

PRODUCT MONOGRAPH

FLUZONE® High-Dose
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 Limited

Toronto, Ontario, Canada

Fabricated by:

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Control #: 238651

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FLUZONE® High-Dose 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: 60 µg of hemagglutinin (HA) for each of 3 strains listed below for a total of 180 µg. (See DESCRIPTION.)

Clinically Relevant Non-medicinal Ingredients: Formaldehyde, egg protein, Triton® X-100[†].

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

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

DESCRIPTION

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, inactivated with formaldehyde, concentrated and purified by zonal centrifugation on a sucrose gradient, split with Triton® X-100, further purified and then suspended in sodium phosphate-buffered isotonic sodium chloride solution. The FLUZONE® High-Dose process uses an additional concentration factor after the ultrafiltration step in order to obtain a higher HA antigen concentration.

FLUZONE® High-Dose complies with the WHO (World Health Organization) recommendation (Northern hemisphere) for the 2020-2021 season. The strains for the 2020-2021 season are: A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09 - like strain, A/Hong Kong/2671/2019 (H3N2) - like strain and B/Washington/02/2019 - like strain.

INDICATIONS AND CLINICAL USE

FLUZONE® High-Dose 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.

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

CONTRAINDICATIONS

FLUZONE® High-Dose 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® 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.

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

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

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)

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. (2)

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. (2) 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. (2)

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

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. (1)

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. (1) (See ADVERSE REACTIONS)

Special Populations

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.

Nursing Women

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.

Geriatrics

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

Pediatrics

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

experience with FLUZONE® High-Dose and FLUZONE®.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, adverse reaction rates observed in the clinical trial(s) of a vaccine cannot be directly compared to rates in the clinical trial(s) 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 events that appear to be related to vaccine use and for approximate rates of these reactions.

The safety of FLUZONE® High-Dose compared to FLUZONE® was evaluated in 3,833 adults (≥65 years of age) in a clinical trial conducted in the United States. (3) 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 1.

Table 1: 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 (3)

	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®

Data from Post-Marketing Experience

The following additional events have been reported during the post-approval use of FLUZONE® High-Dose or FLUZONE® in other countries. 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.

Events Reported During Post-Approval Use of FLUZONE®:

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

Asthenia/fatigue, pain in extremity, chest pain

Gastrointestinal Disorders

Vomiting

Other Events Reported During Post-Approval Use of FLUZONE® High-Dose:

Gastrointestinal Disorders:

Nausea, diarrhea

General Disorders and Administration Site Conditions:

Chills

Physicians, nurses and pharmacists should report any adverse occurrences temporally related to the administration of the product in accordance with local requirements and to the

Pharmacovigilance Department, Sanofi Canada, 2905 Place Louis-R-Renaud, Laval, QC, H7V 0A3, Canada, 1-888-621-1146 (phone).

DRUG INTERACTIONS

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

Concomitant Vaccine Administration

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

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

DOSAGE AND ADMINISTRATION

Recommended Dose

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.

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 the deltoid muscle.

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.

OVERDOSAGE

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 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. (4)

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. (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) (5)

Pharmacodynamics

Seroprotection is generally obtained within 4 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. (6) (7)

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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

FLUZONE® High-Dose is supplied as a clear to slightly opalescent suspension in a prefilled syringe.

Composition

This vaccine complies with the World Health Organization (WHO) recommendation (Northern Hemisphere) for the 2020-2021 season. For the 2020-2021 season FLUZONE® High-Dose

contains the following:

Active Ingredients

0.5 mL dose: 60 µg HA of each strain listed below:

A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09 - like strain [A/Guangdong-Maonan/SWL1536/2019 CNIC-1909]

A/Hong Kong/2671/2019 (H3N2) - like strain [A/Hong Kong/2671/2019 IVR-208]

B/Washington/02/2019 - like strain [B/Washington/02/2019 wild type virus].

Other Ingredients

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

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.

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

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

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

Product information as of April 2020.

Manufactured by:

Sanofi Pasteur Inc.

Swiftwater, PA 18370 USA

Distributed by:

Sanofi Pasteur Limited

Toronto, Ontario, Canada

R6-0420 Canada

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

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

For the 2020-2021 season FLUZONE® High-Dose contains the following strains:

A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09 - like strain [A/Guangdong-Maonan/SWL1536/2019 CNIC-1909]

A/Hong Kong/2671/2019 (H3N2) - like strain [A/Hong Kong/2671/2019 IVR-208]

B/Washington/02/2019 - like strain [B/Washington/02/2019 wild type virus].

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 allantoic fluid is harvested and inactivated with formaldehyde. Influenza virus is concentrated and purified on a linear sucrose density gradient solution using a continuous flow centrifuge. The virus is then chemically disrupted using a nonionic surfactant (Triton® X-100 - a registered trademark of Union Carbide, Co.) producing “split virus”. The split virus is then further purified by ultrafiltration and diluted to appropriate sodium phosphate-buffered isotonic sodium chloride solution. The FLUZONE® High-Dose process uses an additional concentration factor after the ultrafiltration step in order to obtain a higher hemagglutinin (HA) antigen concentration.

FLUZONE® High-Dose has been standardized according to USPHS (US Public Health Service) requirements for the 2020-2021 influenza season and is formulated to contain 180 micrograms (µg) HA per 0.5 mL dose, in the recommended ratio of 60 µg HA of each strain.

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

CLINICAL TRIALS

Study Demographics and Trial Design

Two clinical trials were conducted in the United States (see Table 2) with FLUZONE® High-Dose formulated using strains A (H1N1), A (H3N2), and B (either of the Victoria or Yamagata lineage).

Table 2: Summary of Demographics and Study Design of the Trials with FLUZONE® High-Dose (Full Analysis Set)* (3) (8)

Study	Study Design	Dosage and Route of Administration	Study Participants N = Number	Mean Age (Years) and Range	Gender N = Number Males/Females
FIM05	Randomized, double-blind, multi-centre comparative trial with FLUZONE® High-Dose or FLUZONE® (2006-2007 formulation).	0.5 mL Intramuscular	N = 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	N = 31983	72.2 (57.3, 100.0)	N = 13889/18094

* Full analysis set included participants who actually received study vaccine

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 3, 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 3: 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 $\geq 1:40$. The percentages of participants who had a titre of $\geq 1:40$ at baseline were comparable for both groups for all three strains.

Table 4 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 4: Percentage of Subjects Achieving Seroprotection* at 28 Days Post-Vaccination (Immunogenicity Analysis Set)†

Influenza Strain	FLUZONE® High-Dose N = 2576‡		FLUZONE® N = 1275‡		FLUZONE® High-Dose minus FLUZONE®
	n§/M**	% $\geq 1:40$ (95% CI)	n§/M**	% $\geq 1:40$ (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 $\geq 1:40$ at Day 28

† Immunogenicity analysis set: subjects who participated in immunogenicity assessments

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

§ 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

EFFICACY

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 5, FLUZONE® High-Dose vaccine demonstrated superior efficacy compared to FLUZONE® in preventing laboratory-confirmed ILI (p-value against $H_0: VE \leq 9.1\% = 0.022$ one-sided).

Table 5: Relative Efficacy Against Laboratory-Confirmed Influenza* Regardless of Similarity to the Vaccine Components, Associated with Influenza-Like Illness†, Adults 65 Years of Age and Older (Per-protocol Analysis Set)‡

	FLUZONE® High-Dose N = 15,892§ n (%)**	FLUZONE® N = 15,911§ n (%)**	Relative Efficacy % (95% CI)
Any type/subtype††	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
- § N is the number of vaccinated participants in the per-protocol analysis set for efficacy assessments
- ** n is the number of participants with protocol-defined influenza-like illness with laboratory confirmation
- †† 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 H₀: 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

SAFETY

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 6 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 6: 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‡ (%)	Severe§ (%)	Any (%)	Moderate‡ (%)	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** ($\geq 37.5^{\circ}\text{C}$)	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
- ‡ 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: $> 38^{\circ}\text{C}$ to $\leq 39^{\circ}\text{C}$; 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: $> 39^{\circ}\text{C}$; 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.

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.

TOXICOLOGY

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

ADDITIONAL RELEVANT INFORMATION

Influenza infection in adults 65 years of age and older is associated with significant morbidity and mortality. The heightened susceptibility to influenza-related complications in older adults is due in large part to natural and progressive weakening of the immune system over time. This phenomenon, known as immunosenescence, also renders seniors less responsive to standard dose influenza vaccine. (9) Another study showed that for the influenza seasons 1998-1999 through to 2004-2005, the range of standard dose vaccine effectiveness was 62% to 76% in persons 15-64 years of age and 26% to 52% in those ≥ 65 years of age. (10)

REFERENCES

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3Data on File. FIM05 - Phase III Lot Consistency, Immunogenicity and Safety Study of Three Lots of Fluzone High Dose Vaccine Compared with One Lot of Standard Fluzone® in Adults 65 Years of Age.

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8Data on File. FIM12 - Efficacy Study of Fluzone® High-Dose Vaccine Compared With Fluzone® Vaccine In Elderly Adults

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

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

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

Product information as of April 2020.

Manufactured by:

Sanofi Pasteur Inc.

Swiftwater, PA 18370 USA

Distributed by:

Sanofi Pasteur Limited

Toronto, Ontario, Canada

R6-0420 Canada

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

FLUZONE® High-Dose

**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® High-Dose 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® High-Dose. Contact your doctor, nurse or pharmacist if you have any questions about the vaccine.

ABOUT THIS VACCINE

What the vaccine is 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 containing 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® 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.

When it should not be used:

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

- egg or egg products
- any component of FLUZONE® High-Dose

What the medicinal ingredient is:

This vaccine complies with the WHO (World Health Organization) recommendation (Northern hemisphere) for the 2020-2021 season.

Each 0.5 mL dose of FLUZONE® High-Dose contains killed split viruses from three strains of influenza virus for the 2020-2021 season. The viruses in FLUZONE® High-Dose are:

- A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09 - like strain
- A/Hong Kong/2671/2019 (H3N2) - like strain
- B/Washington/02/2019 - like strain

What the important non-medicinal ingredients are:

Sodium phosphate-buffered, isotonic sodium chloride solution, formaldehyde and Triton® X-100.

Does not contain adjuvant, preservative, or antibiotics.

What dosage forms it comes in:

Individual doses in a prefilled syringe.

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

For persons 65 years or older - recommended dose is 0.5 mL.

Inject the vaccine into the deltoid (shoulder) muscle.

WARNINGS AND PRECAUTIONS

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.

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

- **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 the vaccine is not given carefully.
- **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 after a previous influenza vaccination.**

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

INTERACTIONS WITH THIS VACCINE

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

PROPER USE OF THIS VACCINE

Usual dose:

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:

Not Applicable for this vaccine.

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® 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 pain where you got the injection and muscle pain.

Severe allergic reactions to 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. Other side effects may occur. Talk to your doctor or nurse before receiving FLUZONE® High-Dose.

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

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

HOW TO STORE IT

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

Do not use vaccine after expiration date.

Keep FLUZONE® High-Dose 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.sanofi.ca or by contacting the vaccine producer, Sanofi Pasteur Limited, 1755 Steeles Avenue West, Toronto, Ontario, M2R 3T4.

Phone: 1-888-621-1146 or 416-667-2779.

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

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