PRODUCT MONOGRAPH

FLUMIST®

Influenza Vaccine (live, attenuated)

Intranasal spray

(ATC Code: J07BB03)

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intranasal	Spray, 0.2 mL	Gelatin hydrolysate (porcine Type A), sucrose, arginine, gentamicin. *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

FLUMIST® [influenza vaccine (live, attenuated)] is a live, trivalent vaccine for administration by intranasal spray. Each 0.2 mL dose 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 2014-2015 season are A/California/7/2009 (H1N1)pdm09-like virus, A/Texas/50/2012 (H3N2)-like virus, and B/Massachusetts/2/2012-like virus. This influenza vaccine complies with the WHO recommendation (northern hemisphere) for the 2014-2015 influenza season.

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 strains) or 39°C (Type A strains), temperatures at which many wild-type influenza viruses grow efficiently); and (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.

INDICATIONS AND CLINICAL USE

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.

CONTRAINDICATIONS

FLUMIST® is contraindicated in individuals with a history of hypersensitivity, especially anaphylactic reactions, to eggs, egg proteins, gentamicin, gelatin, or arginine or to any other

ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION and PACKAGING section of the Product Monograph.

FLUMIST® is contraindicated in individuals with a history of hypersensitivity to previous influenza vaccination.

WARNINGS AND PRECAUTIONS

General

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.

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 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 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.

Special Populations

Pregnant and Nursing Women:

Animal reproduction studies and studies in pregnant or lactating women have not been conducted with FLUMIST.

The effect of the vaccine on embryo-fetal and pre-weaning development was 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 either study. No adverse effects on pre-weaning development were observed in the rat study. No fetal malformations or other evidence of teratogenesis were observed.

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

It is not known whether FLUMIST is excreted in human milk. Therefore, as some viruses are excreted in human milk caution should be exercised if FLUMIST is administered to nursing mothers.

Pediatrics (<24 months of age):

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In clinical studies, the safety of FLUMIST® was evaluated in over 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 clinical studies in all ages was nasal congestion/rhinorrhea.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Reactions in Children and Adolescents

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 1 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 1 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
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 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).

Adverse Reactions in Adults

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

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] (%)
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 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.

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 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 septicemia escherichial and malnutrition protein-calorie, bronchopenumonia, 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.

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 children, adolescents, and adults were considered by the medical monitor or investigator to be related to FLUMIST.

Post-Market Adverse Drug 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

DRUG INTERACTIONS

Table 3 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 to15 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.

DOSAGE AND ADMINISTRATION

Recommended Dose

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.

Administration

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

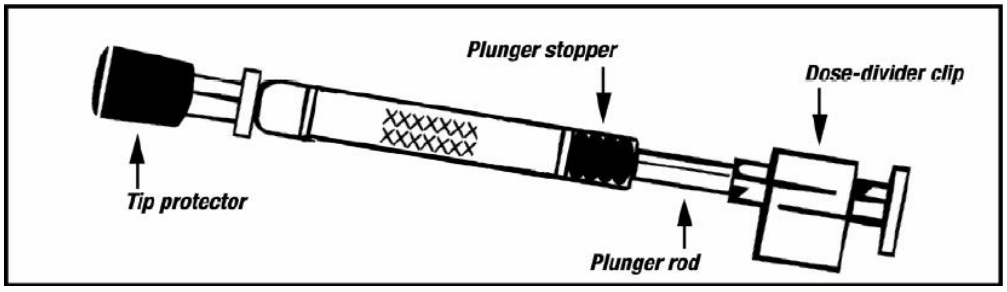
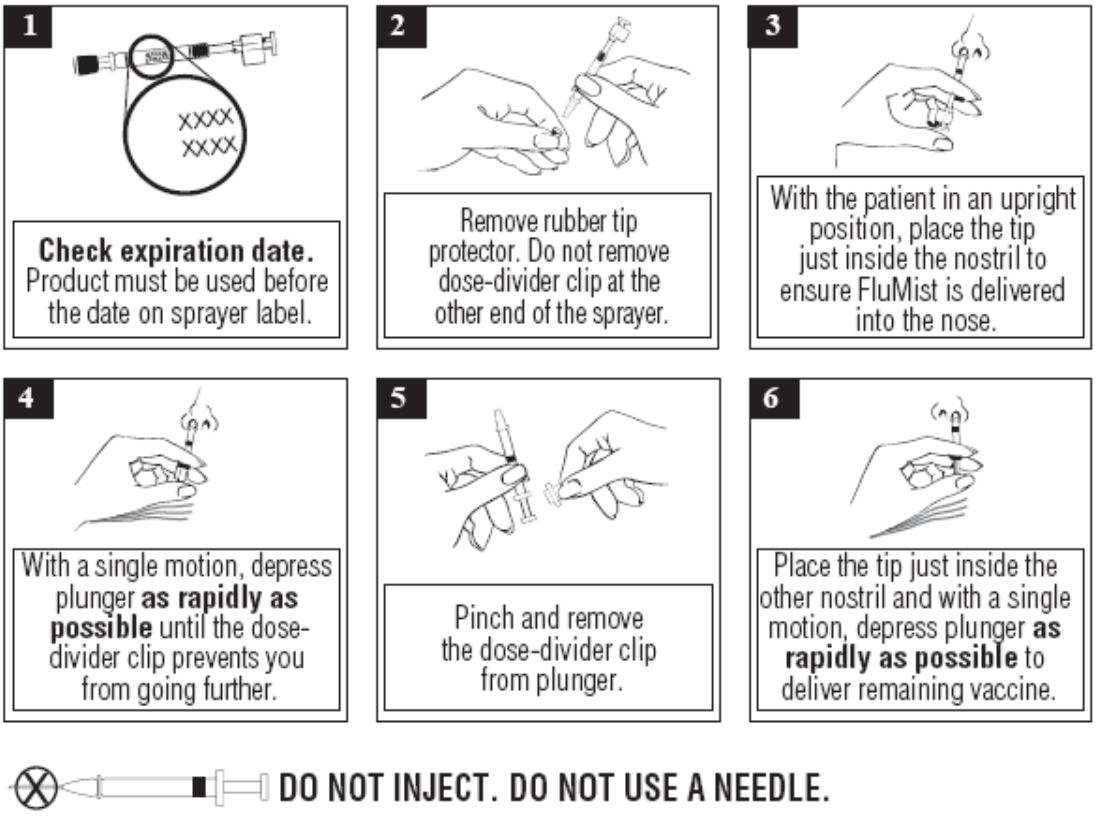


Figure 2



Note: Active inhalation (i.e., sniffing) is not required by the patient during FluMist administration

OVERDOSAGE

No data are available relevant to overdose with FLUMIST vaccine.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Immune mechanisms conferring protection against influenza following receipt of FLUMIST® vaccine 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 one type B) representing the influenza viruses likely to be circulating in North America in the upcoming winter.

STORAGE AND STABILITY

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.

Use the product as indicated by the expiration date on the sprayer label.

DOSAGE FORMS, COMPOSITION AND PACKAGING

FLUMIST® is a spray for intranasal delivery.

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, 5 sprayers, and a package of 1 sprayer.

Each 0.2 mL dose contains $10^{6.5\text{-}7.5}$ FFU (fluorescent focus units) of live attenuated influenza virus reassortants of each of the three strains for the specific season.

Excipients include: sucrose, dibasic potassium phosphate, monobasic potassium phosphate, gelatin hydrolysate (porcine Type A), arginine hydrochloride, monosodium glutamate, gentamicin (a trace residual) and ovalbumin (a trace residual). FLUMIST contains no preservatives (e.g., no thimerosal). The intranasal sprayer contains no latex.

PART II: SCIENTIFIC INFORMATION

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 strains) or 39°C (Type A strains), temperatures at which many wild-type influenza viruses grow efficiently); and (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; white small particles may be present.

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 2014-2015 season are A/California/7/2009 (H1N1)pdm09-like virus, A/Texas/50/2012 (H3N2)-like virus, and B/Massachusetts/2/2012-like virus. This influenza vaccine complies with the WHO recommendation (northern hemisphere) for the 2014-2015 influenza season.

CLINICAL TRIALS

FLUMIST® [influenza vaccine (live, attenuated)] 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 4 and 5 for a summary of FLUMIST efficacy results in children.

Table 4 FLUMIST Efficacy in Placebo-Controlled Pediatric Studies

Study #	Age range	Number of subjects	Influenza season	Efficacy (95% CI)[a] Matched strains	Efficacy (95% CI)[a] 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)[b]	72.0% (61.9, 79.8)[b]
			2002	73.6% (33.3, 91.2)[c]	46.6% (14.9, 67.2)[c]
D153-P513	6 to 35 months	2,107	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)[c]	64.2% (44.2, 77.3)[c]
AV006	15 to 71 months	1,259	1996-1997	93.4% (87.5, 96.5)[b]	93.4% (87.5, 96.5)[b]
			1997-1998	100% (63.1, 100)	87.1% (77.7, 92.6)[d]

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

[b] 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.

[c] 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.

[d] 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 4, 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 5 FLUMIST Relative Efficacy in Active-Controlled (Injectable Influenza Vaccine) Pediatric Studies

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

[a] Age range as described in the protocol for the study
[b] Reduction in culture-confirmed influenza-like illness relative to injectable influenza vaccine

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 5).

Adult studies

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

Table 6 FLUMIST Efficacy in Controlled Adult Studies

Study #	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 immunocompromised 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.

DETAILED PHARMACOLOGY

A primary pharmacodynamics study was conducted in ferrets as part of the strategy to evaluate the current refrigerated and previous frozen formulations of FLUMIST. Titers of vaccine virus in nasal specimens increased between 8 hours and 1 day post vaccination, remained elevated through day 5 and returned to low levels by 7 days after vaccination. This pattern of shedding of vaccine virus was indistinguishable between animals receiving each formulation. Measurements of immunity assessed by hemagglutination inhibition (HAI) showed that neutralization titers present in the sera were similar between each formulation. Following challenge of vaccinated animals with wild-type influenza strains, results demonstrated that both vaccine formulations were protective and prevented replication of wild type virus in the lungs and significantly decreased the level of replication of challenge virus in the upper airways. The study demonstrated that the performance of the refrigerated and frozen formulations were similar with respect to vaccine take and viral replication, immune response induction and protection of animals from wild-type virus challenge.

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.

TOXICOLOGY

Toxicology studies performed include:

- A single/repeat dose toxicity study in ferrets (intranasal inoculation of $10^{6.5\text{-}7.5}$ FFU per strain FLUMIST, administered at weeks 0, 4, 14, followed for 15 weeks total)
- Two developmental toxicity studies (rats and ferrets)
- Two ocular toxicity studies to study the effects of inadvertent instillation of FLUMIST into the eyes in rabbits (Draize tests: 0.1 mL vaccine applied to eye and conjunctival sac)

No significant toxicity was observed in any of the toxicology studies. 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 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.

The effect of the vaccine on embryo-fetal and pre-weaning development was evaluated in a developmental toxicity study using 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 $TCID_{50}$), 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.

Both ocular toxicity studies showed that FLUMIST was well tolerated when administrated intraocular in rabbits.

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

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(Publication of Clinical Trial D153-P502)

PART III: CONSUMER INFORMATION

FLUMIST®
INFLUENZA VACCINE (LIVE, ATTENUATED)

This leaflet is part III of a three-part "Product Monograph" published when FLUMIST was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about FLUMIST. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

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

What it does:
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.

When it should not be used:
Do not take FLUMIST if you have had an allergic reaction to any of the ingredients contained in FLUMIST, especially to eggs, to egg proteins, gentamicin (a trace residual), gelatin, or arginine. Do not take FLUMIST if you have had an allergic reaction to previous flu vaccination.

What the medicinal ingredient is:
Influenza vaccine (live, attenuated)

What the important nonmedicinal ingredients are:
Gelatin hydrolysate (porcine Type A), sucrose, arginine and gentamicin.

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

For a full listing of non-medicinal ingredients see Part 1 of the Product Monograph.

What dosage forms it comes in:
FLUMIST is a spray for nasal administration.

Each 0.2 mL dose contains $10^{6.5\text{-}7.5}$ 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 2013-2014 season are: A/California/7/2009 (H1N1)pdm09-like virus, A/Texas/50/2012 (H3N2)-like virus and B/Massachusetts/2/2012-like virus.

WARNINGS AND PRECAUTIONS

BEFORE you use FLUMIST, talk to your doctor or pharmacist 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

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with FLUMIST include:

- *if 2 to 17 years old:* aspirin or medicines containing aspirin
- prescription medicines used to treat flu

PROPER USE OF THIS MEDICATION

FLUMIST is given by health care 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

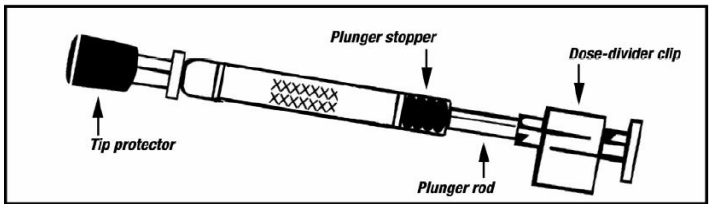
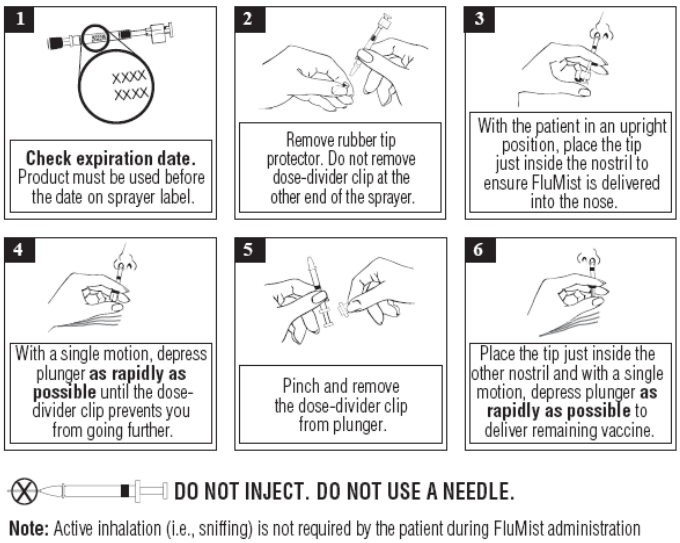


Figure 2



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.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, FLUMIST can cause side effects, although not everybody gets them. Ask your doctor, nurse or pharmacist if you want more information about possible side effects from FLUMIST.

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

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

This is not a complete list of side effects. For any unexpected effects while taking FLUMIST, contact your doctor or pharmacist.

HOW TO STORE IT

FLUMIST must be stored in a refrigerator (2°C – 8°C) upon receipt and until use. DO NOT FREEZE.

Use FLUMIST as indicated by the expiry date on the sprayer label.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.

For health care professionals:
If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local Health Unit in your province/territory.

For the General Public:
Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada

By toll-free telephone: 866-844-0018
By toll-free fax: 866-844-5931
Email: caefi@phac-aspc.gc.ca
Web: http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php

Mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road
A/L 6502A
Ottawa, ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

MORE INFORMATION

NOTE: This INFORMATION FOR THE CONSUMER leaflet provides you with the most current information at the time of printing. For the most current information, the Consumer Information Leaflet plus the full Product Monograph, prepared for health professionals can be found at:
www.astrazeneca.ca,
or by contacting the sponsor, AstraZeneca Canada Inc. at:
Customer Inquiries – 1 (800) 668-6000
Renseignements – 1 (800) 461-3787

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