PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

FLUZONE High-Dose®

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

Each 0.5 mL dose contains 60 mcg haemagglutinin of each

Influenza Virus Type A (H1N1), Type A (H3N2), Type B (Victoria) strains

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	[12/2024]
7 Warnings and Precautions, General, Immune, Neurologic, Syncope	[12/2024]

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

FLUZONE® High-Dose (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 65 years 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 (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of FLUZONE® High-Dose administration in children less than 18 years of age have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

- Geriatrics (≥65 years of age): FLUZONE® High-Dose vaccine is indicated for active immunization for the prevention of influenza in adults 65 years of age and older.

2 CONTRAINDICATIONS

- FLUZONE® High-Dose is contraindicated in 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

FLUZONE® High-Dose should be administered as a single 0.5 mL injection by the intramuscular route in adults 65 years of age and older.

Fractional doses (doses <0.5 mL) 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.

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.

FLUZONE® High-Dose should not be administered into the buttocks.

Shake the prefilled syringe well to uniformly distribute the suspension before administering the dose.

Aseptic technique must be used. Use a separate, sterile needle, 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.

4.5 Missed Dose

Not applicable for this vaccine.

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 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular injection	**Dosage Form:** Suspension for injection. **Active Ingredients:** Each 0.5 mL dose is formulated to contain 60 mcg of hemagglutinin (HA) of each strain listed below: A/Victoria/4897/2022 (H1N1)pdm09-like strain (A/Victoria/4897/2022, IVR-238) A/Croatia/10136RV/2023 (H3N2)-like strain (A/Croatia/10136RV/2023, X-425A) B/Austria/1359417/2021-like strain (B/Michigan/01/2021, wild type).	Formaldehyde, egg protein, Triton® X-100*. * Triton® X-100 is a registered trademark of Union Carbide, Co.

Description

FLUZONE® High-Dose is supplied as a colourless opalescent suspension in a prefilled syringe.

FLUZONE® High-Dose [Influenza Virus Vaccine Trivalent Types A and B (Split Virion)] for intramuscular use, is a sterile suspension containing three strains of influenza viruses propagated in embryonated chicken eggs. The virus-containing fluid is harvested and inactivated with formaldehyde. Influenza virus is concentrated and purified in a linear sucrose density gradient solution using a continuous flow centrifuge. The virus is then chemically disrupted using a non-ionic surfactant, octylphenol ethoxylate (Triton® X-100) producing a "split-virus". The split virus is then further purified by diafiltration against phosphate buffered chloride saline.

FLUZONE® High-Dose complies with the World Health Organization (WHO) recommendation (Northern Hemisphere) for the 2025 – 2026 season and contains the following:

Active Ingredients:

Each 0.5 mL dose is formulated to contain 60 mcg hemagglutinin of influenza virus of:

A/Victoria/4897/2022 (H1N1)pdm09-like strain (A/Victoria/4897/2022, IVR-238)
A/Croatia/10136RV/2023 (H3N2)-like strain (A/Croatia/10136RV/2023, X-425A) and
B/Austria/1359417/2021-like strain (B/Michigan/01/2021, wild type).

Other Ingredients:

Phosphate Buffered Saline (sodium chloride 6.51 g/L; sodium phosphate (dibasic anhydrous) 3.83 g/L; sodium phosphate (monobasic anhydrous) 0.410 g/L), Water for Injection quantity sufficient up to 0.5mL and Triton® X-100 NMT 250 mcg.

Antibiotics, gelatin and thimerosal are not used in the manufacture of FLUZONE® High-Dose.

Packaging

FLUZONE® High-Dose is supplied in single dose prefilled syringes.

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

FLUZONE® High-Dose is available in packages of:

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

7 WARNINGS AND PRECAUTIONS

General

Before administration of FLUZONE® High-Dose, health-care providers should inform the recipient or 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® High-Dose, as now constituted, is not effective against all possible strains of influenza virus. Protection is highest against those strains of virus from which the vaccine is prepared or against closely related strains.

As each dose may contain traces of formaldehyde, ovalbumin and Triton® X-100, which are used during vaccine production, caution should be exercised when the vaccine is administered to persons with known hypersensitivity to one of these substances. (See 2 CONTRAINDICATIONS).

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.

Hematologic

Because any intramuscular injection can cause injection site hematoma in persons with any bleeding disorders, such as haemophilia or thrombocytopenia, or in persons on anticoagulant therapy, intramuscular injections with FLUZONE® High-Dose 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.

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.

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

Healthcare 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.

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 some protection is still likely to occur.

Neurologic

Guillain-Barré syndrome (GBS) has been temporally associated with the administration of influenza vaccine. If GBS has occurred within 6 weeks following previous influenza vaccination, the decision to give FLUZONE® High-Dose should be based on careful consideration of the potential benefits and risks. (See 8 ADVERSE REACTIONS).

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

Syncope

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.

7.1 Special Populations

7.1.1 Pregnant Women

Animal reproductive studies have not been conducted with FLUZONE® High-Dose. It is also not known whether FLUZONE® High-Dose can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. FLUZONE® High-Dose is indicated for persons 65 years of age and older.

7.1.2 Breast-feeding

It is not known whether FLUZONE® High-Dose is excreted in human milk. FLUZONE® High-Dose is indicated for persons 65 years of age and older.

7.1.3 Pediatrics

FLUZONE® High-Dose is not indicated in persons younger than 65 years of age.

7.1.4 Geriatrics

Safety, immunogenicity and efficacy of FLUZONE® High-Dose Quadrivalent have been evaluated in adults 65 years of age and older.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse event information is derived from clinical trials and worldwide post-marketing experience with FLUZONE® High-Dose and FLUZONE®.

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 safety of FLUZONE® High-Dose compared to FLUZONE® was evaluated in 3833 adults (≥65 years of age) in a clinical trial conducted in the United States. The most common injection site reaction reported in participants receiving either FLUZONE® High-Dose or FLUZONE® was pain, while myalgia was the most frequent systemic reaction. Onset was usually within the first 3 days after vaccination and a majority of the reactions resolved within 3 days.

The frequency of the solicited injection site and systemic reactions reported within 7 days post-vaccination are shown in Table 2.

Table 2: Percentage of Solicited Injection-Site and Systemic Reactions Within 7 Days After Vaccination with FLUZONE® High-Dose or FLUZONE®, Adults 65 Years of Age and Older

	FLUZONE® High-Dose **N = 2569-2572*** **Percentage**	**FLUZONE®** **N = 1258-1260*** **Percentage**
Injection site reactions		
Pain	35.6	24.3
Erythema	14.9	10.8
Swelling	8.9	5.8
Systemic reactions		
Myalgia	21.4	18.3
Malaise	18.0	14.0
Headache	16.8	14.4
Fever¥ (≥37.5°C)	3.6	2.3

* N is the number of vaccinated participants with available data for the events listed

¥ Fever - The percentage of temperature measurements that were taken by oral route or not recorded were 97.9% and 2.1%, respectively, for FLUZONE® High-Dose; and 98.6% and 1.4%, respectively, for FLUZONE®

Safety of FLUZONE® High-Dose in Adult 65 Years of Age and Older

In clinical trial FIM05, adults 65 years of age and older were randomized to receive either FLUZONE® High-Dose or FLUZONE® (2006-2007 formulation) in a multi-centre, double-blind trial conducted in the US. The safety analysis set included 2573 FLUZONE® High-Dose recipients and 1260 FLUZONE® recipients.

Table 3 summarizes solicited injection-site and systemic reactions reported within 7 days post-vaccination via diary cards. Onset was usually within the first 3 days after vaccination and a majority of the reactions resolved within 3 days. Solicited injection-site and systemic reactions were more frequent after vaccination with FLUZONE® High-Dose compared to FLUZONE®.

Table 3: Frequency of Solicited Injection-Site and Systemic Reactions Within 7 Days After Vaccination with FLUZONE® High-Dose or FLUZONE®, Adults 65 Years of Age and Older (Safety Analysis Set)*

	FLUZONE® High-Dose N = 2569-2572**			FLUZONE® N = 1258-1260**		
	Any (%)	Moderate[β] (%)	Severe[§] (%)	Any (%)	Moderate[β] (%)	Severe[§] (%)
Injection site reactions						
Pain	35.6	3.7	0.3	24.3	1.7	0.2
Erythema	14.9	1.9	1.8	10.8	0.8	0.6
Swelling	8.9	1.6	1.5	5.8	1.3	0.6
Systemic reactions						
Myalgia	21.4	4.2	1.6	18.3	3.2	0.2
Malaise	18.0	4.7	1.6	14.0	3.7	0.6
Headache	16.8	3.1	1.1	14.4	2.5	0.3
Fever[¥] (≥37.5°C)	3.6	1.1	0.0	2.3	0.2	0.1

* Safety analysis set included participants who received study vaccine and provided data on at least one post vaccination assessment

** N is the number of vaccinated participants with available data for the events listed

β Moderate - Injection-site pain: sufficiently discomforting to interfere with normal behavior or activities; Injection-site erythema and Injection-site swelling: ≥2.5 cm to <5 cm; Fever: >38°C to ≤39°C; Myalgia, Malaise, and Headache: interferes with daily activities

§ Severe - Injection-site pain: incapacitating, unable to perform usual activities; Injection-site erythema and Injection-site swelling: ≥5 cm; Fever: >39°C; Myalgia, Malaise, and Headache: prevents daily activities

¥ Fever - The percentage of temperature measurements that were taken by oral route or not recorded were 97.9% and 2.1%, respectively, for FLUZONE® High-Dose; and 98.6% and 1.4%, respectively, for FLUZONE®

Within 6 months post-vaccination, 156 (6.1%) FLUZONE® High-Dose recipients and 93 (7.4%) FLUZONE® recipients experienced a serious adverse event (SAE). No deaths were reported within 28 days post-vaccination. A total of 23 deaths were reported during Days 29 – 180 post-vaccination: 16 (0.6%)

among FLUZONE® High-Dose recipients and 7 (0.6%) among FLUZONE® recipients. The majority of these participants had a medical history of cardiac, hepatic, neoplastic, renal, and/or respiratory diseases. These data do not provide evidence for a causal relationship between deaths and vaccination with FLUZONE® High-Dose.

The following table summarizes all unsolicited adverse reactions with rates ≥0.5% in either group within 28 days after vaccination, by MedDRA System Organ Class and Preferred Term.

Table 4: Unsolicited reactions ≥0.5% within 28 days after vaccination, by System Organ Class and Preferred Term

	FLUZONE® High-Dose (N= 2573) %	**FLUZONE® vaccine (N= 1260) %**
Gastrointestinal disorders		
- Nausea	0.6	0.3
General disorders and administration site conditions		
- Chills	0.5	0.2
- Injection site bruising	0.6	1.0
- Injection site induration	0.6	0.3

There was one report deemed related by the study investigator with FLUZONE® High-Dose exacerbation of Crohn's disease was reported two days after vaccination in a 72 year-old female participant with a relevant medical history of Crohn's ileitis. The study participant had received influenza vaccine annually for the previous eight to nine years and had not experienced a similar reaction.

In clinical trial FIM12, adults 65 years of age and older were randomized to receive either FLUZONE® High-Dose or FLUZONE® (2011-2012 and 2012-2013 formulations). The study compared the efficacy and safety of FLUZONE® High-Dose to those of FLUZONE®. The safety analysis set included 15,992 FLUZONE® High-Dose recipients and 15,991 FLUZONE® recipients.

Within the study surveillance period (approximately 6 to 8 months post-vaccination), 1323 (8.3%) FLUZONE® High-Dose recipients and 1442 (9.0%) FLUZONE® recipients experienced an SAE. Within 30 days post-vaccination, 204 (1.3%) FLUZONE® High-Dose recipients and 200 (1.3%) FLUZONE® recipients experienced an SAE. The majority of these participants had one or more chronic comorbid illnesses. A total of 167 deaths were reported within 6 to 8 months post-vaccination: 83 (0.5%) among FLUZONE® High-Dose recipients and 84 (0.5%) among FLUZONE® recipients. A total of 6 deaths were reported within 30 days post-vaccination: 6 (0.04%) among FLUZONE® High-Dose recipients and 0 (0 %) among FLUZONE® recipients. These data do not provide evidence for a causal relationship between deaths and vaccination with FLUZONE® High-Dose.

Post-Market Adverse Reactions

The following additional events have been reported during the post-approval use of FLUZONE® High-Dose FLUZONE® and QIV-HD. 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, oropharyngeal pain, rhinorrhea, cough, wheezing, throat tightness

Skin and Subcutaneous Tissue Disorders

Stevens-Johnson syndrome, rash

Musculoskeletal and Connective Tissue Disorders

Arthralgia

General Disorders and Administration Site Conditions

Pruritus, asthenia/fatigue, pain in extremities, chest pain, chills

Gastrointestinal Disorders

Vomiting, nausea, diarrhea

Overdose:

Cases of administration of more than the recommended dose have been reported with FLUZONE® High-Dose associated with inadvertent use in the population below 65 years of age due to medication error. When adverse reactions were reported, the information was consistent with the known safety profile of FLUZONE® High-Dose.

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).

9.4 Drug-Drug Interactions

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

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

9.7 Drug-Laboratory Test Interactions

Interference of FLUZONE® High-Dose with laboratory and/or diagnostic tests has not been studied.

Following influenza vaccination, false positive results in serology tests using the ELISA method to detect antibodies against HIV1, hepatitis C, and especially HTLV1 have been reported. An appropriate Western Blot test should be used to confirm or disprove the results of the ELISA test. The transient false positive reactions could be due to a non-specific IgM response induced by influenza vaccine.

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 highest against those strains of virus from which the vaccine is prepared or closely related strains.

Immunity to the surface antigens, particularly HA, 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 trivalent influenza vaccine contains three virus strains (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 4 weeks.

10.3 Pharmacokinetics

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.

12 SPECIAL HANDLING INSTRUCTION

Do not use vaccine after expiration date.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

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

For the 2025 – 2026 season FLUZONE® High-Dose contains the following strains:

- A/Victoria/4897/2022 (H1N1)pdm09-like strain (A/Victoria/4897/2022, IVR-238)
- A/Croatia/10136RV/2023 (H3N2)-like strain (A/Croatia/10136RV/2023, X-425A)
- B/Austria/1359417/2021-like strain (B/Michigan/01/2021, wild type)

Product Characteristics:

FLUZONE® High-Dose, Influenza Virus Vaccine Trivalent 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 fluid is harvested and inactivated with formaldehyde. Influenza virus is concentrated and purified in a linear sucrose density gradient solution using a continuous flow centrifuge. The virus is then chemically disrupted using a non-ionic surfactant, octylphenol ethoxylate (Triton® X-100) producing a "split-virus". The split virus is then further purified by diafiltration against phosphate buffered chloride saline.

FLUZONE® High-Dose has been standardized according to USPHS (US Public Health Service) requirements for the 2025 – 2026 influenza season and is formulated to contain 180 micrograms (mcg) HA per 0.5 mL dose, in the recommended ratio of 60 mcg HA of each strain.

FLUZONE® High-Dose, after shaking well, is colorless and opalescent.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Influenza In Adults 65 Years Of Age And Older.

Two clinical trials were conducted in the United States (see Table 5) with FLUZONE® High-Dose formulated using strains A (H1N1), A (H3N2), and B (either of the Victoria or Yamagata lineage).

Table 5: Summary of Demographics and Study Design of the Trials with FLUZONE® High-Dose (Full Analysis Set) *

Study #	Study Design	Dosage and Route of Administration	Study Subjects (n)	Mean Age (Range)	Sex N= Number of Males/Females
FIM05	Randomized, double-blind, multi-centre comparative trial with FLUZONE® High-Dose or FLUZONE® (2006-2007 formulation).	0.5 mL Intramuscular	3833	72.9 (65, 97)	N = 1825/2008
FIM12	Randomized, double-blind multi-centre, efficacy trial with FLUZONE® High-Dose or FLUZONE® (2011-2012 and 2012-2013 formulations)	0.5 mL Intramuscular	31983	72.2 (57.3, 100.0)	N = 13889/18094

* Full analysis set included participants who actually received study vaccine

Study Results

Efficacy of FLUZONE® High-Dose in Adults 65 Years of Age and Older

In a multi-centre study (FIM12) conducted in the United States and Canada, adults 65 years of age and older were randomized (1:1) to receive either FLUZONE® High-Dose or FLUZONE®. The study was conducted over two influenza seasons (2011-2012 and 2012-2013). The per-protocol analysis set for efficacy assessments included 15,892 FLUZONE® High-Dose recipients and 15,911 FLUZONE® recipients. The majority (67%) of participants in the per-protocol analysis set for efficacy had one or more high-risk chronic comorbid conditions.

The primary endpoint of the study was the occurrence of laboratory-confirmed influenza (as determined by culture or polymerase chain reaction) caused by any influenza viral type/subtype in association with influenza-like illness (ILI), defined as a new onset (or exacerbation) of at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty

breathing; concurrent with at least one of the following systemic signs or symptoms: temperature >37.2°C, chills, tiredness, headaches or myalgia. Participants were monitored for the occurrence of a respiratory illness by both active and passive surveillance, starting 2 weeks post-vaccination for approximately 7 months. After an episode of respiratory illness, nasopharyngeal swab samples were collected for analysis; attack rates and vaccine efficacy were calculated. As shown in Table 6 FLUZONE® High-Dose vaccine demonstrated superior efficacy compared to FLUZONE® in preventing laboratory-confirmed ILI (p-value against H_0:VE ≤ 9.1% = 0.022 one-sided).

Table 6: Relative Efficacy Against Laboratory-Confirmed Influenza* Regardless of Similarity to the Vaccine Components, Associated with Influenza-Like IllnessAdults 65 Years of Age and Older (Per-protocol Analysis Set)*****

	FLUZONE® High-Dose N = 15,892[P] (%) [V]	FLUZONE® N = 15,911 [P] n (%) [V]	Relative Efficacy % (95% CI)
Any type/subtype[β]	227 (1.43)	300 (1.89)	24.2 (9.7; 36.5) [§]
Influenza A	190 (1.20)	249 (1.56)	23.6 (7.4; 37.1)
A (H1N1)	8 (0.05)	9 (0.06)	11.0 (-159.9; 70.1)
A (H3N2)	171 (1.08)	222 (1.40)	22.9 (5.4; 37.2)
Influenza B[¥]	37 (0.23)	51 (0.32)	27.4 (-13.1; 53.8)

* Laboratory-confirmed: culture- or polymerase-chain-reaction-confirmed

** New onset (or exacerbation) of at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrent with at least one of the following systemic signs or symptoms: temperature >37.2°C, chills, tiredness, headaches or myalgia

***Per-protocol analysis set included all persons who had no study protocol deviations that would have impacted efficacy assessments

[P]N is the number of vaccinated participants in the per-protocol analysis set for efficacy assessments

[V]n is the number of participants with protocol-defined influenza-like illness with laboratory confirmation

[β] Primary endpoint

[§]The pre-specified statistical superiority criterion for the primary endpoint (lower limit of the 2-sided 95% CI of the vaccine efficacy of FLUZONE® High-Dose relative to FLUZONE® > 9.1%; p-value against H_0:VE ≤ 9.1% = 0.022 one-sided) was met

[¥]In the first year of the study the influenza B component of the vaccine and the majority of influenza B cases were of the Victoria lineage; in the second year the influenza B component of the vaccine and the majority of influenza B cases were of the Yamagata lineage

14.3 Immunogenicity

Immunogenicity of FLUZONE® High-Dose in Adults 65 Years of Age and Older

In a multi-centre study (FIM05) conducted in the United States, adults 65 years of age and older were randomized to receive either FLUZONE® High-Dose or FLUZONE® (2006-2007 formulation). The study compared the safety and immunogenicity of FLUZONE® High-Dose to those of FLUZONE®. A total of 3851 participants were included in immunogenicity assessments; of these, 2576 were randomized to FLUZONE® High-Dose and 1275 were randomized to FLUZONE®. Females accounted for 51.3% of participants in the FLUZONE® High-Dose group and 54.7% of participants in the FLUZONE® group. In both groups, the mean age was 72.9 years (ranged from 65 through 97 years in the FLUZONE® High-Dose group and 65 through 94 years in the FLUZONE® group); 35% of participants in the FLUZONE® High-Dose group and 36% of participants in the FLUZONE® group were 75 years of age or older.

The primary endpoints of the study were hemagglutination inhibition (HI) GMTs and seroconversion rates 28 days after vaccination. Pre-specified statistical superiority criteria required that the lower limit (LL) of the 2-sided 95% CI of the GMT ratio (FLUZONE® High-Dose divided by FLUZONE®) be greater than 1.50 for at least two of the strains, and if one strain failed, non-inferiority of that strain must be demonstrated (LL>0.67), and that the lower limit of the 2-sided 95% CI of the seroconversion rate difference (FLUZONE® High-Dose minus FLUZONE®) be greater than 10% for at least two of the strains, and if one strain failed, non-inferiority of that strain must be demonstrated (LL>-10%). As shown in Table 7 statistically superior HI GMTs and seroconversion rates after vaccination with FLUZONE® High-Dose compared to FLUZONE® were demonstrated for influenza A subtypes, A (H1N1) and A (H3N2), but not for influenza type B. For strain B, non-inferiority of FLUZONE® High-Dose compared to FLUZONE® was demonstrated for both the HI GMTs and seroconversion rates.

Table 7: Post-Vaccination HI Antibody GMTs and Seroconversion Rates and Analyses of Superiority of FLUZONE® High-Dose Relative to FLUZONE®, Adults 65 Years of Age and Older (Immunogenicity Analysis Set)*

Influenza Strain	GMT		GMT Ratio	Seroconversion %**		Difference	Met Both Pre-defined Superiority Criteria§
	FLUZONE® High-Dose N = 2542-2544***	FLUZONE® N = 1252***	FLUZONE® High-Dose over FLUZONE® (95% CI)	FLUZONE® High-Dose N = 2529-2531***	FLUZONE® N = 1248-1249***	FLUZONE® High-Dose minus FLUZONE® (95% CI)	
A (H1N1)	115.8	67.3	1.7 (1.6; 1.8)	48.6	23.1	25.4 (22.4; 28.5)	Yes
A (H3N2)	608.9	332.5	1.8 (1.7; 2.0)	69.1	50.7	18.4 (15.1; 21.7)	Yes
B	69.1	52.3	1.3 (1.2; 1.4)	41.8	29.9	11.8 (8.6; 15.0)	No

*Immunogenicity analysis set: subjects who participated in immunogenicity assessments
**Seroconversion: Paired samples with pre-vaccination HI titre <1:10 and post-vaccination (day 28) titre ≥1:40 or a minimum 4-fold increase for participants with pre-vaccination titre ≥1:10
***N is the number of vaccinated participants with available data for the immunologic endpoint listed
§ Predefined superiority criterion for the GMT ratio: the lower limit of the 95% CI of the GMT ratio (FLUZONE® High-Dose divided by FLUZONE) is >1.5. Predefined superiority criterion for seroconversion: the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (FLUZONE® High-Dose minus FLUZONE®) is >10%.

A secondary endpoint of the study was the percentage of participants who achieved seroprotection at one month following vaccination with FLUZONE® High-Dose (based on the pooled responses elicited by the three lots) compared to that for FLUZONE® vaccine, where seroprotection was defined as an anti-HA antibody titre ≥1:40. The percentages of participants who had a titre of ≥1:40 at baseline were comparable for both groups for all three strains.

Table 8 shows that for the A (H1N1) strain, seroprotection was achieved by 89.9% of participants in the FLUZONE® High-Dose group compared with 76.8% of participants in the FLUZONE® vaccine group (difference between groups [FLUZONE® High-Dose minus FLUZONE®] of 13.1%); for A (H3N2), seroprotection was achieved by 99.3% compared with 96.5%, respectively (difference of 2.8%); and for B, the values were 79.3% compared with 67.6%, respectively (difference of 11.7%).

Table 8: Percentage of Subjects Achieving Seroprotection* at 28 Days Post-Vaccination (Immunogenicity Analysis Set)**

	FLUZONE® High-Dose N = 2576***		FLUZONE® N = 1275***		FLUZONE® High-Dose minus FLUZONE®
Influenza Strain	**$n^{\beta}/M^{\S}$**	**% ≥1:40 (95% CI)**	**$n^{\beta}/M^{\S}$**	**% ≥1:40 (95% CI)**	**% (95% CI)**
A (H1N1)	2286/2543	89.9 (88.7; 91.0)	961/1252	76.8 (74.3; 79.1)	13.1 (10.5; 15.8)
A (H3N2)	2526/2544	99.3 (98.9; 99.6)	1208/1252	96.5 (95.3; 97.4)	2.8 (1.7; 3.9)
B	2015/2542	79.3 (77.6; 80.8)	846/1252	67.6 (64.9; 70.2)	11.7 (8.7; 14.7)

*Seroprotection: HI Titers ≥1:40 at Day 28

**Immunogenicity analysis set: subjects who participated in immunogenicity assessments

***N is the number of participants in the immunogenicity analysis set

$^{\beta}$ n is the number of participants who achieved seroprotection for the strain

§M is the number of participants with a valid serology result for the strain, including results reported as less than the lower limit of quantification

15 MICROBIOLOGY

No microbiological information is required for this vaccine.

16 NON-CLINICAL TOXICOLOGY

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

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

FLUZONE® High-Dose

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

Read this carefully before you receive FLUZONE® High-Dose and each time you get vaccinated. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about FLUZONE® High-Dose.

What is FLUZONE® High-Dose used for?

FLUZONE® High-Dose is a vaccine used to prevent influenza in adults 65 years of age and older. Influenza (or flu) is an infection caused by the influenza virus.

FLUZONE® High-Dose contains 4 times the amount of antigens compared to the standard dose influenza vaccine, FLUZONE®.

Influenza infection in adults 65 years of age and older is associated with significant morbidity and mortality. Natural and progressive weakening of the immune system over time in older adults (immunosenescence), results in increased susceptibility to influenza-related complications and hospitalization. Also, seniors are less responsive to standard dose influenza vaccine compared to younger adults below 65 years of age.

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® High-Dose work?

FLUZONE® High-Dose 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.

FLUZONE® High-Dose has been shown to induce higher antibody levels and have superior efficacy in preventing laboratory-confirmed influenza (prevented 24% more influenza cases) compared to the standard dose vaccine.

What are the ingredients in FLUZONE® High-Dose?

Medicinal ingredients:

This vaccine complies with the WHO (World Health Organization) recommendation (Northern hemisphere) for the 2025 – 2026 season.

Each 0.5 mL dose of FLUZONE® High-Dose contains split viruses from three inactivated strains of influenza virus for the 2025 – 2026 season. The viruses in FLUZONE® High-Dose are:

- A/Victoria/4897/2022 (H1N1)pdm09-like strain (A/Victoria/4897/2022, IVR-238)
- A/Croatia/10136RV/2023 (H3N2)-like strain (A/Croatia/10136RV/2023, X-425A)
- B/Austria/1359417/2021-like strain (B/Michigan/01/2021, wild type)

Non-medicinal ingredients:

Formaldehyde and Triton® X-100.

Does not contain adjuvant, preservative, or antibiotics.

FLUZONE® High-Dose comes in the following dosage forms:

Individual doses in a prefilled syringe.

The packaging of FLUZONE® High-Dose does not contain any latex.

Do not use FLUZONE® High-Dose if:

you are allergic to:

- the active substances, or
- any of the other ingredients of this vaccine listed in Section 6, or

any component that may be present in very small amounts such as eggs (ovalbumin, chicken proteins), formaldehyde and octylphenol ethoxylate.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take FLUZONE® High-Dose. 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 or bruising easily.** 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 given carefully.
- **An 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.**
- **Have fainted with a previous injection.** Fainting can occur after, or even before, any vaccination. Appropriate measures should be taken to prevent falling injury.

Other warnings you should know about:

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

FLUZONE® High-Dose will not necessarily protect against any other strains of flu virus.

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

If, for any reason you have a blood test within a few days following a flu vaccination, please tell your healthcare professional. False results in some types of blood tests have been reported (for example blood tests to detect antibodies against HIV, hepatitis C) in a few patients who had been recently vaccinated.

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® High-Dose:

- FLUZONE® High-Dose must not be mixed with other vaccines or medicinal products in the same syringe.
- If FLUZONE® High-Dose is to be given at the same time as other vaccines, the vaccines should always be administered in different limbs.
- The immunological response may decrease in case of immunosuppressant treatment such as corticosteroids, cytotoxic drugs or radiotherapy.

How to take FLUZONE® High-Dose:

Usual dose:

- For persons 65 years or older - recommended dose is 0.5 mL. Inject the vaccine into the deltoid (shoulder) muscle.

Overdose:

If you think you, or a person you are caring for, have taken too much FLUZONE® High-Dose contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Not Applicable for this vaccine.

What are possible side effects from using FLUZONE® High-Dose?

These are not all the possible side effects you may have when receiving FLUZONE® High-Dose. 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® High-Dose causing serious harm is extremely small. The small risks associated with FLUZONE® High-Dose 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 and muscle pain.

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.

65 years and older population:

Other side effects reported

Very common (may affect more than 1 in 10 people):
- Reactions at the injection site: pain
- Generally feeling unwell (malaise), headache, muscular pain (myalgia)

Common (may affect up to 1 in 10 people):
- Reactions at the injection site: redness (erythema), swelling, hardness (induration), bruising
- Shivering

Uncommon (may affect up to 1 in 100 people):
- Fever
- Injection site itching (pruritis)
- Feeling sick (nausea), diarrhea, dyspepsia, cough
- Abnormal lack of energy (asthenia), lethargy, pruritis, night sweats, rash, muscular weakness

Rare (may affect up to 1 in 1000 people):
- Fatigue

Not known: frequency cannot be estimated from the available data (based on FLUZONE® of TIV HD data)
- Reduction in the number of certain types of particles in the blood called platelets; a low number of these can result in excessive bruising or bleeding (thrombocytopenia), swollen glands in the neck, armpit or groin (lymphadenopathy)
- Numbness or pins and needles sensation (paresthesia),
- Neurological disorders that may result in stiff neck, confusion, numbness, pain and weakness of the limbs, loss of balance, loss of reflexes, paralysis of part or all the body (encephalomyelitis and transverse myelitis, brachial neuritis, Guillain-Barré Syndrome), fits (convulsions including febrile convulsions), facial palsy (Bell's palsy), vision disorders due to the optic nerves dysfunction (optic neuritis/neuropathy), fainting (syncope)shortly after vaccination
- Blood vessel inflammation (vasculitis) which may result in skin rashes and in very rare cases in temporary kidney problems, blood vessel opening (vasodilatation)

- Joint pain (arthralgia)
- Chest pain
- Skin condition with severe blisters and bleeding in the lips, eyes, mouth, nose and genitals (Stevens-Johnson Syndrome) excess of blood in the white of the eye (ocular hyperemia)
- Inflammation of the throat and the nose: (pharyngitis, rhinitis), wheezing, throat tightness, difficulty breathing (dyspnea)
- Dizziness, vertigo, flushing, hives (urticarial)
- Vomiting

Serious side effects and what to do about them		
Symptom / effect	**Talk to your healthcare professional**	
	Only if severe	**In all cases**
Severe allergic reactions Low blood pressure, rapid shallow breathing, rapid heart rate and weak pulse, cold, clammy skin and dizziness that may lead to collapse (shock) Swelling most apparent in the head and neck, including the face, lips, tongue, throat or any other part of the body and which may cause difficult in swallowing or breathing (angioedema) Skin condition with severe blisters and bleeding (Stevens-Johnson syndrome)		X
Allergic reactions Skin reactions that may spread throughout the body including itching, hives, rash, redness	X	

Talk to your doctor or nurse before receiving FLUZONE® High-Dose.

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. Keep the syringe in the outer carton in order to protect from light.

Do not use vaccine after expiration date.

Keep out of reach and sight of children.

If you want more information about FLUZONE® High-Dose:

- 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 1-800-265-7927.

This leaflet was prepared by Sanofi.

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