this vaccine. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about FLUZONE®.

**What is FLUZONE® 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.

**How does FLUZONE® work?**

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.

**What are the ingredients in FLUZONE®?**

Medicinal ingredients:

This vaccine complies with the WHO (World Health Organization) recommendation (Northern hemisphere) for the YYYY-YYYY season.

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

A(H1N1) -like strain

A(H3N2)-like strain

B/like strain

Non-medicinal ingredients:

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

**FLUZONE® comes in the following dosage forms:**

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

**Do not use FLUZONE® if:**

Anyone who has ever had a severe allergic reaction to:

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

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

- **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.
- **Are pregnant or breast-feeding.** 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.
- **An allergy to egg protein or any component of the vaccine or the container.**
- A 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.**

**Other warnings you should know about:**

**FLUZONE® will only protect against those 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.**

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.

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

**The following may interact with FLUZONE®:**

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

**How to take FLUZONE®:**

**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:**

If you think you, or a person you are caring for, have taken too much FLUZONE®, contact a healthcare professional, 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.

**What are possible side effects from using FLUZONE®?**

These are not all the possible side effects you may have when taking FLUZONE®. If you experience any side effects not listed here, tell your healthcare professional.

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®.

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

#### Reporting Suspected Side Effects for Vaccines

**For the general public:** Should you experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and Sanofi cannot provide medical advice.

**For healthcare professionals:** If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (<http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php>) and send it to your local Health Unit.

#### Storage:

Store in a refrigerator at 2° to 8°C. **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 out of reach and sight of children.

#### If you want more information about FLUZONE®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website [<https://www.sanofi.com/en/canada>], or by calling 1-888-621-1146.

This leaflet was prepared by Sanofi.

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