PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

FLUZONE® High-Dose Quadrivalent

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

Suspension for Intramuscular Injection

Active Immunizing Agent for the Prevention of Influenza

ATC Code: J07BB02

2021-2022 season

A/Victoria/2570/2019 (H1N1) pdm09-like strain [A/Victoria/2570/2019, IVR-215]	60 µg HA
A/Cambodia/e0826360/2020 (H3N2)-like strain [A/Tasmania/503/2020, IVR-221]	60 µg HA
B/Washington/02/2019-like strain [B/Washington/02/2019, wild type]	60 µg HA
B/Phuket/3073/2013-like strain [B/Phuket/3073/2013, wild type]	60 µg HA

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

- FLUZONE® High-Dose Quadrivalent vaccine 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) provides additional guidance on the use of the influenza vaccine in Canada. Please refer to the published Statement on Seasonal Influenza Vaccine for the current season.

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 Quadrivalent 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 Quadrivalent vaccine is indicated for active immunization for the prevention of influenza in adults 65 years of age and older.

2 CONTRAINDICATIONS

FLUZONE® High-Dose Quadrivalent is contraindicated in anyone with a known systemic hypersensitivity reaction after previous administration of any influenza vaccine or to any component of the vaccine (e.g. eggs or egg products). For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage of FLUZONE® High-Dose Quadrivalent is 1 dose of 0.7 mL, annually, in persons 65 years of age and older.

Fractional doses (doses <0.7 mL) should not be given. The safety and efficacy of fractional doses have not been determined.

Health Canada has not authorized an indication for pediatric use in children less than 18 years of age. (See 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics) or in adults less than 65 years of age.

4.4 Administration

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

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

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

Administer the vaccine **intramuscularly**. The preferred site is the deltoid muscle. The vaccine should not be injected into the gluteal region or into areas where there may be a major nerve trunk. For needle length, refer to national recommendations.

Do not administer this product intravenously.

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, to ensure traceability for patient immunization record keeping as well as safety monitoring, 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 brand name and generic name of the vaccine, date and time given, anatomical site and route of administration, quantity of administered dose, lot number and expiry date.

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	**Dosage Form:** Suspension for injection **Active Ingredients:** Each 0.7 mL dose contains 60 µg HA of each strain listed below	octylphenol ethoxylate (Triton® X-100), sodium phosphate buffered isotonic sodium chloride solution. traces of formaldehyde and ovalbumin

FLUZONE® High-Dose Quadrivalent [Influenza Virus Vaccine Quadrivalent Types A and B (Split Virion)] is a sterile aqueous suspension of inactivated influenza virus for intramuscular injection. FLUZONE® High-Dose Quadrivalent contains 4 strains of influenza 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 (octoxinol-9, Triton® X-100) producing a "split-virus." The split-virus is then further purified by diafiltration against phosphate-buffered chloride saline. FLUZONE® High-Dose Quadrivalent is formulated to contain 240 micrograms (µg) hemagglutinin per 0.7 mL dose in the recommended ratio of 60 µg HA of each of the four influenza strains (A/H3N2, A/H1N1, B/Yamagata like, and B/Victoria like).

Antibiotics are not used in the manufacture of FLUZONE® High-Dose Quadrivalent.

There is no thimerosal used in the manufacturing process of FLUZONE® High-Dose Quadrivalent.

FLUZONE® High-Dose Quadrivalent is supplied as a sterile aqueous suspension for injection in a prefilled syringe. After shaking the syringe well, FLUZONE® High-Dose Quadrivalent is essentially clear and slightly opalescent in colour.

This vaccine complies with the World Health Organization (WHO) recommendation (Northern Hemisphere) for the 2021-2022 season. For the 2021-2022 season FLUZONE® High-Dose Quadrivalent contains the following:

Active Ingredients:

Each 0.7 mL dose contains 60 µg HA of each strain listed below:

- A/Victoria/2570/2019 (H1N1) pdm09-like strain [A/Victoria/2570/2019, IVR-215]
- A/Cambodia/e0826360/2020 (H3N2)-like strain [A/Tasmania/503/2020, IVR-221]
- B/Washington/02/2019-like strain [B/Washington/02/2019, wild type]
- B/Phuket/3073/2013-like strain [B/Phuket/3073/2013, wild type]

Other Ingredients:

0.7 mL dose: ≤ 350 µg octylphenol ethoxylate (Triton® X-100), ≤ 200 µg/mL formaldehyde and up to 0.7 mL sodium phosphate buffered isotonic sodium chloride solution.

Each dose may contain traces of ovalbumin. Antibiotics and thimerosal are not used in the manufacture of FLUZONE® High-Dose Quadrivalent.

Packaging

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

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

FLUZONE® High-Dose Quadrivalent is available in packages of:

5 x 0.7 mL (single dose) syringes without attached needle.

10 x 0.7 mL (single dose) syringes without attached needle.

Not all pack sizes may be marketed.

7 WARNINGS AND PRECAUTIONS

General

Before administration of FLUZONE® High-Dose Quadrivalent, 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.

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.

As with any vaccine, vaccination with FLUZONE® High-Dose Quadrivalent may not protect 100% of recipients against influenza illness.

Influenza virus is unpredictable in that significant antigenic changes may occur from time to time. At this time, current influenza virus vaccines are not effective against all possible influenza strains. Protection is highest against 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, a mild disease should not usually be a reason to postpone vaccination.

Hematologic

Because any intramuscular injection can cause an 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 Quadrivalent should not be administered to such 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.

The Canadian Immunization Guide has recommendations for giving vaccinations to persons with bleeding disorders.

Immune

Prior to any vaccination, all known precautions should be taken to prevent hypersensitivity reactions. Epinephrine hydrochloride solution (1:1,000) and other appropriate agents used for the control of immediate allergic reactions must be available to treat unexpected reactions, such as anaphylaxis. 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. 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, ovalbumin and octylphenol ethoxylate, which are used during vaccine production, caution should be exercised when the vaccine is administered to persons with hypersensitivity to one of these substances. See 2 CONTRAINDICATIONS.

The immunogenicity of FLUZONE® High-Dose Quadrivalent may be reduced by immunosuppressive treatment or in individuals with immune deficiency syndromes. In such cases it is recommended to postpone the vaccination until after the immunosuppressive treatment or resolution of the immunosuppressive condition, if feasible. 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

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

Skin

Local reactions at injection site such as pain, erythema, swelling, induration and bruising may occur. See 8 ADVERSE REACTIONS.

7.1 Special Populations

7.1.1 Pregnant Women

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

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

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

7.1.4 Geriatrics

Geriatrics (≥65 years of age): FLUZONE® High-Dose Quadrivalent is indicated for persons 65 years of age and older.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

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 Quadrivalent was assessed in one randomized, active-controlled, modified double-blind Phase III clinical trial conducted in the United States which enrolled 2,670 adults 65 years of age and older. The study compared the safety and immunogenicity of FLUZONE® High-Dose Quadrivalent to those of FLUZONE® High-Dose, which is a trivalent influenza vaccine indicated for adults 65 years of age and older and which also contains 60 µg of hemagglutin for each strain. The safety analysis set included 1,777 FLUZONE® High-Dose Quadrivalent recipients, 443 FLUZONE® High-Dose recipients, and 450 recipients of FLUZONE® High-Dose containing the alternate B influenza strain. Safety results for the FLUZONE® High-Dose and investigational FLUZONE® High-Dose containing the alternate B influenza strain recipients were pooled for the analysis. Safety evaluations were performed during the first 28 days following vaccination. Serious adverse reactions were collected during six months of follow-up.

The overall safety profile of FLUZONE® High-Dose Quadrivalent was comparable to FLUZONE® High-Dose.

The most common reactions occurring after FLUZONE® High-Dose Quadrivalent administration were injection site pain (41%), myalgia (23%), headache (14%) and malaise (13%). Onset usually occurred within the first 3 days after vaccination. The majority of solicited reactions resolved within three days

of vaccination.

Table 2 displays the frequency of the solicited injection site and systemic reactions for FLUZONE® High-Dose Quadrivalent compared to FLUZONE® High-Dose reported within 7 days post-vaccination and collected using standardized diary cards.

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

	FLUZONE® High-Dose Quadrivalent N = 1,777		FLUZONE® High-Dose N = 893	
	n/M	%	n/M	%
Local reactions				
Injection Site Pain	731/1,768	41	324/889	36
Injection Site Erythema	110/1,768	6	51/889	6
Injection Site Swelling	86/1,766	5	42/887	5
Injection Site Induration	66/1,766	4	31/887	4
Injection Site Bruising	23/1,765	1	10/887	1
Systemic reactions				
Malaise	233/1,768	13	119/889	13
Shivering	95/1,768	5	42/889	5
Fever	7/1,761	0	8/885	1

n: number of subjects experiencing the endpoint listed in the first column.
M: number of subjects with available data for the relevant endpoint.

Based on data from FLUZONE® High-Dose, solicited injection site reactions and systemic adverse reactions were slightly more frequent after vaccination with FLUZONE® High-Dose compared to a standard dose vaccine.

Unsolicited adverse reactions for FLUZONE® High-Dose Quadrivalent compared to FLUZONE® High-Dose reported within 28 days after vaccination, respectively, were low with rates of less than one percent for all unsolicited adverse reactions: injection site pruritis (0.5%; 0.1%), fatigue (<0.1%; <0.1%), diarrhea (0.1%; 0.2%), nausea (0.1%; 0.3%), vomiting (<0.1%; 0%), dizziness (<0.1%; 0%), flushing (<0.1%; 0%), pruritis (<0.1%; 0.1), urticaria (<0.1%; 0%), arthralgia (<0.1%; 0%), pain in extremity (<0.1%; 0%), cough (0.2%; 0.1%), and vertigo (0.1%; 0%).

Within 180 days post-vaccination, 80 (4.5%) FLUZONE® High-Dose Quadrivalent recipients and 48 (5.4%) FLUZONE® High-Dose recipients experienced a serious adverse event (SAE). None of the SAEs were assessed as related to the study vaccines.

8.5 Post-Market Adverse Reactions

No post-marketing data is currently available for FLUZONE® High-Dose Quadrivalent.

The following additional adverse events have been spontaneously reported during the post-marketing use of FLUZONE® High-Dose and may occur in people receiving FLUZONE® High-Dose Quadrivalent. 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.

Blood and Lymphatic System Disorders

Thrombocytopenia, lymphadenopathy

Eye Disorders

Ocular hyperemia

Gastrointestinal Disorders

Vomiting

General Disorders and Administration Site Conditions

Asthenia, chest pain

Immune System Disorders

Anaphylaxis, other allergic/hypersensitivity reactions (including 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), paraesthesia

Respiratory, Thoracic and Mediastinal Disorders

Dyspnea, wheezing, throat tightness, oropharyngeal pain, rhinorrhea

Skin and Subcutaneous Tissue Disorders

Stevens-Johnson syndrome

Vascular Disorders

Vasculitis, vasodilatation

Health 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

FLUZONE® High-Dose Quadrivalent should not be mixed with any other vaccine in the same syringe or vial.

There are no data to assess the concomitant administration of FLUZONE® High-Dose Quadrivalent with other vaccines. If FLUZONE® High-Dose Quadrivalent needs to be given at the same time as another injectable vaccine(s), immunization should always be carried out on separate limbs.

9.7 Drug-Laboratory Test Interactions

Interference of FLUZONE® High-Dose Quadrivalent 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 with 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.

Immunization against influenza reduces the risk of influenza illness and complications caused by infection with the strains contained in the vaccine. Global surveillance of influenza identifies yearly antigenic variants. For example, since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. Specific levels of hemagglutination inhibition (HAI) antibody titre post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza virus infection.

Antibodies against one influenza virus type or subtype confer limited or no protection against another. Furthermore, antibodies to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virological basis for seasonal epidemics and the reason for the usual change of one or more strains in each year's influenza vaccine. Therefore, influenza vaccines are standardized to contain the hemagglutinins of influenza virus strains representing the influenza viruses likely to be circulating in the upcoming season.

Annual influenza vaccination is recommended because immunity during the year after vaccination declines and because circulating strains of influenza virus change from year to year.

10.2 Pharmacodynamics

Seroprotection is generally obtained within 4 weeks.

Adults 65 years and older generally have a heightened susceptibility to influenza-related complications due to natural and progressive weakening of the immune system over time known as

immunosenescence. Immunosenescence can also render seniors less responsive to standard dose influenza vaccine.

In clinical trials of adults 65 years of age and older, immunization with FLUZONE® High-Dose (Trivalent) induced a higher immune response to the A-strains contained in the vaccine than did immunization with a standard-dose influenza vaccine. Immune responses to FLUZONE® High-Dose Quadrivalent were shown to be non-inferior to those obtained with FLUZONE® High-Dose (Trivalent) in adults 65 years of age and older and statistically higher for the B strain not contained in FLUZONE® High Dose. See PART II: SCIENTIFIC INFORMATION for further detail regarding clinical trials

10.3 Pharmacokinetics

Duration of Effect: Protection against influenza post-vaccination is expected to persist throughout the influenza season for which the vaccine is indicated.

11 STORAGE, STABILITY AND DISPOSAL

Store at 2° to 8°C (i.e. in a refrigerator). **Do not freeze.** Discard product if exposed to freezing.

12 SPECIAL HANDLING INSTRUCTIONS

Do not use after the expiration date shown on the label.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

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

For the 2021-2022 season FLUZONE® High-Dose Quadrivalent contains the following strains:

- A/Victoria/2570/2019 (H1N1) pdm09-like strain [A/Victoria/2570/2019, IVR-215]
- A/Cambodia/e0826360/2020 (H3N2)-like strain [A/Tasmania/503/2020, IVR-221]
- B/Washington/02/2019-like strain [B/Washington/02/2019, wild type]
- B/Phuket/3073/2013-like strain [B/Phuket/3073/2013, wild type]

Product Characteristics:

FLUZONE® High-Dose Quadrivalent [Influenza Virus Vaccine Quadrivalent Types A and B (Split Virion)] is a sterile aqueous suspension of inactivated influenza virus for intramuscular injection. FLUZONE® High-Dose Quadrivalent contains 4 strains of influenza 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 (octoxinol-9, Triton® X-100) producing a "split-virus." The split-virus is then further purified by diafiltration against phosphate-buffered chloride saline.

FLUZONE® High-Dose Quadrivalent is formulated to contain 240 micrograms (µg) hemagglutinin per 0.7 mL dose in the recommended ratio of 60 µg HA of each of the four influenza strains (A/H3N2, A/H1N1, B/Yamagata like, and B/Victoria like).

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

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Influenza In Adults 65 Years Of Age And Older.

One clinical trial (Table 3) was conducted in the United States to compare the immunogenicity and safety of FLUZONE® High-Dose Quadrivalent to that of FLUZONE® High-Dose in adults 65 years of age and older.

Table 3: Summary of Demographics and Study Design of Pivotal Trial with FLUZONE® High-Dose Quadrivalent (Full Analysis Set)*

Study	Study Design	Dosage and Route of Administration	Study Participants N = Number	Mean Age (Years) and Range	Gender N = Number Males/Females
QHD00013	Randomized, active-controlled, modified double-blind, multi-centre trial with FLUZONE® High-Dose Quadrivalent or FLUZONE® High-Dose (2017-2018 and investigational formulations)	0.7 mL Intramuscular	N = 2,648 QIV-HD: 1,763 TIV-HD1: 439 TIV-HD2: 446	73.0 (65, 100)	N = 1,112/1,536

* Full analysis set included randomized participants who received a dose of study vaccine and had a post-vaccination blood sample HAI result for at least 1 strain.
QIV-HD: FLUZONE® High-Dose Quadrivalent.
TIV-HD1: FLUZONE® High-Dose (2017-2018 formulation containing A/H3N2, A/H1N1, B/Victoria like strains).
TIV-HD2: FLUZONE® High-Dose (investigational formulation containing A/H3N2, A/H1N1, B/Yamagata like strains).

QHD00013 was designed with the objective to demonstrate non-inferior immunogenicity between FLUZONE® High-Dose Quadrivalent and FLUZONE® High-Dose, which allows the efficacy of FLUZONE® High-Dose Quadrivalent to be inferred from that for FLUZONE® High-Dose.

Two clinical trials were conducted in the United States and Canada (see Table 4) with FLUZONE® High-Dose formulated using strains A (H1N1), A (H3N2), and B (either of the Victoria or Yamagata lineage).

Table 4: 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 Participants N = Number	Mean Age (Years) and Range	Gender N = Number Males/Females
FIM05	Randomized, double-blind, multi-centre controlled trial with FLUZONE® High-Dose or FLUZONE® (2006-2007 formulation)	0.5 mL Intramuscular	N = 3,833 FLUZONE® High-Dose: 2,573 FLUZONE®: 1,260	72.9 (65, 97)	N = 1,825/2,008
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 = 31,983 FLUZONE® High-Dose: 15,990 FLUZONE®: 15,993	72.2 (57.3, 100.0)	N = 13,889/18,094

*Full analysis set included participants who actually received study vaccine

Study Results: Efficacy

FIM12 Study

The efficacy experience with FLUZONE® High-Dose (trivalent formulation) is relevant to FLUZONE® High-Dose Quadrivalent since both vaccines are manufactured according to the same process and have overlapping compositions.

In a multi-centre, double-blind efficacy 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 standard-dose FLUZONE® vaccine. 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 ≤ 9.1% = 0.022 one-sided).

Table 5: Relative Efficacy against Laboratory-Confirmed Influenza[a], Regardless of Similarity to the Vaccine Components, Associated with Influenza-Like Illness[b] Adults 65 Years of Age and Older (Per-protocol Analysis Set)[c]

	FLUZONE® High-Dose N[e] = 15,892 n[d] (%)	FLUZONE® N[e] = 15,911 n[d] (%)	Relative Efficacy % (95% CI)
Any type/subtype[f]	227 (1.43)	300 (1.89)	24.2 (9.7; 36.5)[g]
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[h]	37 (0.23)	51 (0.32)	27.4 (-13.1; 53.8)

[a] Laboratory-confirmed: culture- or polymerase-chain-reaction-confirmed.
[b] 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.
[c] Per-protocol analysis set included all persons who had no study protocol deviations that would have impacted efficacy assessments.
[d] n is the number of participants with protocol-defined influenza-like illness with laboratory confirmation.
[e] N is the number of vaccinated participants in the per-protocol analysis set for efficacy assessments.
[f] Primary endpoint.
[g] 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.
[h] 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

QHD00013 Study

QHD00013 was a randomized, active-controlled, modified double-blind Phase III clinical trial conducted in the United States in adults 65 years and older. The objective was to demonstrate the non-inferiority of the immune response to FLUZONE® High-Dose Quadrivalent as compared to FLUZONE® High-Dose in adults 65 years of age and older, as assessed by HAI (hemagglutinin inhibition) Geometric mean antibody titres (GMTs) at Day 28 and seroconversion rates.

A total of 2,670 adults 65 years of age or older were randomized to receive either one dose of FLUZONE® High-Dose Quadrivalent [QIV-HD] or one dose of FLUZONE® High-Dose (one of two formulations of comparator vaccine [TIV-HD1 or TIV-HD2]); each TIV-HD formulation contained a B strain that corresponds to one of the two B strains in FLUZONE® High-Dose Quadrivalent (either a B strain of the Yamagata lineage or a B strain of the Victoria lineage). The mean age was 72.9 years in the FLUZONE® High-Dose Quadrivalent group (ranged from 65 through 100 years) and the mean age was 73.0 in the FLUZONE® High-Dose group (ranged from 65 through 95 years). 35.4% of participants in the FLUZONE® High-Dose Quadrivalent group and 35.8% of participants in the FLUZONE® High-Dose group were 75 years of age or older.

The immunogenicity results of FLUZONE® High-Dose Quadrivalent in the QHD00013 study are summarized Table 6a and Table 6b.

Table 6a: Post-vaccination HAI Antibody GMTs and Analyses of Non-inferiority of Fluzone High-Dose Quadrivalent Relative to Fluzone High-Dose, Adults 65 Years of Age and Older, Per-Protocol Analysis Set [a]

Influenza Strain	GMT			GMT Ratio	Met Predefined Non-inferiority Criteria[e]
	QIV-HD (95% CI) N[b]=1679-1680	TIV-HD1[c] (B1 Victoria) (95% CI) N[b]=423	TIV-HD2[d] (B2 Yamagata) (95% CI) N[b]=430	QIV-HD over TIV-HD (95% CI)	
A (H1N1)[f]	312 (292; 332)	374 (341; 411)		0.83 (0.744; 0.932)	Yes
A (H3N2)[f]	563 (525; 603)	594 (540; 653)		0.95 (0.842; 1.066)	Yes
B1 (Victoria)	516 (488; 545)	476 (426; 532)	--	1.08 (0.958; 1.224)	Yes
B2 (Yamagata)	578 (547; 612)	--	580 (519; 649)	1.00 (0.881; 1.129)	Yes

[a] NCT03282240
[b] N is the number of vaccinated participants with available data for the immunologic endpoint listed

[c] TIV-HD1 contained A/Michigan/45/2015 (H1N1), A/Hong Kong/4801/2014 (H3N2), and B/Brisbane/60/2008 (B1, Victoria lineage)
[d] TIV-HD2 contained A/Michigan/45/2015 (H1N1), A/Hong Kong/4801/2014 (H3N2), and B/Phuket/3073/2013 (B2, Yamagata lineage)
[e] Predefined noninferiority criterion for the GMT ratio: the lower limit of the 95% CI of the GMT ratio (QIV-HD divided by TIV-HD) is >0.667
[f] Pooled TIV-HD group includes subjects vaccinated with either TIV-HD1 or TIV-HD2 for the A strain comparison

Table 6b: Seroconversion Rates and Analyses of Non-inferiority of Fluzone High-Dose Quadrivalent Relative to Fluzone High-Dose, Adults 65 Years of Age and Older, Per-Protocol Analysis Set [a]

Influenza Strain	Seroconversion Rates (Percentage)[b]			Difference of Seroconversion Rates	Met Predefined Non-inferiority Criteria[f]
	QIV-HD (95% CI) N[c]=1668-1669	TIV-HD1[d] (B1 Victoria) (95% CI) N[c]=420-421	TIV-HD2[e] (B2 Yamagata) (95% CI) N[c]=428	QIV-HD minus TIV-HD (95% CI)	
A (H1N1)[g]	50.4 (48.0; 52.8)	53.7 (50.2; 57.1)		-3.27 (-7.37; 0.86)	Yes
A (H3N2)[g]	49.8 (47.3; 52.2)	50.5 (47.1; 53.9)		-0.71 (-4.83; 3.42)	Yes
B1 (Victoria)	36.5 (34.2; 38.9)	39.0 (34.3; 43.8)	--	-2.41 (-7.66; 2.70)	Yes
B2 (Yamagata)	46.6 (44.2; 49.0)	--	48.4 (43.5; 53.2)	-1.75 (-7.04; 3.53)	Yes

[a] NCT03282240
[b] Seroconversion Rates: For subjects with a pre-vaccination titer <10 (1/dil), proportion of subjects with a post-vaccination titer ≥40 (1/dil) and for subjects with a pre-vaccination titer ≥10 (1/dil), proportion of subjects with a ≥four-fold increase from pre-vaccination to post-vaccination titer
[c] N is the number of vaccinated participants with available data for the immunologic endpoint listed
[d] TIV-HD1 contained A/Michigan/45/2015 (H1N1), A/Hong Kong/4801/2014 (H3N2), and B/Brisbane/60/2008 (B1, Victoria lineage)
[e] TIV-HD2 contained A/Michigan/45/2015 (H1N1), A/Hong Kong/4801/2014 (H3N2), and B/Phuket/3073/2013 (B2, Yamagata lineage)
[f] Predefined noninferiority criterion for seroconversion: the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (QIV-HD minus TIV-HD) is >-10%
[g] Pooled TIV-HD group includes subjects vaccinated with either TIV-HD1 or TIV-HD2 for the A strain comparison

The non-inferiority objective was achieved only when non-inferiority was demonstrated for all 4 strains and for both GMTs and seroconversion rates. Therefore, the Type I error was not inflated and the adjustment for alpha was not needed for multiple statistical testing.

Immunogenicity of FLUZONE® High-Dose Quadrivalent was found to be non-inferior to FLUZONE® High-Dose. The pre-defined non-inferiority immunogenicity criteria for FLUZONE® High-Dose Quadrivalent were met for both GMTs and seroconversion rates for all four of the influenza strains common between the two vaccines. Additionally, FLUZONE® High-Dose Quadrivalent induced a higher immune response, as measured by GMTs and seroconversion rates, with respect to the additional B strain than the immune response induced by FLUZONE® High-Dose that does not contain the corresponding B.

The efficacy results of FLUZONE® High-Dose are thus inferred to FLUZONE® High-Dose Quadrivalent given the demonstration of non-inferiority of immunogenicity between FLUZONE® High-Dose and FLUZONE® High-Dose Quadrivalent in the QHD00013 study.

FIM05 Study

The immunogenicity of FLUZONE® High-Dose (trivalent formulation) is relevant to FLUZONE® High-Dose Quadrivalent since both vaccines are manufactured according to similar processes and have overlapping compositions.

In a multi-centre, double-blind controlled study (FIM05) conducted in the United States, adults 65 years of age and older were randomized to receive either FLUZONE® High-Dose or the standard-dose FLUZONE® vaccine (2006-2007 formulation). The objective was to demonstrate superiority of FLUZONE® High-Dose over a standard dose inactivated influenza vaccine containing 15 micrograms of each strains (2 A strains and 1 B strain), as assessed by seroconversion rates and GMTs.

A total of 3,851 participants were included in immunogenicity assessments; of these, 2,576 were randomized to FLUZONE® High-Dose and 1,275 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)[a]

Influenza Strain	GMT		GMT Ratio	Seroconversion% [b]		% Difference	Met Both Pre-defined Superiority Criteria[d]
	FLUZONE® High-Dose N[c] = 2542-2544 (95% CI)	FLUZONE® N[c] = 1252 (95% CI)	FLUZONE® High-Dose over FLUZONE® (95% CI)	FLUZONE® High-Dose N[c] = 2529-2531 (95% CI)	FLUZONE® N[c] = 1248-1249 (95% CI)	FLUZONE® High-Dose minus FLUZONE® (95% CI)	
A (H1N1)	115.8 (111.4; 120.3)	67.3 (63.7; 71.1)	1.7 (1.6; 1.8)	48.6 (46.6; 50.5)	23.1 (20.8; 25.6)	25.4 (22.4; 28.5)	Yes
A (H3N2)	608.9 (583.5; 635.3)	332.5 (310.4; 356.0)	1.8 (1.7; 2.0)	69.1 (67.3; 70.9)	50.7 (47.9; 53.5)	18.4 (15.1; 21.7)	Yes
B	69.1 (66.6; 71.6)	52.3 (49.5; 55.4)	1.3 (1.2; 1.4)	41.8 (39.8; 43.7)	29.9 (27.4; 32.6)	11.8 (8.6; 15.0)	No

[a] Immunogenicity analysis set: subjects who participated in immunogenicity assessments.
[b] 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
[c] N is the number of vaccinated participants with available data for the immunologic endpoint listed.
[d] Pre-defined 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%.

The adjustment for alpha was not needed for statistical multiple testing as the overall Type I error was no higher than 0.05 under the most conservative statistical assumptions to demonstrate at least 2 strains being superior for FLUZONE® High-Dose to FLUZONE® given that at most 1 strain was superior when one-sided alpha 0.025 for superiority was used.

According to the criteria set in the protocol, FLUZONE® High-Dose elicited a superior immune response compared to a standard dose trivalent inactivated influenza vaccine for both A-strains as measured by seroconversion rates and GMTs.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

FLUZONE® High-Dose Quadrivalent has been evaluated in rabbits in a repeat-dose toxicity study following three intramuscular injections at one human dose and in a local tolerance study following one subcutaneous injection at one human dose. FLUZONE® High-Dose Quadrivalent was shown to be safe and immunogenic, with an expected low local reactogenicity.

Carcinogenicity:

Carcinogenic and mutagenic potential were not assessed as these studies were not considered relevant to this vaccine.

Genotoxicity:

Genotoxicity potential was not assessed as genotoxicity studies were not considered relevant to this vaccine.

Reproductive and Developmental Toxicology:

Developmental and reproductive toxicity studies were not conducted since the intended target population is adults 65 years of age and older.

Special Toxicology:

Special toxicology was not assessed as these studies were not considered relevant to this vaccine.

Juvenile Toxicity:

Juvenile toxicity was not assessed since the intended target population is adults 65 years of age and older.

17 SUPPORTING PRODUCT MONOGRAPHS

FLUZONE® High-Dose, Influenza Virus Vaccine Trivalent Types A and B (Split Virion),
Suspension for Injection, Submission Control 238651, Product Monograph, Sanofi Pasteur.
APR 28, 2020

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

FLUZONE® High-Dose Quadrivalent

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

Read this carefully before you start taking **FLUZONE® High-Dose Quadrivalent** and each time you get a refill. 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 Quadrivalent**.

What is FLUZONE® High-Dose Quadrivalent used for?

FLUZONE® High-Dose Quadrivalent is a vaccine used to prevent influenza in adults 65 years of age and older to protect against four different types of influenza viruses (two A strains and two B strains) contained in the vaccine.

You cannot catch influenza from this vaccine as the virus has been killed and split into small particles that are not infectious.

The National Advisory Committee on Immunization (NACI) advises yearly influenza vaccination for all Canadians who are able to have the vaccine. For more information about influenza and the vaccine, see the NACI Statement on Seasonal Influenza Vaccines for this year.

(https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci.html)

How does FLUZONE® High-Dose Quadrivalent work?

FLUZONE® High-Dose Quadrivalent causes your body to produce its own protection against four different types of influenza virus (2 A strains and 2 B strains). After you get a flu shot, your immune system produces antibodies against the strains of virus that are in the vaccine. Your body takes up to 4 weeks after vaccination to produce antibodies. 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 Quadrivalent contains four times the amount of killed, split virus particles for each type compared to standard-dose influenza vaccines. The higher dose is intended to give people 65 years and older a better immune response and, therefore, better protection against the flu.

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

What are the ingredients in FLUZONE® High-Dose Quadrivalent?

This vaccine complies with the WHO (World Health Organization) recommendation (Northern hemisphere) for the 2021-2022 season.

Medicinal ingredients: Each 0.7 mL dose of FLUZONE® High-Dose Quadrivalent contains 60 mcg of killed split viruses from each of the four strains of influenza virus for the 2021-2022 season. The viruses in FLUZONE® High-Dose Quadrivalent are:

- A/Victoria/2570/2019 (H1N1)pdm09-like strain
- A/Cambodia/e0826360/2020 (H3N2)-like strain
- B/Washington/02/2019-like strain
- B/Phuket/3073/2013-like strain.

Non-medicinal ingredients: Formaldehyde (trace amounts), egg protein (trace amounts), sodium phosphate-buffered isotonic sodium chloride solution, and Triton® X-100.

Does not contain adjuvant, preservative, or antibiotics.

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

Individual doses in a prefilled syringe.

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

Do not use FLUZONE® High-Dose Quadrivalent if:

You have ever had a severe allergic reaction to:

- egg or egg products

- any component of FLUZONE® High-Dose Quadrivalent

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

- **Have any diseases of the immune system or 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.
- **Have a bleeding disorder or are 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.
- **Have an allergy to egg protein or any component of the vaccine.**
- **Have a fever or serious illness.** Wait until you are better before receiving 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.
- **Have a history of Guillain-Barré syndrome (GBS) within 6 weeks after 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 Quadrivalent will help protect against the strains of flu virus contained in the vaccine or those that are closely related. FLUZONE® High-Dose Quadrivalent will not necessarily protect against any other strains of flu virus.

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

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

How to take FLUZONE® High-Dose Quadrivalent:

Usual dose:

For persons 65 years or older - recommended dose is 0.7 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 Quadrivalent, 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 Quadrivalent?

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

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. There may be others such as headache and malaise (feeling unwell), injection site redness and swelling, and shivering.

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
RARE		
Anaphylaxis difficulty breathing, dizziness, a weak and rapid pulse, skin rash		X
Allergic reaction Rash, itching or hives on the skin, swelling of the face, lips, tongue, or other parts of the body		X

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 Pasteur Limited 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 the vaccine if it has been exposed to freezing.

Do not use vaccine after expiration date shown on the label.

Keep out of reach and sight of children.

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

- 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 Sanofi Canada website (www.sanofi.ca) or by contacting the vaccine producer, Sanofi Pasteur Limited at 1- 888-621-1146.

This leaflet was prepared by Sanofi Pasteur Limited.

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