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)

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

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dosage Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (2-9 years)</td>
<td>2 doses (0.2 mL each, approximately 1 month apart) (2.1)</td>
</tr>
<tr>
<td>Children, adolescents and adults (10-49 years)</td>
<td>1 dose (0.2 mL) (2.1)</td>
</tr>
</tbody>
</table>

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

DOSE FORMS AND STRENGTHS
Pre-filled, single-dose intranasal sprayer containing 0.2 mL suspension. (3, 11)

CONTRAINDICATIONS
• Hypersensitivity to eggs, egg proteins, gentamicin, gelatin or arginine or with 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 concurrent 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 the Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967 or http://vaers.hhs.gov.

In countries outside of the United States, report SUSPECTED ADVERSE REACTIONS by contacting MedImmune at drugsafety@medimmune.com or VAERS at 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 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.

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. (1)

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:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dosage Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children age 2 years through 9 years</td>
<td>2 doses (0.2 mL * each, approximately 1 month apart)</td>
</tr>
<tr>
<td>Children, adolescents and adults age 10 through 49 years</td>
<td>1 dose (0.2 mL)</td>
</tr>
</tbody>
</table>

*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

1. Check expiration date. Product must be used before the date on sprayer label.
2. Remove rubber tip protector. Do not remove dose-divider clip at the other end of the sprayer.
3. With the patient in an upright position, place the tip just inside the nostril to ensure the vaccine is delivered into the nose.
4. With a single motion, depress plunger as rapidly as possible until the dose-divider clip prevents you from going further.
5. Pinch and remove the dose-divider clip from plunger.
6. Place the tip just inside the other nostril and with a single motion, depress plunger as rapidly as possible to deliver remaining vaccine.

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

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.
5.2 Asthma/Recurrent Wheezing

Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist should not be administered to children 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 Immuneocompetence

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 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. Information in this section is based on studies conducted with FluMist.

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 1-5 years of age (Relative Risk 3.53, 90% CI: 1.1, 11.57). 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 | Hospitalization | Wheezing |
| | Age Group | FluMist | Active Control |
| | 6-23 months | (n = 396) | | |
| | 24-59 months | (n = 4385) | 2.1 % | 2.5 % |
| | 6-23 months | (n = 396) | 5.9 % | 3.8 % |
| | 24-59 months | (n = 4385) | 2.1 % | 2.5 % |

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.

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.

6.3 Drug Interactions

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.

6.5 Adverse Reactions in Adults

Table 2 Summary of Solicited Events Observed within 10 Days after Dose 1 for Vaccine and/or Either Placebo or Active Control Recipients: Children 2-6 Years of Age

| Table 2 Summary of Solicited Events Observed within 10 Days after Dose 1 for Vaccine and/or Either Placebo or Active Control Recipients: Children 2-6 Years of Age |
|----------------|----------------|----------------|
| Event | FluMist (N=581-1759) | Placebo (N=1244-1034) | Active Control (N=2170) |
| | % | % | % | % | % |
| Runny Nose/ Nasal Congestion | 58 | 50 | 51 | 42 | |
| Decreased Appetite | 21 | 17 | 13 | 12 | 11 |
| 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 | |

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 placebo was: 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 >103°F was observed in 1 to 2% of children 5-8 years of age.

6.6 Concomitant Pediatric and Adolescent Aspirin Therapy and Reye’s Syndrome

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 on the potential for antiviral agents to reduce the effectiveness of Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal, do not administer this vaccine within 48 hours after administration of an antiviral agent. If 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 Viruses 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 or FluMist.

Concurrent administration of FluMist with the measles, mumps and rubella vaccine and the varicella vaccine was studied in 1945 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 Virus Vaccines (FluMist) are manufactured by the same process. Available information for FluMist is presented 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 also 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 the cold-adapted influenza A (H1N1) reassortant virus. 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 microlter/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. (active control) and MedImmune’s Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or 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. Use in individuals 50-64 years of age has not been demonstrated.

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 (ca) cold-adapted (i.e., it replicates efficiently at 25°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°C, a temperature at which many wild-type influenza viruses grow efficiently); and (c) attenuation (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 influenza A(H1N1) 2009 vaccine virus replicates in the nasal sphincter to induce protective immunity.

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

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 virus replication occurs via a replication complex in the nucleus of infected cells. The viral genome is transcribed into mRNAs that are translated into viral proteins. The viral proteins are transported to the cell membrane where they are incorporated into new virions that are released from the infected cell. The released virions then infect other cells in the host and the cycle repeats.

The safety and immunogenicity of Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal or FluMist have not been evaluated in the presence of other vaccines. Therefore, the effects of concomitant administration of FluMist with other vaccines are not known.

Concurrent administration of FluMist with other vaccines may result in interference with the immune response to these other vaccines. The effect of other vaccines on the immune response to FluMist is not known.

12.2 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 Virus Vaccines (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 in 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 influenza (CIDI) defined as a positive culture for a wild-type influenza virus associated with ≤7 days of modified CIDI-ILI. Modified CIDI-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 rate compared to active control as measured by culture-confirmed modified CIDI-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 CIDI-ILI* Caused by Wild-Type Strains in Children <5 Years of Age |
|-----------------|-----------------|-----------------|-----------------|
|                   | Matched Strains |                   |                   |
|                   | N | # of Cases | Rate (cases/N) | N | # of Cases | Rate (cases/N) |
| FluMist |                   |                   |                   |
| Active Control |                   |                   |                   |
| Reduction in Rate for FluMist |                   |                   |                   |
| % | 44.5% | 22.4, 60.6 | 89.2% | 67.7, 97.4 | 72.3% | 48.9, 94.9 |
| Matched Strains |                   |                   |                   |
| N | 3916 | 3 | 1.4% | 3936 | 2 | 0.5% |
| A/H1N1 |                   |                   |                   |
| N | 3916 | 0 | 0.0% | 3936 | 0 | 0.0% |
| A/H3N2 |                   |                   |                   |
| N | 3916 | 0 | 0.0% | 3936 | 0 | 0.0% |
| A/H3N2 |                   |                   |                   |
| N | 3916 | 0 | 0.0% | 3936 | 0 | 0.0% |

Regardless of Match |                   |                   |                   |
| N | 3916 | 0 | 0.0% | 3936 | 0 | 0.0% |

*Modified CIDI-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.

† Injectable influenza vaccine made by Sanofi Pasteur Inc.

‡ Reduction in rate was adjusted for country, age, prior influenza vaccination status, and wheezing history status.
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 1 and received a single dose of FluMist or placebo. See Table 4 for a description of the results.

### Table 4

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Table 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>FluMist</td>
<td>AV006</td>
</tr>
<tr>
<td>N=1653</td>
<td>N=1111</td>
</tr>
<tr>
<td>N=549</td>
<td>N=418</td>
</tr>
<tr>
<td>Any strain</td>
<td>58 (3.4%)</td>
</tr>
<tr>
<td>A/H1N1</td>
<td>23 (1.4%)</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>4 (0.2%)</td>
</tr>
<tr>
<td>B</td>
<td>29 (1.8%)</td>
</tr>
</tbody>
</table>

**Number and percent of subjects in per-protocol efficacy analysis population with culture-confirmed influenza illness.**

- **a** Includes A/H1N1 and A/H1N2 strains.
- **b** Number and percent of subjects in per-protocol efficacy analysis population of each treatment group for each study for the “any strain” analysis.
- **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** For D153-P501, influenza circulated through 12 months following vaccination.

### 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. Ninety and eighteen-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 day care 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 B (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 atp 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 day care setting was 0.58% (95% CI 0.1, 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.

### References


### 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, INTRANALESAL 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**

See the package insert. 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, LLC**

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