**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use **Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal** safely and effectively. See full prescribing information for **Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal**

**Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal**
**Manufactured by MedImmune, LLC**
**Intranasal Spray**
**Initial U.S. Approval: 2003**

**----------RECENT MAJOR CHANGES----------**

| | |
|---|---|
| Indications and Usage (1) | 09/2009 |
| Dosage and Administration, Dosing Information (2.1) | 09/2009 |

**----------INDICATIONS AND USAGE----------**

Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is indicated for the active immunization of individuals 2-49 years of age against influenza disease caused by pandemic (H1N1) 2009 virus. (1)

**----------DOSAGE AND ADMINISTRATION----------**

Based on currently available information the vaccination regimen is as follows:

| Age Group | Dosage Schedule |
|---|---|
| Children (2-9 years) | 2 doses (0.2 mL each, approximately 1 month apart) (2.1) |
| Children, adolescents and adults (10-49 years) | 1 dose (0.2 mL) (2.1) |

Each 0.2 mL dose is administered as 0.1 mL per nostril. (2.1)

**----------DOSAGE FORMS AND STRENGTHS----------**

Prefilled single-dose intranasal sprayer containing 0.2 mL suspension. (3, 11)

**----------CONTRAINDICATIONS----------**

- Hypersensitivity to eggs, egg proteins, gentamicin, gelatin or arginine or life threatening reactions to previous influenza vaccination. (4.1)
- Concomitant aspirin therapy in children and adolescents. (4.2)

**----------WARNINGS AND PRECAUTIONS----------**

- Do not administer Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal to children <24 months of age because of increased risk of hospitalization and wheezing. (5.1)
- Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal should not be administered to any individuals with asthma or children < 5 years of age with recurrent wheezing because of the potential for increased risk of wheezing post vaccination. (5.2)
- If Guillain-Barré syndrome has occurred with any prior influenza vaccination, the decision to give Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal should be based on careful consideration of the potential benefits and risks. (5.3)
- Administration of Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal, a live virus vaccine, to immunocompromised persons should be based on careful consideration of potential benefits and risks. (5.4)
- Safety has not been established in individuals with underlying medical conditions predisposing them to wild-type influenza infection complications. (5.5)

**----------ADVERSE REACTIONS----------**

ADVERSE REACTIONS information is based on studies conducted with seasonal trivalent Influenza Vaccine Live, Intranasal (FluMist) manufactured by MedImmune.

Most common adverse reactions (≥ 10% in FluMist and at least 5% greater than in control) are runny nose or nasal congestion in all ages, fever >100°F in children 2-6 years of age, and sore throat in adults. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact MedImmune at 1-877-633-4411 or VAERS at 1-800-822-7967 or *http://vaers.hhs.gov.***

**----------DRUG INTERACTIONS----------**

- Antiviral agents active against influenza A and/or B: Do not administer Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal until 48 hours after antiviral cessation. Antiviral agents should not be administered until 2 weeks after Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal administration unless medically necessary. (7.2)

**----------USE IN SPECIFIC POPULATIONS----------**

- Safety and effectiveness of Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal have not been studied in pregnant women or nursing mothers. (8.1, 8.3)

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 09/2009**

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**FULL PRESCRIBING INFORMATION: CONTENTS***



*Sections or subsections omitted from the full prescribing information are not listed.

# FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is indicated for the active immunization of individuals 2-49 years of age against influenza disease caused by pandemic (H1N1) 2009 virus.

## 2 DOSAGE AND ADMINISTRATION

**FOR INTRANASAL ADMINISTRATION BY A HEALTH CARE PROVIDER.**

### 2.1 Dosing Information

Clinical studies are ongoing with Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal to determine the optimal number of doses.

Available data show that children 9 years of age and younger are largely serologically naïve to the pandemic (H1N1) 2009 virus [1]. Based upon these data Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal should be administered as follows:

| Age Group | Dosage Schedule |
|---|---|
| Children age 2 years through 9 years | 2 doses (0.2 mL* each, approximately 1 month apart) |
| Children, adolescents and adults age 10 through 49 years | 1 dose (0.2 mL*) |

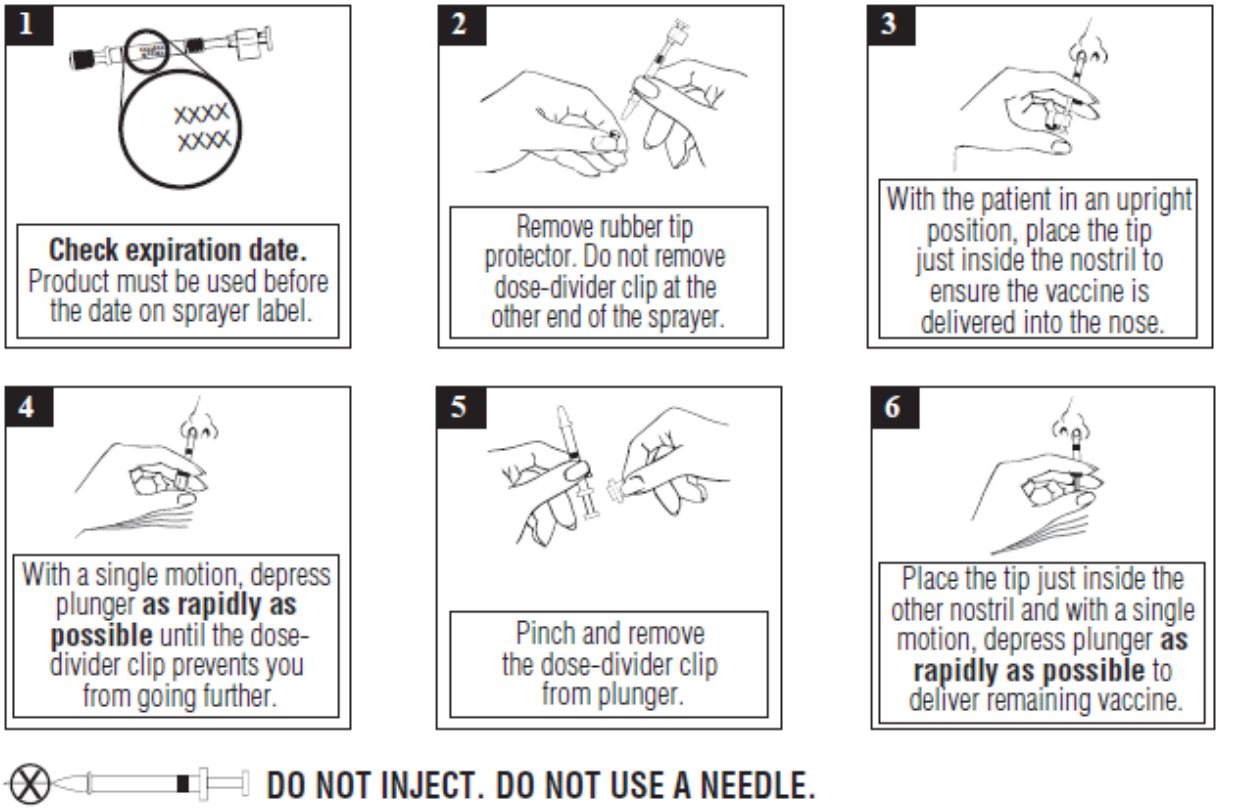
* Administer as 0.1 mL per nostril.

Each 0.2 mL dose is administered as 0.1 mL per nostril.

### 2.2 Administration Instructions

Each sprayer contains a single dose; approximately one-half of the contents should be administered into each nostril. Refer to the administration diagram (Figure 1) for step-by-step administration instructions. Once the vaccine 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**




## 3 DOSAGE FORMS AND STRENGTHS

Pre-filled, single-dose intranasal sprayer containing 0.2 mL suspension *[See Description (11)]*.

## 4 CONTRAINDICATIONS

### 4.1 Hypersensitivity

Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is contraindicated in individuals with a history of hypersensitivity, especially anaphylactic reactions, to eggs, egg proteins, gentamicin, gelatin, or arginine or with life-threatening reactions to previous influenza vaccinations.

## 4.2 Concomitant Pediatric and Adolescent Aspirin Therapy and Reye's Syndrome

Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is contraindicated in children and adolescents (2-17 years of age) receiving aspirin therapy or aspirin-containing therapy, because of the association of Reye's syndrome with aspirin and wild-type influenza infection.

# 5 WARNINGS AND PRECAUTIONS

MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal and seasonal trivalent Influenza Vaccine Live, Intranasal (FluMist) are manufactured by the same process. Information in this section is based on studies conducted with FluMist.

## 5.1 Risks in Children <24 Months of Age

Do not administer Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist to children <24 months of age. In clinical trials, an increased risk of wheezing post-vaccination was observed in FluMist recipients <24 months of age. An increase in hospitalizations was observed in children <24 months of age after vaccination with FluMist. [S*ee Adverse Reactions (6.1).*]

## 5.2 Asthma/Recurrent Wheezing

Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist should not be administered to any individuals with asthma or children < 5 years of age with recurrent wheezing because of the potential for increased risk of wheezing post vaccination unless the potential benefit outweighs the potential risk.

Do not administer Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist to individuals with severe asthma or active wheezing because these individuals have not been studied in clinical trials.

## 5.3 Guillain-Barré Syndrome

If Guillain-Barré syndrome has occurred within 6 weeks of any prior influenza vaccination, the decision to give Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist should be based on careful consideration of the potential benefits and potential risks [*see also Adverse Reactions (6.2)].*

## 5.4 Altered Immunocompetence

Administration of Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal, or FluMist live virus vaccine, to immunocompromised persons should be based on careful consideration of potential benefits and risks. Although FluMist was studied in 57 asymptomatic or mildly symptomatic adults with HIV infection *[see Clinical Studies (14.3)],* data supporting the safety and effectiveness of FluMist administration in immunocompromised individuals are limited.

## 5.5 Medical Conditions Predisposing to Influenza Complications

The safety of Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist in individuals with underlying medical conditions that may predispose them to complications following wild-type influenza infection has not been established. Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal should not be administered unless the potential benefit outweighs the potential risk.

## 5.6 Management of Acute Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine *[see Contraindications (4.1)]*.

## 5.7 Limitations of Vaccine Effectiveness

Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal may not protect all individuals receiving the vaccine.

# 6 ADVERSE REACTIONS

MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal and seasonal trivalent Influenza Vaccine Live, Intranasal (FluMist) are manufactured by the same process.

The data in this section were obtained from clinical trials and post-marketing experience with FluMist.

Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is not approved for use in children <24 months of age. In a clinical trial with FluMist, among children 6-23 months of age, wheezing requiring bronchodilator therapy or with significant respiratory symptoms occurred in 5.9% of FluMist recipients compared to 3.8% of active control (injectable influenza vaccine made by Sanofi Pasteur Inc.) recipients (Relative Risk 1.5, 95% CI: 1.2, 2.1). Wheezing was not increased in children ≥24 months of age.

Hypersensitivity, including anaphylactic reaction, has been reported during post-marketing experience with FluMist.

[See *Warnings and Precautions (5.1)* and *Adverse Reactions (6.1, 6.2)*.]

## 6.1 Adverse Reactions in Clinical Trials

*Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.*

A total of 9537 children and adolescents 1-17 years of age and 3041 adults 18-64 years of age received FluMist in randomized, placebo-controlled Studies D153-P501, AV006, D153-P526, AV019 and AV009 described below. In addition, 4179 children 6-59 months of age received FluMist in Study MI-CP111, a randomized, active-controlled trial. Among pediatric FluMist recipients 6 months-17 years of age, 50% were female; in the study of adults, 55% were female. In MI-CP111, AV006, D153-P526, AV019 and AV009, subjects were White (71%), Hispanic (11%), Asian (7%), Black (6%), and Other (5%), while in D153-P501, 99% of subjects were Asian.

***Adverse Reactions in Children and Adolescents***

In a placebo-controlled safety study (AV019) conducted in a large Health Maintenance Organization (HMO) in children 1-17 years of age (n = 9689), an increase in asthma events, captured by review of diagnostic codes, was observed in children <5 years of age (Relative Risk 3.53, 90% CI: 1.1, 15.7). This observation was prospectively evaluated in Study MI-CP111.

In MI-CP111, an active-controlled study, increases in wheezing and hospitalization (for any cause) were observed in children <24 months of age, as shown in Table 1.

**Table 1**

**Percentages of Children with Hospitalizations and Wheezing from MI-CP111**

| Adverse Reaction | Age Group | FluMist | Active Control[a] |
|---|---|---|---|
| Hospitalizations[b] | 6-23 months (n = 3967) | 4.2 % | 3.2 % |
| | 24-59 months (n= 4385) | 2.1 % | 2.5 % |
| Wheezing[c] | 6-23 months (n = 3967) | 5.9 % | 3.8 % |
| | 24-59 months (n = 4385) | 2.1 % | 2.5 % |

[a] Injectable influenza vaccine made by Sanofi Pasteur Inc.
[b] From randomization through 180 days post last vaccination.
[c] Wheezing requiring bronchodilator therapy or with significant respiratory symptoms evaluated from randomization through 42 days post last vaccination.

Most hospitalizations observed were gastrointestinal and respiratory tract infections and occurred more than 6 weeks post vaccination. In post hoc analysis, rates of hospitalization in children 6-11 months of age (n = 1376) were 6.1% in FluMist recipients and 2.6% in active control recipients.

Table 2 shows an analysis of pooled solicited events, occurring in at least 1% of FluMist recipients and at a higher rate compared to placebo, post Dose 1 for Study D153-P501 and AV006 and solicited events post Dose 1 for Study MI-CP111. Solicited events were those about which parents/guardians were specifically queried after vaccination with FluMist. In these studies, solicited events were documented for 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 2**

**Summary of Solicited Events Observed within 10 Days after Dose 1 for Vaccine[a] and either Placebo or Active Control Recipients; Children 2-6 Years of Age**

| | D153-P501 & AV006 | | MI-CP111 | |
|---|---|---|---|---|
| | FluMist N=876-1759[c] | Placebo N=424-1034[c] | FluMist N=2170[c] | Active Control[b] N=2165[c] |
| **Event** | **%** | **%** | **%** | **%** |
| Runny Nose/ Nasal Congestion | 58 | 50 | 51 | 42 |
| Decreased Appetite | 21 | 17 | 13 | 12 |
| Irritability | 21 | 19 | 12 | 11 |
| Decreased Activity (Lethargy) | 14 | 11 | 7 | 6 |
| Sore Throat | 11 | 9 | 5 | 6 |
| Headache | 9 | 7 | 3 | 3 |
| Muscle Aches | 6 | 3 | 2 | 2 |
| Chills | 4 | 3 | 2 | 2 |
| Fever | | | | |
| 100-101°F Oral | 9 | 6 | 6 | 4 |
| 101-102°F Oral | 4 | 3 | 4 | 3 |

[a] Frozen formulation used in AV006; Refrigerated formulation used in D153-P501 and MI-CP111.

[b] Injectable influenza vaccine made by Sanofi Pasteur Inc.

[c] Number of evaluable subjects (those who returned diary cards) for each event. Range reflects differences in data collection between the 2 pooled studies.

In clinical studies D153-P501 and AV006, other adverse reactions in children occurring in at least 1% of FluMist recipients and at a higher rate compared to placebo were: abdominal pain (2% FluMist vs. 0% placebo) and otitis media (3% FluMist vs. 1% placebo).

An additional adverse reaction identified in the active-controlled trial, MI-CP111, occurring in at least 1% of FluMist recipients and at a higher rate compared to active control was sneezing (2% FluMist vs. 1% active control).

In a separate trial (MI-CP112) that compared the refrigerated and frozen formulations of FluMist in children and adults 5-49 years of age, the solicited events and other adverse

events were consistent with observations from previous trials. Fever of >103°F was observed in 1 to 2% of children 5-8 years of age.

In a separate placebo-controlled trial (D153-P526) using the refrigerated formulation in a subset of older children and adolescents 9-17 years of age who received one dose of FluMist, the solicited events and other adverse events were generally consistent with observations from previous trials. Abdominal pain was reported in 12% of FluMist recipients compared to 4% of placebo recipients and decreased activity was reported in 6% of FluMist recipients compared to 0% of placebo recipients.

***Adverse Reactions in Adults***

In adults 18-49 years of age in Study AV009, summary of solicited adverse events occurring in at least 1% of FluMist recipients and at a higher rate compared to placebo include runny nose (44% FluMist vs. 27% placebo), headache (40% FluMist vs. 38% placebo), sore throat (28% FluMist vs. 17% placebo), tiredness/weakness (26% FluMist vs. 22% placebo), muscle aches (17% FluMist vs. 15% placebo), cough (14% FluMist vs. 11% placebo), and chills (9% FluMist vs. 6% placebo).

In addition to the solicited events, other adverse reactions from Study AV009 occurring in at least 1% of FluMist recipients and at a higher rate compared to placebo were: nasal congestion (9% FluMist vs. 2% placebo) and sinusitis (4% FluMist vs. 2% placebo).

## 6.2 Postmarketing Experience

*The following adverse reactions have been identified during postapproval 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 disorder: Exacerbation of symptoms of mitochondrial encephalomyopathy (Leigh syndrome).

Gastrointestinal disorders: Nausea, vomiting, diarrhea

Immune system disorders: Hypersensitivity reactions (including anaphylactic reaction, facial edema and urticaria)

Nervous system disorders: Guillain-Barré syndrome, Bell's Palsy

Respiratory, thoracic and mediastinal disorders: Epistaxis

Skin and subcutaneous tissue disorders: Rash

## 7 DRUG INTERACTIONS

MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal and seasonal trivalent Influenza Vaccine Live, Intranasal (FluMist) are manufactured by the same process. Available information for FluMist is provided in this section.

### 7.1 Aspirin Therapy

Do not administer Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist to children or adolescents who are receiving aspirin therapy or aspirin-containing therapy *[see Contraindications (4.2)]*.

### 7.2 Antiviral Agents Against Influenza A and/or B

The concurrent use of Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist with antiviral agents that are active against influenza A and/or B viruses has not been evaluated. However, based upon the potential for antiviral agents to reduce the effectiveness of Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal, do not administer this vaccine until 48 hours after the cessation of antiviral therapy and antiviral agents should not be administered until two weeks after administration of this vaccine unless medically indicated. If antiviral agents and Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist are administered concomitantly, revaccination should be considered when appropriate.

### 7.3 Concomitant Inactivated Vaccines

There are no data on the concomitant administration of Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal and seasonal trivalent Influenza Virus Vaccines.

The safety and immunogenicity of Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist when administered concurrently with inactivated vaccines have not been determined. Studies of FluMist excluded subjects who received any inactivated or subunit vaccine within two weeks of enrollment. Therefore, healthcare providers should consider the risks and benefits of concurrent administration of Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal with inactivated vaccines.

### 7.4 Concomitant Live Vaccines

There are no data on the concomitant administration of Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal and FluMist.

Concurrent administration of FluMist with the measles, mumps and rubella vaccine and the varicella vaccine was studied in 1245 children 12-15 months of age. Adverse events were similar to those seen in other clinical trials with FluMist *[see Adverse Reactions*

*(6.1)]*. No evidence of interference with immune responses to measles, mumps, rubella, varicella and FluMist vaccines was observed. Concurrent administration of FluMist with the measles, mumps and rubella vaccine and the varicella vaccine in children >15 months of age has not been studied.

## 7.5 Intranasal Products

There are no data regarding co-administration of Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist with other intranasal preparations.

## 8 USE IN SPECIFIC POPULATIONS

MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal and seasonal trivalent Influenza Vaccine Live, Intranasal (FluMist) are manufactured by the same process. Available information for FluMist is provided in this section.

## 8.1 Pregnancy

**Pregnancy Category C**

Animal reproduction studies have not been conducted with Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist. It is not known whether Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist should be given to a pregnant woman only if clearly needed.

The effect of FluMist on embryo-fetal and pre-weaning development was evaluated in a developmental toxicity study using pregnant rats receiving the frozen formulation. Groups of animals were administered FluMist 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), 250 microliter/rat/occasion (approximately 110-140 human dose equivalents), by intranasal instillation. No adverse effects on pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed. There were no FluMist related fetal malformations or other evidence of teratogenesis noted in this study.

## 8.3 Nursing Mothers

It is not known whether Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist is excreted in human milk. Therefore, as some viruses are excreted in human milk and additionally, because of the possibility of shedding of vaccine virus and the close proximity of a nursing infant and mother, caution should be exercised if Influenza A

(H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist is administered to nursing mothers.

## 8.4 Pediatric Use

Safety and effectiveness of FluMist has been demonstrated for children 2 years of age and older with reduction in culture-confirmed influenza rates compared to active control (injectable influenza vaccine made by Sanofi Pasteur Inc.) and placebo *[see Clinical Studies (14.1)]*. Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is not approved for use in children <24 months of age. FluMist use in children <24 months has been associated with increased risk of hospitalization and wheezing in clinical trials *[see Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)]*.

## 8.5 Geriatric Use

Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is not approved for use in individuals ≥65 years of age. Subjects with underlying high-risk medical conditions (n=200) were studied for safety. Compared to controls, FluMist recipients had a higher rate of sore throat.

## 8.6 Use in Individuals 50-64 Years of Age

Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is not approved for use in individuals 50-64 years of age. In Study AV009, effectiveness of FluMist was not demonstrated in individuals 50-64 years of age (n=641). Solicited adverse events were similar in type and frequency to those reported in younger adults.

## 11 DESCRIPTION

Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is a live monovalent vaccine for administration by intranasal spray. The influenza virus strain in Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is (a) *cold-adapted* (*ca*) (i.e., it replicates efficiently at 25$^{o}$C, a temperature that is restrictive for replication of many wild-type influenza viruses); (b) *temperature-sensitive (ts)* (i.e., it is restricted in replication at 39$^{o}$C, a temperature at which many wild-type influenza viruses grow efficiently); and (c) *attenuated (att)* (it does 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 virus replicates in the nasopharynx to induce protective immunity.

No evidence of reversion has been observed in the recovered vaccine strains that have been tested (135 of possible 250 recovered isolates) using FluMist *[see Clinical Studies*

*(14.5)]*. For the reassortant virus in Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal, the six internal gene segments responsible for *ca*, *ts*, and *att* phenotypes are derived from a master donor virus (MDV), and the two segments that encode the two surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA), are derived from the corresponding antigenically relevant pandemic (H1N1) 2009 wild-type virus. Thus, the virus contained in Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal, maintains the replication characteristics and phenotypic properties of the MDV and expresses the HA and NA of the pandemic (H1N1) 2009 virus. For the MDV, at least five genetic loci in three different internal gene segments contribute to the *ts* and *att* phenotypes; five genetic loci in three gene segments control the *ca* property.

Specific pathogen-free (SPF) eggs are inoculated with the reassortant strain and incubated to allow vaccine virus replication. The allantoic fluid of these eggs is harvested, pooled and then clarified by filtration. The virus is concentrated by ultracentrifugation and diluted with stabilizing buffer to obtain the final sucrose and potassium phosphate concentrations. The viral harvests are then sterile filtered to produce monovalent bulks. Each lot is tested for *ca*, *ts*, and *att* phenotypes and is also tested extensively by *in vitro* and *in vivo* methods to detect adventitious agents. Monovalent bulks are diluted as required to attain the desired potency with stabilizing buffers. The bulk vaccine is then filled directly into individual sprayers for nasal administration.

Each pre-filled refrigerated Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal sprayer contains a single 0.2 mL dose. Each 0.2 mL dose contains $10^{6.5-7.5}$ FFU of the live attenuated influenza virus reassortant of the pandemic (H1N1) 2009 virus: A/California/7/2009 (H1N1)v. Each 0.2 mL dose also contains 0.188 mg/dose monosodium glutamate, 2.00 mg/dose hydrolyzed porcine gelatin, 2.42 mg/dose arginine, 13.68 mg/dose sucrose, 2.26 mg/dose dibasic potassium phosphate, 0.96 mg/dose monobasic potassium phosphate, and <0.015 mcg/mL gentamicin sulfate. The vaccine contains no preservatives.

The tip attached to the sprayer is equipped with a nozzle that produces a fine mist that is primarily deposited in the nose and nasopharynx. Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is a colorless to pale yellow liquid and is clear to slightly cloudy.

## 12 CLINICAL PHARMACOLOGY

### 12.1 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. For example, since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. 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.

### 12.3 Pharmacokinetics

**Biodistribution**

A biodistribution study of intranasally administered radiolabeled placebo was conducted in 7 healthy adult volunteers. The mean percentage of the delivered doses detected were as follows: nasal cavity 89.7%, stomach 2.6%, brain 2.4%, and lung 0.4%. The clinical significance of these findings is unknown.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Neither Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal nor FluMist have been evaluated for carcinogenic or mutagenic potential or potential to impair fertility.

## 14 CLINICAL STUDIES

MedImmune's Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal and the seasonal trivalent Influenza Vaccine Live, Intranasal (FluMist) are manufactured by the same process.

Data in this section were obtained in clinical studies conducted with FluMist.

FluMist, in refrigerated and frozen formulations, was administered to approximately 35,000 subjects in controlled clinical studies. FluMist has been studied in placebo-controlled trials over multiple years, using different vaccine strains. Comparative efficacy

has been studied where FluMist was compared to an inactivated influenza vaccine made by Sanofi Pasteur Inc.

## 14.1 Studies in Children and Adolescents

***Study MI-CP111: Pediatric Comparative Study***

A multinational, randomized, double-blind, active-controlled trial (MI-CP111) was performed to assess the efficacy and safety of FluMist compared to an injectable influenza vaccine made by Sanofi Pasteur Inc. (active control) in children <5 years of age, using the refrigerated formulation. During the 2004-2005 influenza season, a total number of 3916 children <5 years of age and without severe asthma, without use of bronchodilator or steroids and without wheezing within the prior 6 weeks were randomized to FluMist and 3936 were randomized to active control. Participants were then followed through the influenza season to identify illness caused by influenza virus. As the primary endpoint, culture-confirmed modified CDC-ILI (CDC-defined influenza-like illness) was defined as a positive culture for a wild-type influenza virus associated within ±7 days of modified CDC-ILI. Modified CDC-ILI was defined as fever (temperature ≥100°F oral or equivalent) plus cough, sore throat, or runny nose/nasal congestion on the same or consecutive days.

In the primary efficacy analysis, FluMist demonstrated a 44.5% (95% CI: 22.4, 60.6) reduction in influenza rate compared to active control as measured by culture-confirmed modified CDC-ILI caused by wild-type strains antigenically similar to those contained in the vaccine. See Table 3 for a description of the results by strain and antigenic similarity.

**Table 3**
**Comparative Efficacy against Culture-Confirmed Modified CDC-ILI[a] Caused by Wild-Type Strains in Children <5 Years of Age**

| | | | | | Active Control[b] | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | # of Cases | Rate (cases/N) | N | # of Cases | Rate (cases/N) | % Reduction in Rate for FluMist[c] | 95% CI |
| Matched Strains | | | | | | | | | |
| All strains | | 3916 | 53 | 1.4% | 3936 | 93 | 2.4% | 44.5% | 22.4, 60.6 |
| A/H1N1 | | 3916 | 3 | 0.1% | 3936 | 27 | 0.7% | 89.2% | 67.7, 97.4 |
| A/H3N2 | | 3916 | 0 | 0.0% | 3936 | 0 | 0.0% | -- | -- |
| B | | 3916 | 50 | 1.3% | 3936 | 67 | 1.7% | 27.3% | -4.8, 49.9 |
| Mismatched Strains | | | | | | | | | |
| All strains | | 3916 | 102 | 2.6% | 3936 | 245 | 6.2% | 58.2% | 47.4, 67.0 |
| A/H1N1 | **N** | 3916 | 0 | 0.0% | 3936 | 0 | 0.0% | -- | -- |
| A/H3N2 | | 3916 | 37 | 0.9% | 3936 | 178 | 4.5% | 79.2% | 70.6, 85.7 |
| B | **FluMist** | 3916 | 66 | 1.7% | 3936 | 71 | 1.8% | 6.3% | -31.6, 33.3 |
| Regardless of Match | | | | | | | | | |
| All strains | | 3916 | 153 | 3.9% | 3936 | 338 | 8.6% | 54.9% | 45.4, 62.9 |
| A/H1N1 | | 3916 | 3 | 0.1% | 3936 | 27 | 0.7% | 89.2% | 67.7, 97.4 |
| A/H3N2 | | 3916 | 37 | 0.9% | 3936 | 178 | 4.5% | 79.2% | 70.6, 85.7 |
| B | | 3916 | 115 | 2.9% | 3936 | 136 | 3.5% | 16.1% | -7.7, 34.7 |

*ATP Population.*

[a] Modified CDC-ILI was defined as fever (temperature ≥100°F oral or equivalent) plus cough, sore throat, or runny nose/nasal congestion on the same or consecutive days.
[b] Injectable influenza vaccine made by Sanofi Pasteur Inc.
[c] Reduction in rate was adjusted for country, age, prior influenza vaccination status, and wheezing history status.

***Study D153-P501: Pediatric Study***

A randomized, double-blind, placebo-controlled trial (D153-P501) was performed to evaluate the efficacy of FluMist in children 12 to 35 months of age without high-risk medical conditions against culture-confirmed influenza illness, using the refrigerated formulation. A total of 3174 children were randomized 3:2 (vaccine:placebo) to receive 2 doses of study vaccine or placebo at least 28 days apart in Year 1. See Table 4 for a description of the results.

***Study AV006: Pediatric Study***

AV006 was a multi-center, randomized, double-blind, placebo-controlled trial performed in U.S. children without high-risk medical conditions to evaluate the efficacy of FluMist against culture-confirmed influenza over two successive seasons using the frozen formulation. The primary endpoint of the trial was the prevention of culture-confirmed influenza illness due to antigenically matched wild-type influenza in children, who received two doses of vaccine in the first year and a single revaccination dose in the second year. During the first year of the study 1602 children 15-71 months of age were randomized 2:1 (vaccine:placebo). Approximately 85% of the participants in the first year returned for the second year of the study. In Year 2, children remained in the same treatment group as in year one and received a single dose of FluMist or placebo. See Table 4 for a description of the results.

**Table 4**
**D153-P501 & AV006, Years 1[a]: Efficacy of FluMist vs. Placebo against Culture-Confirmed Influenza Illness due to Wild-Type Strains**

| | D153-P501 | | | AV006 | | |
|---|---|---|---|---|---|---|
| | FluMist n[b] (%) | Placebo n[b] (%) | % Efficacy (95% CI) | FluMist n[b] (%) | Placebo n[b] (%) | % Efficacy (95% CI) |
| | N[c]=1653 | N[c]=1111 | | N[c]=849 | N[c]=410 | |
| Any strain | 56 (3.4%) | 139 (12.5%) | 72.9%[d] (62.8, 80.5) | 10 (1%) | 73 (18%) | 93.4% (87.5, 96.5) |
| A/H1N1 | 23 (1.4%) | 81 (7.3%) | 80.9% (69.4, 88.5)[e] | 0 | 0 | -- |
| A/H3N2 | 4 (0.2%) | 27 (2.4%) | 90.0% (71.4, 97.5) | 4 (0.5%) | 48 (12%) | 96.0% (89.4, 98.5) |
| B | 29 (1.8%) | 35 (3.2%) | 44.3% (6.2, 67.2) | 6 (0.7%) | 31 (7%) | 90.5% (78.0, 95.9) |

[a] D153-P501 and AV006 data are for subjects who received two doses of study vaccine.
[b] Number and percent of subjects in per-protocol efficacy analysis population with culture-confirmed influenza illness.
[c] Number of subjects in per-protocol efficacy analysis population of each treatment group of each study for the "any strain" analysis.
[d] For D153-P501, influenza circulated through 12 months following vaccination.
[e] Estimate includes A/H1N1 and A/H1N2 strains. Both were considered antigenically similar to the vaccine.

During the second year of Study AV006, the primary circulating strain was the A/Sydney/05/97 H3N2 strain, which was antigenically dissimilar from the H3N2 strain represented in the vaccine, A/Wuhan/359/95; FluMist demonstrated 87.0% (95% CI: 77.0, 92.6) efficacy against culture-confirmed influenza illness.

## 14.2 Study in Adults

AV009 was a multi-center, randomized, double-blind, placebo-controlled trial to evaluate effectiveness in adults 18-64 years of age without high-risk medical conditions. Participants were randomized 2:1, vaccine:placebo. Cultures for influenza virus were not obtained from subjects in the trial, so that the efficacy against culture-confirmed influenza was not assessed. The A/Wuhan/359/95 (H3N2) strain, which was contained in FluMist, was antigenically distinct from the predominant circulating strain of influenza virus during the trial period, A/Sydney/05/97 (H3N2). Type A/Wuhan (H3N2) and Type B strains also circulated in the U.S. during the study period. The primary endpoint of the trial was the reduction in the proportion of participants with one or more episodes of any febrile illness and prospective secondary endpoints were severe febrile illness, and febrile upper respiratory illness. Effectiveness for any of the three endpoints was not demonstrated in a subgroup of adults 50-64 years of age. Primary and secondary effectiveness endpoints from the age group 18-49 years of age are presented in Table 5. Effectiveness was not demonstrated for the primary endpoint in adults 18-49 years of age.

**Table 5**
**Effectiveness of FluMist[a] in Adults 18–49 Years of Age During the 7-week Site-Specific Outbreak Period**

| Endpoint | **FluMist** N=2411[b] n (%) | **Placebo** N=1226[b] n (%) | **Percent Reduction** | **(95% CI)** |
|---|---|---|---|---|
| **Participants with one or more events of:**[c] | | | | |
| Primary Endpoint: | | | | |
| Any febrile illness | 331 (13.73) | 189 (15.42) | **10.9** | (-5.1, 24.4) |
| Secondary Endpoints: | | | | |
| Severe febrile illness | 250 (10.37) | 158 (12.89) | **19.5** | (3.0, 33.2) |
| Febrile upper respiratory illness | 213 (8.83) | 142 (11.58) | **23.7** | (6.7, 37.5) |

[a] Frozen formulation used.
[b] Number of evaluable subjects (92.7% and 93.0% of FluMist and placebo recipients, respectively).
[c] The predominantly circulating virus during the trial period was A/Sydney/05/97 (H3N2), an antigenic variant not included in the vaccine.

Effectiveness was shown in a post-hoc analysis using CDC-ILI in the age group 18-49 years.

## 14.3 Study in Adults with Human Immunodeficiency Virus (HIV) Infection

Safety and shedding of vaccine virus following FluMist administration were evaluated in 57 HIV-infected [median CD4 cell count of 541 cells/$mm^3$] and 54 HIV-negative adults 18-58 years of age in a randomized, double-blind, placebo controlled trial using the frozen formulation. No serious adverse events were reported during the one-month follow-up period. Vaccine strain (type B) virus was detected in 1 of 28 HIV-infected subjects on Day 5 only and none of the HIV-negative FluMist recipients. 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.

## 14.4 Refrigerated Formulation Study

A double-blind, randomized multi-center trial was conducted to evaluate the comparative immunogenicity and safety of refrigerated and frozen formulations of FluMist in individuals 5 to 49 years of age without high risk medical conditions. Nine hundred and eighty-one subjects were randomized at a 1:1 ratio to receive either vaccine formulation. Subjects 5-8 years of age received two doses of study vaccine 46-60 days apart; subjects 9-49 years of age received one dose of study vaccine. The study met its primary endpoint. The GMT ratios of refrigerated and frozen formulations (adjusted for baseline serostatus) for H1N1, H3N2 and B strains, respectively, were 1.24, 1.02 and 1.00 in the two dose group and 1.14, 1.12 and 0.96 in the one dose group.

## 14.5 Transmission Study

FluMist contains live attenuated influenza viruses that must infect and replicate in cells lining the nasopharynx of the recipient to induce immunity. Vaccine viruses capable of infection and replication can be cultured from nasal secretions obtained from vaccine recipients. The relationship of viral replication in a vaccine recipient and transmission of vaccine viruses to other individuals has not been established.

Using the frozen formulation, a prospective, randomized, double-blind, placebo-controlled trial was performed in a daycare setting in children <3 years of age to assess the transmission of vaccine viruses from a vaccinated individual to a non-vaccinated individual. A total of 197 children 8-36 months of age were randomized to receive one dose of FluMist (n=98) or placebo (n=99). Virus shedding was evaluated for 21 days by culture of nasal swab specimens. Wild-type A (H3N2) influenza virus was documented to have circulated in the community and in the study population during the trial, whereas Type A (H1N1) and Type B strains did not.

At least one vaccine strain was isolated from 80% of FluMist recipients; strains were recovered from 1-21 days post vaccination (mean duration of 7.6 days ± 3.4 days). The cold-adapted *(ca)* and temperature-sensitive (*ts)* phenotypes were preserved in 135 tested of 250 strains isolated at

the local laboratory. Ten influenza isolates (9 influenza A, 1 influenza B) were cultured from a total of seven placebo subjects. One placebo subject had mild symptomatic Type B virus infection confirmed as a transmitted vaccine virus by a FluMist recipient in the same playgroup. This Type B isolate retained the *ca*, *ts*, and *att* phenotypes of the vaccine strain, and had the same genetic sequence when compared to a Type B virus cultured from a vaccine recipient within the same playgroup. Four of the influenza Type A isolates were confirmed as wild-type A/Panama (H3N2). The remaining isolates could not be further characterized.

Assuming a single transmission event (isolation of the Type B vaccine strain), the probability of a young child acquiring vaccine virus following close contact with a single FluMist vaccinee in this daycare setting was 0.58% (95% CI: 0, 1.7) based on the Reed-Frost model. With documented transmission of one Type B in one placebo subject and possible transmission of Type A viruses in four placebo subjects, the probability of acquiring a transmitted vaccine virus was estimated to be 2.4% (95% CI: 0.13, 4.6), using the Reed-Frost model.

The duration of FluMist vaccine virus replication and shedding have not been established.

## 15 REFERENCES

1. Centers for Disease Control and Prevention. Serum Cross-Reactive Antibody Response to a Novel Influenza A (H1N1) Virus After Vaccination with Seasonal Influenza Vaccine. *MMWR 2009*; 58(19): 521-524.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is supplied for intranasal delivery in a package of 10 pre-filled, single-use sprayers.
NDC 66019-200-10

### Storage and Handling

Once Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal has been administered, the sprayer should be disposed of according to the standard procedures for medical waste (e.g., sharps container or biohazard container).

**INFLUENZA A (H1N1) 2009 MONOVALENT VACCINE LIVE, INTRANASAL SHOULD BE STORED IN A REFRIGERATOR BETWEEN 2-8°C (35-46°F) UPON RECEIPT AND UNTIL USE. THE PRODUCT MUST BE USED BEFORE THE EXPIRATION DATE ON THE SPRAYER LABEL.**

**DO NOT FREEZE.**

The cold chain (2 to 8°C) must be maintained when transporting Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal.

## 17 PATIENT COUNSELING INFORMATION

Vaccine recipients or their parents/guardians should be informed by the health care provider of the potential benefits and risks of Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal, and should be advised that there are two influenza vaccine formulations for this influenza season, the monovalent vaccine against disease caused by pandemic (H1N1) 2009 virus and seasonal trivalent influenza vaccine.

### 17.1 Asthma and Recurrent Wheezing

Ask the vaccinee or their parent/guardian if the vaccinee has asthma. For children <5 years of age, also ask if the vaccinee has recurrent wheezing since this may be an asthma equivalent in this age group.

### 17.2 Vaccination with a Live Virus Vaccine

Vaccine recipients or their parents/guardians should be informed by the health care provider that Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is an attenuated live virus vaccine and has the potential for transmission to immunocompromised household contacts.

### 17.3 Adverse Event Reporting

The vaccine recipient or the parent/guardian accompanying the vaccine recipient should be told to report any suspected adverse events to the physician or clinic where the vaccine was administered.

FluMist® is a registered trademark of MedImmune, LLC.

MedImmune

**Manufactured by:**

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Gaithersburg, MD 20878

1-877-633-4411

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