FluMist® Influenza Virus Vaccine Live, Intranasal
Intranasal Spray
2007-2008 Formula

Indications and Usage (1) 9/2007
Dosage and Administration, Dosing Information (2.1) 9/2007
Warnings and Precautions (5) 9/2007

FluMist is a live attenuated influenza virus vaccine indicated for the active immunization of individuals 2-49 years of age against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

Dosage and Administration

For intranasal administration by a health care provider:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Vaccination Status</th>
<th>Dosage Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (2-8 years)</td>
<td>Not previously vaccinated with influenza vaccine</td>
<td>2 doses (0.2 mL* each, at least 1 month apart) (2.1)</td>
</tr>
<tr>
<td>Children (2-8 years)</td>
<td>Previously vaccinated with influenza vaccine</td>
<td>1 dose (0.2 mL*) (2.1)</td>
</tr>
<tr>
<td>Children, adolescents and adults (9-49 years)</td>
<td>Not applicable</td>
<td>1 dose (0.2 mL*) (2.1)</td>
</tr>
</tbody>
</table>

* Administer as 0.1 mL per nostril.

Dosage Forms and Strengths

0.2 mL pre-filled, single-use intranasal spray (3)
Each 0.2 mL dose contains 10^5-10^6 FFU (fluorescent focus units) of live attenuated influenza virus reassortants of each of the three strains for the 2007-2008 season: A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004. (3)

Indications

FULL PRESCRIBING INFORMATION

CONTRAINDICATIONS

- Do not administer FluMist to children <24 months because of increased risk of hospitalization and wheezing observed in clinical trials. (5.1)
- FluMist should not be administered to any individuals with asthma and 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 within 6 weeks of any prior influenza vaccination, the decision to give FluMist should be based on careful consideration of the potential benefits and risks. (5.3)
- Administration of FluMist, 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

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 and http://vaers.hhs.gov.

Drug Interactions

- Antiviral agents active against influenza A and/or B: Do not administer FluMist until 48 hours after antiviral cessation. Antiviral agents should not be administered within 2 weeks after FluMist administration unless medically necessary. (7.2)

Use in Specific Populations

- Safety and effectiveness of FluMist have not been studied in pregnant women or nursing mothers. (8.1, 8.3)
- FluMist is not indicated for use in children <2 years of age. (8.4)
- FluMist is not indicated for use in individuals ≥50 years of age. (8.5, 8.6)

Warnings and Precautions

Antiviral Agents Against Influenza A and/or B

- If safety and effectiveness of FluMist have not been studied in pregnant women or nursing mothers. (8.1, 8.3)
- FluMist is not indicated for use in children <2 years of age. (8.4)
- FluMist is not indicated for use in individuals ≥50 years of age. (8.5, 8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 09/2007

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Revised: 09/2007

Full Prescribing Information

1 Indications and Usage

FluMist is a live attenuated influenza virus vaccine indicated for the active immunization of individuals 2-49 years of age against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

2 Dosage and Administration

For intranasal administration by a health care provider:

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<th>Vaccination Status</th>
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<td>Not previously vaccinated with influenza vaccine</td>
<td>2 doses (0.2 mL* each, at least 1 month apart) (2.1)</td>
</tr>
<tr>
<td>Children (2-8 years)</td>
<td>Previously vaccinated with influenza vaccine</td>
<td>1 dose (0.2 mL*) (2.1)</td>
</tr>
<tr>
<td>Children, adolescents and adults (9-49 years)</td>
<td>Not applicable</td>
<td>1 dose (0.2 mL*) (2.1)</td>
</tr>
</tbody>
</table>

* Administer as 0.1 mL per nostril.

For children age 2-8 years who have not previously received influenza vaccine, the recommended schedule is two 0.1 mL doses (0.1 mL per nostril) followed by a second 0.2 mL dose (0.1 mL per nostril) given at least 1 month later.

For all other individuals, including children age 2-8 years who have previously received influenza vaccine, the recommended schedule is one 0.2 mL dose (0.1 mL per nostril).

FluMist should be administered prior to exposure to influenza. Annual revaccination with influenza vaccine is recommended.

2.1 Dosing Information

FluMist should be administered according to the following schedule:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Vaccination Status</th>
<th>Dosage Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children age 2 years through 8 years</td>
<td>Not previously vaccinated with influenza vaccine</td>
<td>2 doses (0.2 mL* each, at least 1 month apart)</td>
</tr>
<tr>
<td>Children age 2 years through 8 years</td>
<td>Previously vaccinated with influenza vaccine</td>
<td>1 dose (0.2 mL*)</td>
</tr>
<tr>
<td>Children, adolescents and adults age 9 through 49 years</td>
<td>Not applicable</td>
<td>1 dose (0.2 mL*)</td>
</tr>
</tbody>
</table>

* Administer as 0.1 mL per nostril.

For children age 2 years through 8 years who have not previously received influenza vaccine, the recommended dosage schedule for nasal administration is one 0.2 mL dose (0.1 mL per nostril) followed by a second 0.2 mL dose (0.1 mL per nostril) given at least 1 month later.

For all other individuals, including children age 2-8 years who have previously received influenza vaccine, the recommended schedule is one 0.2 mL dose (0.1 mL per nostril).

FluMist should be administered prior to exposure to influenza. Annual revaccination with influenza vaccine is recommended.

2.2 Administration Instructions

Each sprayer contains a single dose of FluMist; approximately one-half of the contents should be administered into each nostril. 0.1 mL (i.e., half of the dose from a single FluMist sprayer) is administered into each nostril while the recipient is in an upright position. Insert the tip of the sprayer just inside the nose and rapidly depress the plunger until the dose-divider clip stops the plunger. The dose-divider clip is removed from the sprayer to administer the second half of the dose (0.1 mL) into the other nostril. 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).
3 DOSAGE FORMS AND STRENGTHS

0.2 mL pre-filled, single-use intranasal spray.

Each 0.2 mL dose of FluMist is formulated to contain 10^{7.5} FFU (fluorescent focus units) each of three live attenuated influenza virus reassortants: A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004 [1].

4 CONTRAINDICATIONS

4.1 Hypersensitivity

FluMist is contraindicated in individuals with a history of hypersensitivity, especially anaphylactic reactions, to eggs, egg proteins, gelatin, or anyone with or life-threatening reactions to previous influenza vaccinations.

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

FluMist 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

5.1 Risks in Children <24 Months of Age

Do not administer 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. [See Adverse Reactions (6.1)].

5.2 Asthma/Recurrent Wheezing

FluMist should not be administered to any individuals with asthma and children < 5 years of age with recurrent wheezing because of the potential for increased risk of wheezing post vaccination until the potential benefit outweighs the potential risk.

Do not administer 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 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 FluMist, a 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 FluMist in individuals with underlying medical conditions that may predispose them to complications following wild-type influenza infection has not been established. FluMist should not be administered unless the potential benefit outweighs the potential risk.

5.6 Preventing and Managing Allergic Vaccine Reactions

Prior to vaccination, review the individual’s medical history for possible sensitivity to influenza vaccine or vaccine components. Treatment must be readily available in the event of an acute anaphylactic reaction following vaccination [see Contraindications (4.1)].

5.7 Limitations of Vaccine Effectiveness

FluMist may not protect all individuals receiving the vaccine.

6 ADVERSE REACTIONS

FluMist is not indicated in children <24 months of age. In a clinical trial, 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 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 post-marketing. [See Warnings and Precautions (5.1) and Adverse Reactions (6.1, 6.2)].

16.1 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.

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

<table>
<thead>
<tr>
<th>Event</th>
<th>FluMist placebo</th>
<th>Vaccine placebo</th>
<th>FluMist active control</th>
<th>Placebo active control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Runny Nose</td>
<td>58%</td>
<td>50%</td>
<td>51%</td>
<td>42%</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>21%</td>
<td>17%</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>Discontinued Appetite</td>
<td>14%</td>
<td>11%</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Irritability</td>
<td>9%</td>
<td>7%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Decreased Activity (Lethargy)</td>
<td>11%</td>
<td>9%</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Sore Throat</td>
<td>9%</td>
<td>7%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Headache</td>
<td>6%</td>
<td>3%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Muscle Aches</td>
<td>4%</td>
<td>3%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Chills</td>
<td>100-101°F Oral</td>
<td>9%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Fever</td>
<td>4%</td>
<td>3%</td>
<td>4%</td>
<td>3%</td>
</tr>
</tbody>
</table>

* Frozen formulation used in AV006; Refrigerated formulation used in D153-P501 and MI-CP111.

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 14% of FluMist recipients compared to 0% of placebo 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.

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.

1. 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.

2. In 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.

3. 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.

4. From randomization through 180 days post last vaccination.

5. Wheezing requiring bronchodilator therapy or with significant respiratory symptoms evaluated from randomization through 42 days post last vaccination.

Most hospitalizations 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.
7 DRUG INTERACTIONS

7.1 Aspirin Therapy

Do not administer 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 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 FluMist, do not administer FluMist until 48 hours after the cessation of antiviral therapy and antiviral agents should not be administered until two weeks after administration of FluMist unless medically indicated. If antiviral agents and FluMist are administered concomitantly, revaccination should be considered when appropriate.

7.3 Concomitant Inactivated Vaccines

The safety and immunogenicity of FluMist when administered concurrently with inactivated vaccines have not been determined. Studies of FluMist excluded subjects who received any inactivated or subunit vaccines within two weeks of vaccination. Therefore, healthcare providers should consider the risks and benefits of concurrent administration of FluMist with inactivated vaccines.

7.4 Concomitant Live Vaccines

Concurrent administration of FluMist with the measles, mumps and rabies 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 influenza, varicella, or rabies vaccine was observed. The safety and immunogenicity in children >15 months of age have not been studied.

7.5 Intranasal Products

There are no data regarding co-administration of FluMist with other intranasal preparations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with FluMist. It is not known whether FluMist can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. FluMist should be given to a pregnant woman only if clearly needed. The effect of FluMist on embryonic and fetal growth has been evaluated in a developmental toxicity study using pregnant rats receiving the frozen formulation. 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). 250 μL intranasal per day (approximately 110-140 human dose equivalents based on TGD₃₅), by intranasal instillation. No adverse effects on pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed. There were no vaccine related fetal malformations or other evidence of teratogenicity noted in this study.

8.3 Nursing Mothers

It is not known whether 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 FluMist is administered to nursing mothers.

8.4 Pediatric Use

FluMist is not indicated 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

FluMist is not indicated for use in individuals ≥55 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

FluMist is not indicated for use in individuals 50-64 years of age. In Study AW09, effectiveness 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

FluMist (Influenza Virus Vaccine Live, Intranasal) is a live tetravalent vaccine for administration by intranasal spray. 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 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 possible 250 recovered isolates) [see Clinical Studies (14.5). For each of the three reassortant strains in FluMist, 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 wild-type influenza viruses that have been recommended by the WHO for inclusion in the annual vaccine formulation. Thus, the three viruses contained in FluMist maintain the replication characteristics and phenotypic properties of the MDV and express the HA and NA of wild-type viruses that are related to strains expected to circulate during the 2007-2008 influenza season. For the Type A MDV, at least five genetic loci in three different internal gene segments contribute to the ca phenotype. Two of the three Type B MDV and three of the five ca, ts, and att phenotypes in three gene segments control the ca property.

Specific pathogen-free (SPF) eggs are inoculated with each of the reassortant strains 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. In addition, ethylene diamine tetraacetic acid (EDTA) is added to the dialution buffer for H3N2 strains. The viral harvests are then sterile filtered to produce the 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 from the three strains are subsequently blended and diluted as required to attain the desired potency with stabilizing buffers to produce the trivalent bulk vaccine. The bulk vaccine is then filled directly into individual sprayers for nasal administration. Each pre-filled refrigerated FluMist sprayer contains a 0.2 mL dose. Each 0.2 mL dose contains 10³-10⁴ HA units of live attenuated influenza virus reassortants of each of the three strains: A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Nigeria/250/2004 [1]. Each 0.2 mL dose also contains 0.186 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 monosodium phosphate, and <0.015 mcg/mL gentamicin sulfate. FluMist 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. FluMist is 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 are not understood. Juvenile, 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. Therefore, influenza vaccines are standardized to contain the strains (i.e., typically two Type A and one Type B), representing the influenza viruses likely to be circulating in the United States in the upcoming season. Annual revaccination with the current vaccine is recommended because immunity declines during the year after vaccination, and because circulating strains of influenza virus change from year to year.

12.2 Biodistribution

A biodistribution study of intranasally administered radioabeled placebo was conducted in 7 healthy adult volunteers. The mean percentage of the delivered dose detected was as follows: nasal cavity 70.7%; 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

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

14 CLINICAL STUDIES

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 each year of the influenza season.
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 with high-risk medical conditions against culture-confirmed influenza illness, using the frozen 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 17-71 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>Effectiveness of FluMist vs. Placebo Against Culture-Confirmed Influenza Illness due to Wild-Type Strains</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FluMist</strong></td>
</tr>
<tr>
<td>N=1653</td>
</tr>
<tr>
<td>Any strain</td>
</tr>
<tr>
<td>A/H1N1</td>
</tr>
<tr>
<td>A/H3N2</td>
</tr>
<tr>
<td>B</td>
</tr>
</tbody>
</table>

### 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 of 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 virus from a vaccinated individual to a non-vaccinated individual. A total of 117 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. The 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 B 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, 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 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

### 16 HOW SUPPLIED/STORAGE AND HANDLING

- **FluMist** is supplied for intranasal delivery in a package of 10 pre-filled, single-use sprayers.
- **NDC 60619-105-01**

- **Storage and Handling**

  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).

**FLUMIST SHOULD BE STORED IN A REFRIGERATOR BETWEEN 2-8°C (35-46°F) UNTIL USE AND UPON RECEIPT AND UNTIL USE BEFORE THE EXPIRATION DATE ON THE SPRAYER LABEL.**

DO NOT FREEZE.

The cold chain (2 to 8°C) must be maintained when transporting FluMist.

### 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 FluMist, and the need for two doses at least 1 month apart in children 2-8 years of age who have not previously received 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 FluMist 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 Vaccines, Inc.

**MedImmune**

Manufactured by: MedImmune Vaccines, Inc.

Gaithersburg, MD 20878

For other product information regarding FluMist, call 1-877-FLUMIST (358-6478).

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