PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

FLUMIST®

Influenza Vaccine (live, attenuated)

Nasal spray, suspension

Each 0.2 mL dose contains $10^{6.5-7.5}$ fluorescent focus units of Influenza Virus Type A (H1N1), Type A (H3N2) and Type B (Victoria) strains

Nasal Use

Active Immunizing Agent

ATC Code: J07BB03

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RECENT MAJOR LABEL CHANGES
Not Applicable.

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

FLUMIST [influenza vaccine (live, attenuated)] is indicated for the active immunization of individuals 2-59 years of age against influenza caused by virus subtypes A, and type B contained in the vaccine.

1.1 Pediatrics

Pediatrics (2 – 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of FLUMIST in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (see 8.2.1 Clinical Trial Adverse Reactions – Pediatrics and 14 CLINICAL TRIALS).

1.2 Geriatrics

Geriatrics (> 59 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

FLUMIST [influenza vaccine (live, attenuated)] is contraindicated in individuals with:

- a history of hypersensitivity, especially anaphylactic reactions, to gentamicin, gelatin, or arginine or to any other non-medicinal ingredient in the formulation, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- severe allergic reaction (e.g., anaphylaxis) to eggs or to egg proteins (e.g., ovalbumin).
- a history of hypersensitivity to previous influenza vaccination.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

FLUMIST [influenza vaccine (live, attenuated)] is a spray for intranasal administration by a health care professional. The recommended dose for previously vaccinated and unvaccinated children and adults is:

Age Group	Vaccination Status	Dosage Schedule
Children (2-8 years)	Not previously vaccinated with seasonal influenza vaccine	2 doses (0.2 mL[a] each, at least 4 weeks apart)
	Previously vaccinated with seasonal influenza vaccine	1 dose (0.2 mL[a])
Children, adolescents and adults 9-59 years	Not applicable	1 dose (0.2 mL[a])

[a]Administer as 0.1 mL per nostril

For children 2-8 years of age not previously vaccinated with seasonal influenza vaccine, 2 doses of FLUMIST, 4 weeks apart, is recommended.

Annual revaccination with influenza vaccine is recommended because immunity declines over time, and because circulating strains of influenza virus can change from year to year.

4.4 Administration

Do not use FLUMIST if damaged, for example if the plunger is loose or displaced from the sprayer or if there are any signs of leakage.

Each sprayer (shown in Figure 1) contains a single dose of FLUMIST; approximately one-half of the contents should be administered into each nostril. Refer to the administration diagram (Figure 2) for step-by-step administration instructions. Once FLUMIST has been administered, the sprayer should be disposed of according to the standard procedures for medical waste (e.g., sharps container or biohazard container).

Figure 1

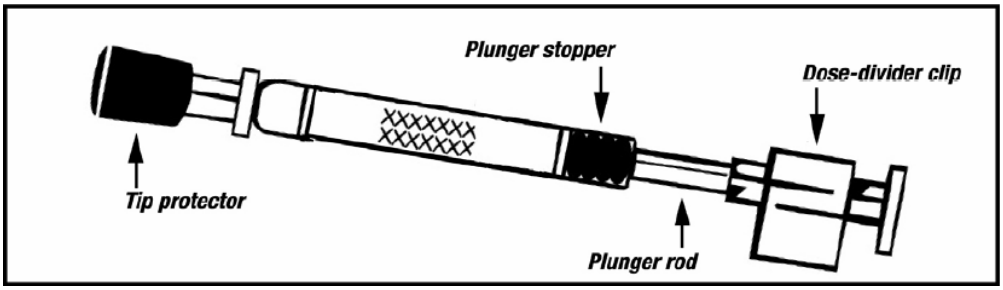
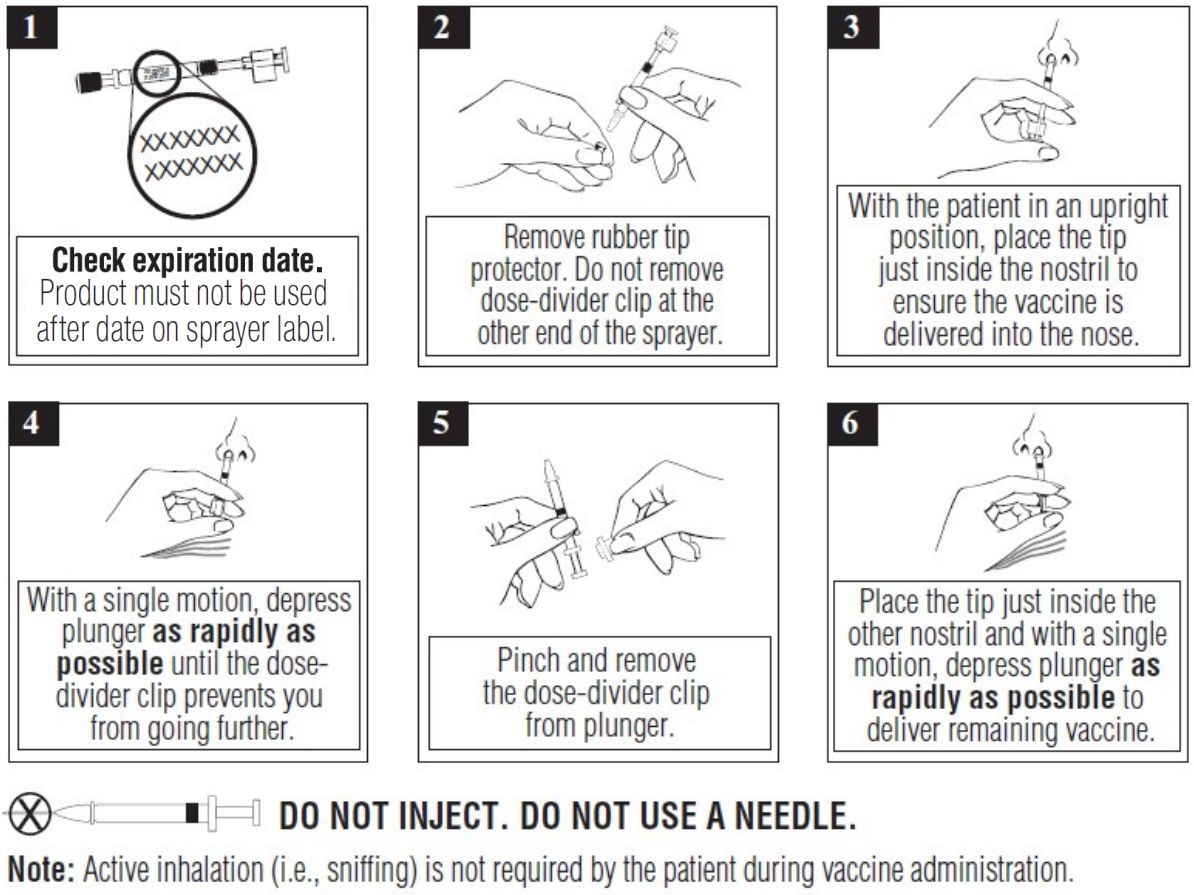


Figure 2



5 OVERDOSAGE

No data are available relevant to overdose with FLUMIST [influenza vaccine (live, attenuated)] vaccine.

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 and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Nasal Use	Nasal spray, suspension, 0.2 mL, each 0.2 mL contains $10^{6.5-7.5}$ FFU (fluorescent focus units) of live attenuated influenza virus reassortants of each of the three strains listed below	arginine hydrochloride, dibasic potassium phosphate, gelatin hydrolysate (porcine Type A), gentamicin (a trace residual), monobasic potassium phosphate, monosodium glutamate, ovalbumin (a trace residual), sucrose

FLUMIST is supplied as a 0.2 mL pre-filled, single-use glass sprayer (see Figure 1) and is available as a package of 10 sprayers and a package of 1 sprayer.

Each 0.2 mL dose contains $10^{6.5-7.5}$ FFU of live attenuated influenza virus reassortants of each of the three strains for the specific season. The three strains used for the 20XX-20XX season are: A/XXX/XXX/XXX (H1N1) (A/XXX/XXX/XXX (H1N1) pdm09-like virus), A/XXX/XXX/XXX (H3N2) (A/XXX/XXX/XXX (H3N2)-like virus) and B/XXX/XXX/XXX (Victoria lineage).

FLUMIST [influenza vaccine (live, attenuated)] contains no preservatives (e.g., no thimerosal). The intranasal sprayer contains no latex.

7 WARNINGS AND PRECAUTIONS

General

Prior to administration of any dose of FLUMIST, the vaccine recipient should be asked about personal medical history, family medical history, recent and current health status, including immunization history, main allergies and any adverse events associated with previous immunizations (see 2 CONTRAINDICATIONS).

As with most vaccines, supervision and treatment by an appropriately trained healthcare professional should always be readily available in case of an anaphylactic event following the administration of the vaccine.

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

As with other vaccines, vaccination with FLUMIST should be postponed in case of acute severe febrile illness until symptoms have abated. However, the presence of mild non-serious febrile illness (such as mild upper respiratory tract infections) should not result in the deferral of vaccination.

Immune

As with any vaccine, immunization with FLUMIST may not protect 100% of susceptible individuals.

Administration of FLUMIST, a live attenuated virus vaccine, to immunosuppressed persons should be based on careful consideration of potential benefits and risks. Data supporting the safety and efficacy of FLUMIST in immunocompromised individuals are limited. FLUMIST has been administered to approximately 170 children and adults with mild to moderate immunosuppression due to HIV infections and 10 children with mild to moderate immunosuppression due to cancer (see 14 CLINICAL TRIALS).

Vaccine recipients should be informed that FLUMIST is an attenuated live virus vaccine and has the potential for transmission to immunocompromised contacts. Vaccine recipients should attempt to avoid, whenever possible, close association with severely immunocompromised individuals (e.g., bone marrow transplant recipients requiring isolation) for at least 2 weeks following vaccination. Peak incidence of vaccine virus recovery occurred 2-3 days post-vaccination in clinical studies. In circumstances where contact with severely immunocompromised individuals is unavoidable, the potential risk of transmission of the influenza vaccine virus should be weighed against the risk of acquiring and transmitting wild-type influenza virus.

Those under the age of 18 years receiving aspirin therapy or aspirin-containing therapy should avoid vaccination with FLUMIST due to the association of Reye's syndrome with aspirin and wild-type influenza infection.

Neurologic

If Guillain-Barré syndrome has occurred within 6 weeks of any prior influenza vaccination, the decision to give FLUMIST should be based on careful consideration of the potential benefits and potential risks (see 8 ADVERSE REACTIONS).

Respiratory

FLUMIST should not be administered to individuals with severe asthma (e.g. currently requiring therapy with oral glucocorticosteroids or high dose inhaled glucocorticosteroids) or active wheezing (medically attended wheezing in the seven days prior to vaccination) because these individuals have not been adequately studied in clinical trials.

7.1 Special Populations

7.1.1 Pregnant Women

Studies in pregnant women have not been conducted with FLUMIST.

In the AstraZeneca Safety Pharmacovigilance Database, there were 329 case reports of live attenuated influenza vaccine (LAIV) administration to pregnant women. Pregnancy outcome was provided in 167 cases: 111/167 (66.1%) cases had healthy babies or live births; 26/167 (15.5%) cases with elective abortions; 23/167 (13.7%) cases with spontaneous abortions; and 7/167 (4.2%) cases with a non-healthy baby. A search of the US Vaccine Adverse Event Reporting System (VAERS) identified 27 case reports of LAIV administration to pregnant

women. There were 3/27 (11%) cases with spontaneous abortions. The occurrence of spontaneous abortions reported is consistent with rates in the general population: approximately 10% to 20% of pregnancies result in clinically recognized spontaneous abortion.

The effects of FLUMIST on embryo-fetal and pre-weaning development were evaluated in developmental toxicity studies of pregnant rats and pregnant ferrets. No adverse effects on pregnancy, parturition, lactation or embryo-fetal development were observed in any of the studies and, in addition no adverse effects on pre-weaning development were observed in the rat studies. There were no fetal malformations or other evidence of teratogenesis observed (see 16 NON-CLINICAL TOXICOLOGY).

FLUMIST should be given to pregnant women only if clearly needed.

7.1.2 Breast-feeding

Studies in lactating women have not been conducted with FLUMIST.

There are very limited data from the use of FLUMIST in lactating women. Therefore, as some viruses are excreted in human milk caution should be exercised if FLUMIST is administered to nursing mothers.

No adverse effects on lactation were observed in developmental toxicity studies of pregnant rats and pregnant ferrets (see 7.1.1 Pregnant Women).

7.1.3 Pediatrics

Pediatrics (< 2 years of age): Do not administer FLUMIST to children <24 months of age due to increased risk of wheezing (see 8 ADVERSE REACTIONS).

7.1.4 Geriatrics

Geriatrics (> 59 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of FLUMIST was evaluated in studies that enrolled 28,500 children and adolescents 2 to 17 years of age and over 4,350 adults 18-59 years of age. The most common adverse reaction observed in FLUMIST clinical studies in all ages was nasal congestion/rhinorrhea.

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.

Twelve placebo controlled studies and three active controlled studies were pooled to evaluate solicited events in adults 18-59 years of age. Table 2 presents an analysis of solicited events

occurring in at least 1% of FLUMIST recipients and includes rates for these solicited events from active controlled studies. A total of 3,301 adults 18-59 years of age received FLUMIST dosing and provided data for the pooled safety analysis in controlled studies. In these studies, solicited events were documented for 6 days post vaccination.

Table 2 Summary of Solicited Events Observed During Days 0 to 6 Post Dose in FLUMIST and either Placebo or Active Control Recipients; Adults 18-59 years of age

Solicited Event	Placebo Controlled Studies[a]		Active Controlled Studies[b]	
	FluMist N = 64 - 3,265[c] (%)	Placebo N = 65 - 1,711[c] (%)	FluMist N = 10 - 80[c] (%)	Injectable Influenza Vaccine N = 11 - 77[c] (%)
Any solicited event	69.1	58.9	62.5	58.4
Runny/stuffy nose	43.6	26.2	40.0	33.8
Headache	37.5	34.5	25.0	36.4
Sore throat	24.7	15.2	15.0	11.7
Malaise [d]	23.8	19.3	11.4	20.5
Muscle ache	15.4	13.7	16.3	18.2
Cough	13.1	10.2	18.8	14.3
Chills	7.7	5.6	6.3	6.5
Decreased appetite	5.8	8.9	2.3	9.1
Abdominal pain/stomach ache	4.7	6.2	0.0	9.1
Vomiting	3.5	3.8	2.3	2.3
Fever				
≥ 38.0°C	0.9	1.2	2.5	0.0
≥ 38.5°C	0.2	0.4	1.3	0.0
≥ 39.0°C	0.1	0.0	1.3	0.0

[a] Includes Studies AV001, AV003, AV004, AV005, AV009, D145-P501, D153-P001, D153-P003, D153-P004, D153-P507, D153-P510 and DMID 98-005.
[b] Includes Studies AV003, D153-P003, and D153-P004.
[c] Number of subjects evaluated for the specific solicited event. Range reflects differences in data collection between pooled studies.
[d] Collected as decreased activity/tiredness/weakness/malaise.

Serious Adverse Events: In the pooled safety analysis for subjects 18 to 59 years of age, 0.18% (8/4,376) of subjects exposed to FLUMIST reported at least 1 SAE during Days 0 to 28 post dose. Two gastroenteritis events were reported; all other events occurred in 1 subject each. In placebo controlled studies, 0.18% (6/3,315) of subjects who received FLUMIST and

0.29% (5/1,740) of subjects who received placebo reported at least 1 SAE during Days 0 to 28 post dose.

Death: Among the over 4,350 adults 18-59 years of age who received FLUMIST in clinical studies, there were 2 deaths reported within 180 days of FLUMIST dosing: one due to homicide and one due to drowning. In addition, 4 subjects died within 180 days of receipt of concurrent FLUMIST and injectable influenza vaccine in a study that enrolled subjects with stable chronic obstructive pulmonary disease (COPD): two due to COPD; one due to a gastrointestinal hemorrhage; and one due to an acute myocardial infarction.

None of the deaths described in adults were considered by the medical monitor or investigator to be related to FLUMIST.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Seven placebo controlled studies and four active controlled studies were pooled to evaluate solicited events occurring in children and adolescents 2-17 years of age. Table 3 presents an analysis of solicited events post dose 1 occurring in at least 1% of FLUMIST recipients and includes rates for these solicited events from active controlled studies. A total of 7,336 children and adolescents 2 to 17 years of age received at least 1 dose of FLUMIST in Year 1 of dosing in controlled studies and provided data for the pooled safety analysis.

Solicited events were those about which parents/guardians were specifically queried after vaccination with FLUMIST. In these studies, solicited events were documented within 10 days post vaccination. Solicited events post dose 2 for FLUMIST were similar to those post dose 1, and were generally observed at a lower frequency.

Table 3 Summary of Solicited Events Observed During Days 0 to 10 after Dose 1 for FLUMIST and either Placebo or Active Control Recipients; Children and Adolescents 2-17 Years of Age

Solicited Event	Placebo Controlled Studies [a]		Active Controlled Studies [b]	
	FluMist N = 258 - 3,245[c] (%)	Placebo N = 191 to 1,994[c] (%)	FluMist N = 3,931 to 4,108[c] (%)	Injectable Influenza Vaccine N = 3,982 to 4,118[c] (%)
Any solicited event	74.2	69.5	70.4	64.8
Runny/stuffy nose	63.7	56.9	56.7	45.0
Cough	39.9	41.6	33.6	35.6
Decreased appetite	24.1	21.7	15.9	15.2
Irritability	21.2	19.7	13.8	12.5

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Solicited Event	Placebo Controlled Studies [a]		Active Controlled Studies [b]	
	FluMist N = 258 - 3,245[c] (%)	Placebo N = 191 to 1,994[c] (%)	FluMist N = 3,931 to 4,108[c] (%)	Injectable Influenza Vaccine N = 3,982 to 4,118[c] (%)
Abdominal pain	14.1	12.3	12.3	11.5
Decreased activity [d]	13.8	11.7	13.1	11.8
Headache	13.4	6.5	13.8	12.3
Vomiting	12.3	13.7	6.8	6.9
Sore throat	10.1	8.2	11.6	11.2
Muscle ache	8.1	5.2	5.7	6.9
Chills	6.2	7.8	5.8	5.1
Fever				
≥ 38.0°C	11.2	9.7	9.3	8.6
≥ 38.5°C	6.0	5.6	5.1	5.1
≥ 39.0°C	2.5	2.5	2.3	2.4
≥ 39.5°C	1.1	1.0	0.8	0.9

[a] Includes Studies D153-P002, D153-P501 Year 1, D153-P502 Year 1, D153-P504 Year 1, D153-P511, D153-P513, and D153-P526. Follow-up time for Study D153-P526 was Days 0-6 post dose.
[b] Includes Studies MI-CP111, D153-P002, D153-P514, and D153-P515
[c] Number of subjects evaluated for the specific solicited event. Range reflects differences in data collection between pooled studies.
[d] Collected as decreased activity/tiredness/weakness/malaise.

In MI-CP111, an active-controlled study, an increased rate of wheezing through 42 days was observed in children 6-23 months of age (5.9% (117/1992) FLUMIST versus 3.8% (75/1975) injectable influenza vaccine) (see 7 WARNINGS AND PRECAUTIONS). The rate of wheezing was not increased in FLUMIST recipients 24 months and older (2.1% FLUMIST versus 2.5% injectable influenza vaccine).

In the same study, an increased rate of hospitalizations (for any cause) through 180 days after final vaccination dose was observed in children 6-11 months of age (6.1% (42/684) FLUMIST versus 2.6% (18/683) injectable influenza vaccine). The rate of hospitalizations was not increased in FLUMIST recipients 12 months and older (2.5% FLUMIST versus 2.9% injectable influenza vaccine).

Serious Adverse Events: In the pooled safety analysis for subjects 2 to 17 years of age, 0.45% (129/28,873) of subjects exposed to FLUMIST reported at least 1 serious adverse event (SAE) during Days 0 to 42 post dose in the first year of dosing. The majority of these were either infectious (0.23%) or respiratory (0.05%) events, including gastroenteritis, pneumonia, otitis media, and asthma. Of the 2.22% (182/8,202) subjects who reported at least 1 SAE during Days 0 to 180 post dose in the first year of dosing, the majority reported infectious (1.52%), respiratory (0.28%) or gastrointestinal (0.23%) events, including pneumonia, gastroenteritis, asthma, and otitis media. During Days 0 to 42 post dosing, in studies with an active control, 0.75% (32/4,245) of subjects who received FLUMIST and 1.01% (43/4,278) subjects who received injectable influenza vaccine reported at least 1 SAE, and in placebo controlled studies, 0.49% (52/10,693) of subjects who received FLUMIST and 0.55% (31/5,677) of subjects who received placebo reported at least 1 SAE. During Days 0 to 180 post dosing, in studies with an active control, 2.28% (94/4,130) of subjects who received FLUMIST and 2.45% (102/4,163) of subjects who received injectable influenza vaccine reported at least 1 SAE, and in placebo controlled studies, 2.91% (70/2,408) of subjects who received FLUMIST and 2.72% (42/1,546) subjects who received placebo reported at least 1 SAE.

Death: Among the over 40,000 children and adolescents less than 18 years of age who received FLUMIST in clinical studies, there were eight deaths reported within 180 days of FLUMIST dosing. Of the 8 deaths, 4 occurred within 42 days after the last dose of FLUMIST due to escherichial septicaemia and protein-calorie malnutrition, bronchopneumonia, accidental drowning, and accident at home and 4 occurred between 43 and 180 days after FLUMIST dosing due to diarrhea and sepsis, encephalopathy, suffocation, and posterior fossa tumor and malignant hyperthermia.

None of the deaths described in children and adolescents were considered by the medical monitor or investigator to be related to FLUMIST.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of FLUMIST. Because these reactions 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.

Congenital, familial and genetic:	Exacerbation of symptoms of mitochondrial encephalomyopathy (Leigh syndrome)
Immune system:	Hypersensitivity reactions (including anaphylactic reaction, facial edema and urticaria)
Nervous system:	Guillain-Barré syndrome, Bell's Palsy
Respiratory, thoracic and mediastinal:	Epistaxis
Skin and subcutaneous tissue:	Rash

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Table 4 describes the established or potential Drug-Drug interaction studies with FLUMIST.

Table 4 Established or Potential Drug-Drug Interactions

FLUMIST	Effect	Clinical comment
Antiviral agents that are active against influenza A and/or B viruses	Not evaluated	Based upon the potential for influenza antiviral agents to reduce the effectiveness of FLUMIST, it is recommended not to administer FLUMIST until 48 hours after the cessation of influenza antiviral therapy. It is recommended not to administer influenza antiviral agents until two weeks after administration of FLUMIST unless medically indicated. If influenza antiviral agents and FLUMIST are administered concomitantly, revaccination should be considered when appropriate.
Aspirin therapy and aspirin-containing therapy	Association of Reye's syndrome with aspirin and wild-type influenza infection.	Those under the age of 18 years receiving aspirin therapy or aspirin-containing therapy should avoid vaccination with FLUMIST. Do not use aspirin-containing therapy in children younger than 18 years of age for 4 weeks after vaccination with FLUMIST unless medically indicated.
Concomitant vaccines	No interaction: measles, mumps, rubella, varicella vaccines	Concurrent administration of FLUMIST has been studied with: • measles, mumps and rubella vaccine (819 children 11 to 23 months of age) • measles, mumps and rubella vaccine and the varicella vaccine (430 children 12 to 15 months of age) Adverse events were similar to those seen in other clinical studies with FLUMIST. No evidence of interference with immune responses to measles, mumps, rubella, varicella, or FLUMIST was observed.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Immune mechanisms conferring protection against influenza following receipt of FLUMIST [influenza vaccine (live, attenuated)] are not fully understood. Likewise, naturally acquired immunity to wild-type influenza has not been completely elucidated. Serum antibodies, mucosal antibodies and influenza-specific T cells may play a role in prevention and recovery from infection.

Influenza illness and its complications follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. Antibody against one influenza virus type or subtype confers limited or no protection against another. Furthermore, antibody 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 virologic basis for seasonal epidemics and the reason for the usual change of one or more new strains in each year's influenza vaccine. Therefore, influenza vaccines are standardized to the WHO recommendation (northern hemisphere) to contain the strains (i.e., typically two subtype A and a type B lineage) representing the influenza viruses likely to be circulating in North America in the upcoming winter.

10.2 Pharmacodynamics

FLUMIST is designed to induce a broad immune response that resembles the response generated by wild-type influenza infection without causing influenza illness. Immune mechanisms triggered include influenza-specific serum antibodies, mucosal antibodies and cell-mediated immunity, which may contribute to protection conferred by FLUMIST. Responses to FLUMIST vary depending on age of the individual and prior experience with influenza. Additionally, young, unprimed, seronegative children show more robust antibody responses compared to older children and adults. For further information see 14 CLINICAL TRIALS.

Safety Pharmacology

A safety pharmacology study was performed using a murine model to demonstrate a lack of neurovirulence of FLUMIST vaccine strains. A murine-adapted neurotropic virus strain, A/NWS-33, was used to establish the system to study viral transmission to the central nervous system and replication. Eighteen monovalent live attenuated FLUMIST vaccine strains and one trivalent FLUMIST vaccine were used to evaluate the neurovirulent potential of these vaccine strains. Mice were inoculated with 3 $\log_{10}$ $TCID_{50}$ of the neurotropic virus control intranasally; brain tissue harvested 7 days later had evidence of influenza viral RNA ranging from 7.68×10^2 to 1.05×10^5 copies/mg of viral RNA. In contrast, when mice were inoculated with 5 $\log_{10}$ $TCID_{50}$ of any of the type A or type B vaccine strains viral RNA was not detected. Similarly, no viral RNA was detected in the mouse brain tissue following intranasal administration of trivalent FLUMIST consisting of A/New Caledonia/20/99 (H1N1), A/Wisconsin/67/05 (H3N2) and B/Malaysia/2506/04.

FLUMIST vaccine viruses, either in monovalent or trivalent formulation, did not exhibit any neurotropism or neurovirulence in mice.

11 STORAGE, STABILITY AND DISPOSAL

Store in a refrigerator (2°C – 8°C) upon receipt and until use. DO NOT FREEZE.

A single temperature excursion up to 25°C for 12 hours has been shown to have no adverse impact on the vaccine. After a temperature excursion, the vaccine should be returned immediately to the recommended storage condition (2°C – 8°C) and used as soon as feasible. Subsequent excursions are not permitted.

Keep the nasal sprayer in the outer carton in order to protect from light.

Use the product before the expiration date on the sprayer label.

12 SPECIAL HANDLING INSTRUCTIONS

Any unused vaccine or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Influenza vaccine (live, attenuated).

Physicochemical properties: The influenza virus strains in FLUMIST are:

(a) cold-adapted (ca) (i.e., they replicate efficiently at 25°C, a temperature that is restrictive for replication of many wild-type influenza viruses);
(b) temperature-sensitive (ts) (i.e., they are restricted in replication at 37°C (Type B strain) or 39°C (Type A strains), temperatures at which many wild-type influenza viruses grow efficiently);
(c) attenuated (att) (they do not produce classic influenza-like illness in the ferret model of human influenza infection). The cumulative effect of the antigenic properties and the ca, ts, and att phenotypes is that the attenuated vaccine viruses replicate in the nasopharynx and induce protective immunity.

Product Characteristics: The spray is a colourless to pale yellow, clear to opalescent liquid; small white particles may be present.

FLUMIST [influenza vaccine (live, attenuated)] is a live, trivalent vaccine for administration by intranasal spray. FLUMIST contains three vaccine virus strains: an A/H1N1 strain, an A/H3N2 strain and a B strain. FLUMIST contains a B strain from the B/Victoria lineage. Each pre-filled FLUMIST sprayer contains a single 0.2 mL dose that contains $10^{6.5\text{-}7.5}$ FFU (fluorescent focus units) of live attenuated influenza virus reassortants of each of three strains propagated in specific pathogen-free (SPF) eggs from SPF chicken flocks. The three strains used for the 20XX-20XX season are: A/XXX/XXX/XXX (H1N1) (A/XXX/XXX/XXX (H1N1)pdm09-like virus), A/ XXX/XXX/XXX (H3N2) (A/XXX/XXX/XXX (H3N2)-like virus) and B/XXX/XXX/XXX (Victoria lineage). This influenza vaccine complies with the WHO recommendation (northern hemisphere) for the 20XX-20XX influenza season.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Active Immunization Against Influenza

FLUMIST Clinical Studies

FLUMIST has been administered to over 30,000 subjects in controlled clinical studies over multiple years, in various regions and using different vaccine strains. Many clinical studies in the development of FLUMIST evaluated the efficacy endpoint of incidence of culture-confirmed influenza-like illness relative to placebo or injectable influenza vaccine.

Pediatric studies: The efficacy of FLUMIST has been demonstrated in 9 pediatric controlled studies comprising over 20,000 children, conducted during 7 influenza seasons. Four placebo-controlled studies included second season revaccination. FLUMIST demonstrated superiority in 3 active-controlled studies with injectable influenza vaccine. See Table 5 and Table 6 for a summary of FLUMIST efficacy results in children.

Table 5 FLUMIST Efficacy in Placebo-Controlled Pediatric Studies

Study Number	Age range	Number of subjects[a]	Influenza season	Efficacy (95% CI)[b] Matched strains	Efficacy (95% CI)[b] All strains regardless of match
D153-P502	6 to 35 months	1,616	2000-2001	85.4% (74.3 92.2)	85.9% (76.3, 92.0)
			2001-2002	88.7% (82.0, 93.2)	85.8% (78.6, 90.9)
D153-P504	6 to 35 months	1,886	2001	73.5% (63.6, 81.0)[c]	72.0% (61.9, 79.8)[c]
			2002	73.6% (33.3, 91.2)[d]	46.6% (14.9, 67.2)[d]
D153-P513	6 to 35 months	1,041	2002	62.2% (43.6, 75.2)	48.6% (28.8, 63.3)
D153-P522	11 to 24 months	1,150	2002-2003	78.4% (50.9, 91.3)	63.8% (36.2, 79.8)
D153-P501	12 to 35 months	2,764	2000-2001	72.9% (62.8, 80.5)	70.1% (60.9, 77.3)
			2001-2002	84.3% (70.1, 92.4)[d]	64.2% (44.2, 77.3)[d]
AV006	15 to 71 months	1,259	1996-1997	93.4% (87.5, 96.5)[c]	93.4% (87.5, 96.5)[c]
			1997-1998	100% (63.1, 100)	87.1% (77.7, 92.6)[e]

[a] Number of study participants for year 1 efficacy analysis.

[b] Reduction in culture-confirmed influenza-like illness relative to placebo.

[c] Data presented for clinical trials AV006 and D153-P504 are for subjects who received two doses of study vaccine. In previously unvaccinated children who received one dose in year 1, efficacy was 88.8% (95% CI: 64.5, 96.5) and 88.8% (95% CI: 64.5, 96.5), respectively in AV006, and 57.7% (95% CI: 44.7, 67.9) and 56.3% (95% CI: 43.1, 66.7), respectively in D153-P504, thus supporting the need for two doses of vaccine in previously unvaccinated children.

[d] In children who received 2 doses in year 1 and placebo in year 2, efficacy in year 2 was 57.0% (95% CI: 6.1, 81.7) and 35.3% (95% CI: -0.3, 58.7), respectively, in D153-P504 and 56.2% (95% CI: 30.5, 72.7) and 44.8% (95% CI: 18.2, 62.9), respectively, in D153-P501, thus supporting the need for second-season revaccination.

[e] The primary circulating strain was antigenically dissimilar from the H3N2 strain represented in the vaccine; efficacy against the mismatched A/H3N2 strain was 85.9% (95% CI: 75.3, 91.9).

As presented in Table 5, FLUMIST consistently demonstrated high rates of efficacy against culture-confirmed influenza illness due to matched strains and against influenza illness due to all strains regardless of antigenic match compared to placebo. During the first seasonal outbreak following FLUMIST vaccination, absolute efficacy against matched strains ranged from 62% to 93%. In analyses for all strains regardless of antigenic match, FLUMIST absolute efficacy during the first season ranged from 49% to 93%. In clinical studies AV006 and D153-P504, 1 dose of FLUMIST in previously unvaccinated children demonstrated statistically significant efficacy; however, the efficacy of two doses was higher than the efficacy of 1 dose, thus supporting the need for two doses of vaccine in previously unvaccinated children. In the 4 studies that examined the efficacy of second-season revaccination, FLUMIST efficacy ranged from 74% to 100% for matched strains, and from 47% to 87% for all strains regardless of antigenic match. Efficacy against matched strains after second-season revaccination was either the same as, or higher than, efficacy after the primary (first season) vaccination, confirming the benefit of second-season FLUMIST revaccination. In two separate studies (D154-P501 and D154-P504), 2 doses of FLUMIST in Year 1 was associated with efficacy that

persisted into the subsequent season however, annual revaccination with FLUMIST is recommended because protection is lower in the second year following vaccination, and because circulating strains of influenza virus can change from year to year.

Table 6 FLUMIST Relative Efficacy in Active-Controlled (Injectable Influenza Vaccine) Pediatric Studies

Study Number	Age range[a]	Number of subjects[b]	Influenza season	Vaccine Efficacy (95% CI)[c] Matched strains	Vaccine Efficacy (95% CI)[c] All strains regardless of match
MI-CP111	6 to 59 months	7,852	2004-2005	44.5% (22.4, 60.6)	54.9% (45.4, 62.9)[d]
D153-P514	6 to 71 months	2,085	2002-2003	52.7% (21.6, 72.2)	52.4% (24.6, 70.5)[e]
D153-P515	6-17 years	2,211	2002-2003	34.7% (3.9, 56.0)	31.9% (1.1, 53.5)

[a] Age range as described in the protocol for the study.
[b] Number of study participants in the per-protocol population.
[c] Reduction in culture-confirmed influenza-like illness relative to injectable influenza vaccine.
[d] Vaccine efficacy was 55.7% (95% CI: 39.9, 67.6) in 3,686 children 6-23 months of age and 54.4% (95% CI: 41.8, 64.5) in 4,166 children 24-59 months of age.
[e] Vaccine efficacy was 64.4% (95% CI: 1.4, 88.8) in 476 children 6-23 months of age and 48.2% (95% CI: 12.7, 70.0) in 1,609 children 24-71 months of age.

In three active comparator studies involving >12,000 children, FLUMIST consistently demonstrated statistically significant superior efficacy relative to injectable, trivalent inactivated influenza vaccine against culture confirmed influenza illness caused by wild-type virus strains antigenically matched to those in the vaccine, as well as against illness caused by all strains regardless of antigenic match.

Compared to injectable, trivalent inactivated influenza vaccine, FLUMIST reduced the number of cases of culture-confirmed influenza illness by 35% to 53% for illness due to matched strains and by 32% to 55% for illness due to all strains regardless of antigenic match (see Table 6).

Adult studies: Data supporting the efficacy of FLUMIST in adults comes from 3 controlled clinical studies, including a wild-type influenza challenge study.

Table 7 FLUMIST Efficacy in Controlled Adult Studies

Study Number	Study Design	Age range/ Number of subjects (n)	Influenza season	Efficacy
AV003	Influenza challenge study. Double-blind, placebo- and active-controlled. Challenged 29 days after FLUMIST or control with wild-type influenza (A/H1N1, A/H3N2 or B).	18-40 Y n=103	N/A	FLUMIST: 85% efficacy (95% CI: 28, 100) Injectable influenza vaccine: 71% efficacy (95% CI: 2, 97) Efficacy was measured by wild-type virus shedding or serologic response.
AV009	Double-blind, placebo-controlled study.	18-65 Y N=4,561	1997-1998	During influenza outbreak periods, the mismatched A/Sydney (H3N2) strain predominantly circulated. FLUMIST: 9.7% reduction (p=0.19) in the incidence of the primary endpoint, any febrile illness (incidence=13.2% FLUMIST, 14.6% placebo). FLUMIST demonstrated statistically significant reductions in the occurrence of other febrile illness endpoints by 17.4%-21.9% compared to placebo. Culture confirmation of influenza infection was not performed in this study.
D153-P507	Double-blind, placebo-controlled study	≥60 Y n=3,242	2001	FLUMIST reduced the attack rate for culture-confirmed matched influenza strains by 42.3% (95% CI: 21.6, 57.8) (attack rates: 4.3% FLUMIST, 7.5% placebo). The efficacy of FLUMIST was 41.6% (95% CI: 20.9, 57.1) against all strains regardless of match.

A published study was conducted on University campuses in Michigan, USA to analyze the safety and efficacy of FLUMIST and an injectable, trivalent inactivated influenza vaccine in adults 18 to 49 years of age. The three-year study was randomized, placebo controlled, and double-blind for vaccine versus placebo but open-label for nasal spray versus injection. In Years 1 and 2, the efficacy of FLUMIST and the injectable influenza vaccine were not statistically different. In Year 3 (2007-2008), 1,952 subjects were randomized and there was a 45% (95% CI: 3, 69) reduction in culture-confirmed cases of influenza among recipients of the injectable influenza vaccine as compared with recipients of FLUMIST.

Studies in HIV-Infected individuals: Safety and shedding of vaccine virus following FLUMIST administration were evaluated in 28 HIV-infected [median CD4 cell count of 604 cells/mm^3] and 27 HIV-negative adults 18-58 years of age in a randomized, double-blind, placebo controlled trial. In this study, there were no serious adverse events attributable to FLUMIST, and vaccine virus shedding in HIV-infected individuals was comparable to that seen in healthy populations. No adverse effects on HIV viral load or CD4 counts were identified following FLUMIST. The effectiveness of FLUMIST in preventing influenza illness in HIV-infected individuals has not been evaluated. A published study with 122 HIV-infected children 5-17 years of age receiving FLUMIST as well as stable antiretroviral therapy showed similar findings.

14.3 Immunogenicity

The immunogenicity of FLUMIST is described in 14.1 Clinical Trials by Indication.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Repeat-dose toxicity: In a single/repeat-dose toxicity study, no significant toxicity was observed in ferrets receiving intranasal inoculation of $10^{6.5-7.5}$ FFU per strain FLUMIST, at weeks 0, 4, 14, and followed for 15 weeks total. No test-material related toxicity was observed except for increased incidence of inflammation of nasal turbinates and lymph node hyperplasia observed in the repeat dose toxicity study with FLUMIST at interim necropsy in both vaccine and saline placebo groups (likely due to intranasal inoculation three days prior to necropsy). This inflammatory response was transient; these observations were not noted during terminal necropsy.

Carcinogenicity

FLUMIST has not been evaluated for carcinogenic or mutagenic potential or potential to impair fertility.

Reproductive and Developmental Toxicology

In developmental toxicity studies with FLUMIST (rats and ferrets), the effect of the vaccine on embryo-fetal and pre-weaning development was evaluated in pregnant rats receiving FLUMIST. Groups of animals were administered the vaccine either once (during the period of organogenesis on gestation day 6) or twice (prior to gestation and during the period of

organogenesis on gestation day 6), 250mcL/rat/occasion (approximately 110-140 human dose equivalents based on TCID50), by intranasal instillation. No adverse effects on pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed. Ferrets were administered a single dose (200 mcL/ferret) of FLUMIST, either prior to implantation or during organogenesis. There were no vaccine related fetal malformations or other evidence of teratogenesis noted in either study.

Special Toxicology

Ocular Toxicity: Two ocular toxicity studies evaluated the effects of the inadvertent instillation of FLUMIST into the eyes in rabbits (Draize tests: 0.1 mL vaccine applied to eye and conjunctival sac). Both ocular toxicity studies showed that FLUMIST was well tolerated when administrated intraocular in rabbits.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

FLUMIST®
influenza vaccine (live, attenuated)

Read this carefully before you or your child(ren) start taking **FLUMIST** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your or your child's healthcare professional about your or your child(ren) medical condition and treatment and ask if there is any new information about **FLUMIST**.

What is FLUMIST used for?
- FLUMIST is a vaccine used to prevent the flu in people between 2 to 59 years of age.

How does FLUMIST work?
FLUMIST is a vaccine against the flu. The vaccine is made from strains of the flu that are expected to come within the next year in North America.

What are the ingredients in FLUMIST?
Medicinal ingredients: Influenza vaccine (live, attenuated).
Non-medicinal ingredients: Arginine hydrochloride, dibasic potassium phosphate, gelatin hydrolysate (porcine Type A), gentamicin (a trace residual), monobasic potassium phosphate, monosodium glutamate, ovalbumin (a trace residual) and sucrose.

FLUMIST contains no preservatives (e.g. no thimerosal). The intranasal sprayer contains no latex.

FLUMIST comes in the following dosage forms:
FLUMIST is a 0.2 mL spray for nasal administration.

Each 0.2 mL dose contains $10^{6.5-7.5}$ FFU (fluorescent focus units) of live attenuated influenza virus reassortants of each of the three virus strains for the specific season. The three strains used for the 20XX-20XX season are: A/XXX/XXX/XXX (H1N1) (A/XXX/XXX/XXX (H1N1)pdm09-like virus), A/XXX/XXX/XXX (H3N2) (A/XXX/XXX/XXX (H3N2)-like virus) and B/XXX/XXX/XXX (Victoria lineage).

Do not use FLUMIST if you or your child(ren) have:
- Had an allergic reaction to gentamicin (a trace residual), gelatin, arginine or any of the other ingredients contained in FLUMIST.
- Ever had a **severe allergic reaction** to eggs or egg proteins.
- Had an allergic reaction to previous flu vaccination.

To help avoid side effects and ensure proper use, talk to your or your child's healthcare professional before you or your child(ren) take FLUMIST. Talk about any health conditions or problems you may have, including if you or your child(ren):
- Are under the age of 18 years receiving aspirin or medicines containing aspirin.
- Have severe asthma or active wheezing.
- Have had Guillain-Barré syndrome with a previous flu shot.

- Are immunosuppressed due to disease or drug treatment, or associate with people who are immunosuppressed.
- Are pregnant or intend to become pregnant or are nursing.

Tell your or your child's healthcare professional about all the medicines you or your child(ren) take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with FLUMIST:
- *if 2 to 17 years old:* aspirin or medicines containing aspirin.
- prescription medicines used to treat flu.

How to take FLUMIST:
FLUMIST is given by healthcare professionals.

FLUMIST is needle-free. FLUMIST must only be used as a nasal spray. FLUMIST must not be injected.

FLUMIST is a gentle mist and will be given as a spray in each nostril. You can breathe normally while FLUMIST is being given. There is no need to actively inhale or sniff.

Administration: FLUMIST is administered by quickly spraying approximately one-half of the contents into each nostril. Please refer to the diagram below for simple step-by-step administration instructions. Once FLUMIST has been administered, the sprayer should be disposed of according to the standard procedures for medical waste (e.g., sharps container or biohazard container).

Figure 1

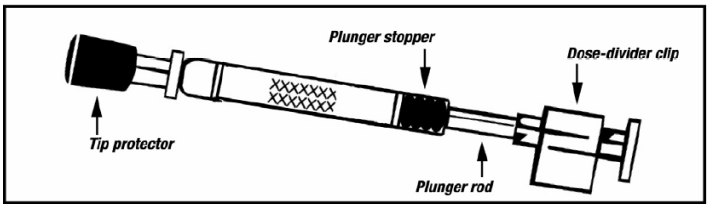
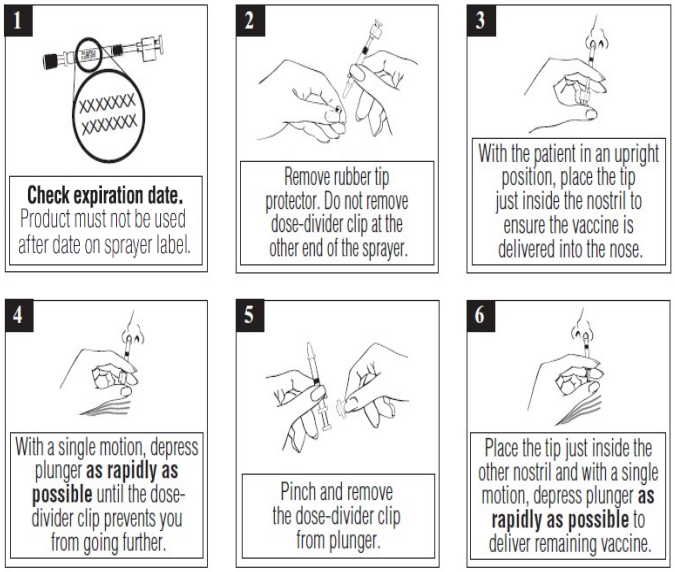


Figure 2



Usual dose:
One 0.2 mL dose of FLUMIST per year; about one-half of the contents will be sprayed into each nostril.

Children (2-8 years) who have not previously been vaccinated with the flu shot should receive a second dose 4 weeks after the first dose.

Overdose:
There is no relevant information available on overdose with FLUMIST vaccine.

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

What are possible side effects from using FLUMIST?
These are not all the possible side effects you or your child may have when taking FLUMIST. If you or your child(ren) experience any side effects not listed here, tell your or your child's healthcare professional.

Very common (occurs in more than 1 in 10 people)
- **Children**: runny or stuffy nose, reduced appetite, weakness, headache, and fever.
- **Adults**: runny or stuffy nose, headache, sore throat, weakness and cough.

Common (occurs in less than 1 in 10 people)
- **Children**: muscle aches
- **Adults:** chills

Uncommon (occurs in less than 1 in 100 people)
- rash
- nose bleed

Rare (occurs in less than 1 in 1,000 people)
- allergic reactions

Very rare (occurs in less than 1 in 10,000 people)
- Guillain-Barré syndrome

Unknown
- worsening of symptoms of Leigh syndrome

If you or your child(ren) have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your or your child's 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 AstraZeneca Canada Inc. 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:
- FLUMIST must be stored in a refrigerator (2°C – 8°C) upon receipt and until use. DO NOT FREEZE.
- Keep the nasal sprayer in the outer carton in order to protect from light.
- Use FLUMIST before the expiry date on the sprayer label.

Keep out of reach and sight of children.

If you want more information about FLUMIST:
- Talk to your or your child's healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website: www.astrazeneca.ca, or by calling 1-800-668-6000.

This leaflet was prepared by AstraZeneca Canada Inc., Mississauga, Ontario L4Y 1M4.

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