FluMist® Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. (1, 11) FluMist Quadrivalent is approved for use in persons 2 through 49 years of age. (1)

**INDICATIONS AND USAGE**

FluMist Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. (1, 11) FluMist Quadrivalent is approved for use in persons 2 through 49 years of age. (1)

**DOSAGE AND ADMINISTRATION**

For intranasal administration by a healthcare provider. (2)

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 years through 8 years</td>
<td>1 or 2 doses&lt;sup&gt;a&lt;/sup&gt;, 0.2 mL&lt;sup&gt;b&lt;/sup&gt; each</td>
<td>If 2 doses, administer at least 1 month apart</td>
</tr>
<tr>
<td>9 years through 49 years</td>
<td>1 dose, 0.2 mL&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> 1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines.

<sup>b</sup> Administer as 0.1 mL per nostril.

<sup>**"**</sup> " indicates information is not applicable

---

**WARNINGS AND PRECAUTIONS**

The most common solicited adverse reactions (≥10% in vaccine recipients and at least 5% greater than in placebo recipients) reported after FluMist were runny nose or nasal congestion (ages 2 years through 49 years), fever over 100°F (children ages 2 years through 6 years), and sore throat (adults ages 18 years through 49 years). Among children and adolescents 2 through 17 years of age who received FluMist Quadrivalent, 32% reported runny nose or nasal congestion and 7% reported fever over 100°F. Among adults 18 through 49 years of age who received FluMist Quadrivalent, 44% reported runny nose or nasal congestion and 19% reported sore throat. (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.

---

**USE IN SPECIFIC POPULATIONS**

- Safety and effectiveness of FluMist Quadrivalent have not been established in pregnant women, nursing mothers, geriatric adults, or children less than 2 years of age. (8.1, 8.3, 8.4, 8.5)
- In clinical trials, in children 6 through 23 months of age, FluMist was associated with an increased risk of hospitalization and wheezing. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

---

**FULL PRESCRIBING INFORMATION**

1 INDICATIONS AND USAGE

FluMist<sup>®</sup> Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine [see Description (11)]. FluMist Quadrivalent is approved for use in persons 2 through 49 years of age.

2 DOSAGE AND ADMINISTRATION

**FOR INTRANASAL ADMINISTRATION BY A HEALTHCARE PROVIDER.**

2.1 Dosing Information

Administer FluMist Quadrivalent according to the following schedule:

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
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</tr>
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<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> 1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines.

<sup>b</sup> Administer as 0.1 mL per nostril.

**"** indicates information is not applicable

2.2 Administration Instructions

Each sprayer contains a single dose (0.2 mL) of FluMist Quadrivalent; administer approximately one half of the contents of the single-dose intranasal sprayer into each nostril (each sprayer contains 0.2 mL of vaccine). Refer to Figure 1 for step-by-step administration instructions. Following administration, dispose of the sprayer according to the standard procedures for medical waste (e.g., sharps container or biohazard container).

---

**ADVERSE REACTIONS**

• Antiviral drugs that are active against influenza A and/or B may reduce the effectiveness of FluMist Quadrivalent if administered within 48 hours before, or within 2 weeks after, receipt of the vaccine. (7.2)

---

**DRUG INTERACTIONS**

- Concomitant aspirin therapy and Reye’s Syndrome in children and adolescents

---

**CONTRAINDICATIONS**

- Severe allergic reaction (e.g., anaphylaxis) to any component of FluMist Quadrivalent, including egg protein, or after a previous dose of any influenza vaccine. (4.1, 11)
- Concomitant aspirin therapy in children and adolescents. (4.2)

---

**USE IN SPECIFIC POPULATIONS**

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DESCRIPTION

10 CLINICAL PHARMACOLOGY

11 DESCRIPTION

12 CLINICAL STUDIES

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

INFORMATION FOR PATIENTS AND THEIR CAREGIVERS

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

---

Figure 1

Note: Active inhalation (i.e., sniffing) is not required by the patient during vaccine administration.
3 DOSAGE FORMS AND STRENGTHS
Each 0.2 mL dose is a suspension supplied in a single-dose pre-filled intranasal sprayer.

4 CONTRAINDICATIONS
4.1 Severe Allergic Reactions
Do not administer FluMist Quadrivalent to persons who have had a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine [see Description (11)] including egg protein, or after a previous dose of any influenza vaccine.

4.2 Concomitant Aspirin Therapy and Reyes’s Syndrome in Children and Adolescents
Do not administer FluMist Quadrivalent to children and adolescents through 17 years of age who are receiving aspirin therapy or aspirin-containing therapy because of the association of Reyes’s syndrome with aspirin and wild-type influenza infection [see Drug Interactions (7.1)].

5 WARNINGS AND PRECAUTIONS
5.1 Risks of Hospitalization and Wheezing in Children Younger than 24 Months of Age
In clinical trials, risks of hospitalization and wheezing were increased in children younger than 2 years of age who received FluMist (trivalent Influenza Vaccine Live, Intranasal) [see Adverse Reactions (6.1)]. This observation with FluMist is relevant to FluMist Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions [see Description (11)].

5.2 Asthma, Recurrent Wheezing, and Active Wheezing
Children younger than 5 years of age with recurrent wheezing and persons of any age with asthma may be at increased risk of wheezing following administration of FluMist Quadrivalent. FluMist Quadrivalent has not been studied in persons with severe asthma or active wheezing.

5.3 Guillain-Barré Syndrome
The 1976 swine influenza vaccine (inactivated) was associated with an elevated risk of Guillain-Barré syndrome (GBS). Evidence for causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, based on data for inactivated influenza vaccines, it is probably slightly more than 1 additional case per 1 million persons vaccinated [1]. If GBS has occurred within 6 weeks of any prior influenza vaccination, the decision to give FluMist Quadrivalent should be based on careful consideration of the potential benefits and potential risks.

5.4 Altered Immunocompetence
FluMist Quadrivalent has not been studied in immunocompromised persons. The effectiveness of FluMist has not been studied in immunocompromised persons. Data on safety and shedding of vaccine virus after administration of FluMist in immunocompromised persons are limited to 173 persons with HIV infection and 10 mild to moderately immunocompromised children and adolescents with cancer [see Clinical Pharmacology (12.2)].

5.5 Medical Conditions Predisposing to Influenza Complications
The safety of FluMist Quadrivalent in individuals with underlying medical conditions that may predispose them to complications following wild-type influenza infection has not been established.

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
FluMist Quadrivalent may not protect all individuals receiving the vaccine.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
FluMist Quadrivalent was not studied in immunocompromised persons. The effectiveness of FluMist has not been studied in immunocompromised persons. Data on safety and shedding of vaccine virus after administration of FluMist in immunocompromised persons are limited to 173 persons with HIV infection and 10 mild to moderately immunocompromised children and adolescents with cancer [see Clinical Pharmacology (12.2)].

6.2 Events in Clinical Trials
In a separate saline placebo-controlled trial (D153-P526) in a subset of older children and adolescents 6 through 17 months of age who received FluMist compared to those who received placebo (Relative Risk = 2.17 ± 1.05), there were 2.17 times more hospitalizations due to any cause following FluMist compared to placebo.

6.3 Summary of Adverse Reactions
Most hospitalizations observed were due to gastrointestinal and respiratory tract infections and occurred in patients who received FluMist 1 for inoculation. In post-hoc analysis, rates of hospitalization in children 6 through 11 months of age were 6.1% (42/684) in FluMist recipients and 2.6% (18/683) in inactivated Influenza Virus Vaccine recipients.

Most hospitalizations observed were due to gastrointestinal and respiratory tract infections and occurred in patients who received FluMist 1 for inoculation. In post-hoc analysis, rates of hospitalization in children 6 through 11 months of age were 6.1% (42/684) in FluMist recipients and 2.6% (18/683) in inactivated Influenza Virus Vaccine recipients.

Table 1: Percentages of Children with Hospitalizations and Wheezing from Study MI-CP111*

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Age Group</th>
<th>FluMist (n/N)</th>
<th>Active Control (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations</td>
<td>6-23 months</td>
<td>4.2% (84/1992)</td>
<td>3.2% (63/1975)</td>
</tr>
<tr>
<td>24-59 months</td>
<td>2.1% (46/2187)</td>
<td>2.5% (56/2198)</td>
<td></td>
</tr>
<tr>
<td>Wheezing</td>
<td>6-23 months</td>
<td>5.9% (117/1992)</td>
<td>3.8% (75/1975)</td>
</tr>
<tr>
<td>24-59 months</td>
<td>2.1% (47/2187)</td>
<td>2.5% (56/2198)</td>
<td></td>
</tr>
</tbody>
</table>

* NCT00128167; see www.clinicaltrials.gov

** Inactivated Influenza Virus Vaccine manufactured by Sanofi Pasteur Inc., administered intramuscularly.

† Hospitalization due to any cause from randomization through 180 days post last vaccination.

‡ Wheezing requiring bronchodilator therapy or accompanied by respiratory distress or hypoxia evaluated from randomization through 42 days post last vaccination.

Table 2: Summary of Solicited Adverse Reactions Occurring Within 14 Days after Dose 1 for FluMist and Either Placebo or Active Control Recipients in Children 2 through 6 Years of Age

<table>
<thead>
<tr>
<th>Event</th>
<th>Adverse Reaction Age Group</th>
<th>FluMist (n/N)</th>
<th>Placebo (n/N)</th>
<th>Active Control (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever ≥ 39°C Oral</td>
<td>16% (157/975)</td>
<td>11% (154/1394)</td>
<td>3% (47/1507)</td>
<td></td>
</tr>
<tr>
<td>Fever ≤ 100°F Oral</td>
<td>9% (86/975)</td>
<td>6% (103/1394)</td>
<td>4% (50/1507)</td>
<td></td>
</tr>
<tr>
<td>Fever ≤ 101.5°F Oral</td>
<td>4% (44/975)</td>
<td>2% (27/1394)</td>
<td>2% (25/1507)</td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td>2% (21/1034)</td>
<td>2% (24/1394)</td>
<td>2% (13/1507)</td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>2% (20/1034)</td>
<td>2% (24/1394)</td>
<td>2% (13/1507)</td>
<td></td>
</tr>
<tr>
<td>Mumps</td>
<td>2% (20/1034)</td>
<td>2% (24/1394)</td>
<td>2% (13/1507)</td>
<td></td>
</tr>
<tr>
<td>Sore Throat</td>
<td>1% (9/1034)</td>
<td>7% (98/1394)</td>
<td>6% (91/1507)</td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1% (9/1034)</td>
<td>2% (23/1394)</td>
<td>2% (17/1507)</td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>1% (9/1034)</td>
<td>2% (22/1394)</td>
<td>2% (16/1507)</td>
<td></td>
</tr>
<tr>
<td>Wheeze</td>
<td>101% (100/100)</td>
<td>100% (100/100)</td>
<td>100% (100/100)</td>
<td></td>
</tr>
</tbody>
</table>

4.2 Dose 2 was observed at a lower frequency compared to Dose 1 for FluMist Quadrivalent and were similar between subjects who received FluMist Quadrivalent and FluMist.
3. Summary of Solicited Adverse Reactions Observed Within 14 Days after Dose 1 for FluMist Quadrivalent and FluMist Recipients in Study MI-CP208 in Children and Adolescents 2 through 17 Years of Age

<table>
<thead>
<tr>
<th>Event</th>
<th>FluMist Quadrivalent (N = 1341-1377a)</th>
<th>FluMist® (N = 901-920b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Runny Nose/Nasal Congestion</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Decreased Activity (Lethargy)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Sore Throat</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Muscle Aches</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 100°F by any route</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>&gt; 100° to 101°F by any route</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 101° to 102°F by any route</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

a Solicited adverse reactions that occurred at a higher rate (≥ 1% rate difference after rounding) in FluMist Quadrivalent recipients compared to FluMist recipients or were identified in previous FluMist trials (see Table 2).

b NCT01091246; see www.clinicaltrials.gov.

c Represents pooled data from the two FluMist study arms (see Clinical Studies [14.2]).

d Number of evaluable subjects for each event.

4. Summary of Solicited Adverse Reactions Observed Within 14 Days after Dose 1 for FluMist Quadrivalent and FluMist Recipients in Study MI-CP185 in Adults 18 through 49 Years of Age

<table>
<thead>
<tr>
<th>Event</th>
<th>FluMist Quadrivalent (N = 1197c)</th>
<th>FluMist® (N = 597d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Runny Nose/Nasal Congestion</td>
<td>44</td>
<td>40</td>
</tr>
<tr>
<td>Headache</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>Sore Throat</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Decreased Activity (Lethargy)</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Muscle Aches</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

c Number of evaluable subjects for each event.

d Number of evaluable subjects for each event.

6.2 Postmarketing Experience

The following events have been spontaneously reported during post approval use of FluMist. Because these events 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. Cardiac disorders. Percarditis.

Congenital, familial, and genetic disorders: Excacerbation 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, meningitis, encephalitis meningitis, vaccine-associated encephalitis.

Respiratory, thoracic, and mediastinal disorders: Epistaxis

Skin and subcutaneous tissue disorders: Rash

7. DRUG INTERACTIONS

Do not administer FluMist Quadrivalent to children and adolescents through 17 years of age who are receiving aspirin therapy or aspirin-containing therapy because of the association of Reye's syndrome with aspirin and wild-type influenza [see Contraindications (4.3)]. Avoid aspirin-containing therapy in these age groups during the first 4 weeks after vaccination with FluMist Quadrivalent unless clearly needed.

7.2 Antiviral Agents Against Influenza A and/or B

Antiviral drugs that are active against influenza A and/or B viruses may reduce the effectiveness of FluMist Quadrivalent if administered within 48 hours before, or within 2 weeks after vaccination. The concurrent use of FluMist Quadrivalent with antiviral agents that are active against influenza A and/or B viruses has not been evaluated. If antiviral agents and FluMist Quadrivalent are administered concomitantly, revaccination should be considered when appropriate.

7.3 Concomitant Administration with Inactivated Vaccines

The safety and immunogenicity of FluMist Quadrivalent when administered concomitantly with inactivated vaccines have not been determined. Studies of FluMist and FluMist Quadrivalent excluded subjects who received any inactivated or subunit vaccine within two weeks of enrollment.

7.4 Concomitant Administration with Other Live Vaccines

Concomitant administration of FluMist Quadrivalent with Mesasies, Mumps, and Rubella Virus Vaccine Live (MMR, manufactured by Merck & Co., Inc.) or the Varicella Virus Vaccine Live (AV009, manufactured by Merck & Co., Inc.) has not been studied. Concomitant administration of FluMist with MMR and the varicella vaccine was studied in children 12 through 15 months of age [see Clinical Studies (14.5)]. Concomitant use of FluMist with the MMR and the varicella vaccine in children older than 15 months of age has not been studied.

8.5 Intranasal Products

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

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

A developmental and reproductive toxicity study has been performed in female rats administered FluMist Quadrivalent either three times (during the period of organogenesis) or six times (prior to gestation and during the period of organogenesis). 210 micrograms/intracervical injection at 150 days to pregnant rats and has revealed no evidence of impaired fertility or harm to the fetus due to FluMist Quadrivalent. There are, however, no adequate and well controlled studies in pregnant women. Because animal studies are not always predictive of human response FluMist Quadrivalent should be administered during pregnancy only if clearly needed.

8.4 Pediatric Use

Safety and effectiveness of FluMist Quadrivalent in children 24 months of age and older is based on data from FluMist clinical studies and a comparison of post-vaccination antibody titers between persons who received FluMist Quadrivalent and those who received FluMist (see Clinical Studies [14.2]). FluMist Quadrivalent is not approved for use in children younger than 24 months of age because use of FluMist in children 6 through 23 months has been associated with increased risks of hospitalization and wheezing in clinical trials [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].

8.5 Geriatric Use

FluMist Quadrivalent is not approved for use in persons 65 years of age and older because in a clinical study (AV009), effectiveness of FluMist to prevent febrile illness was not demonstrated in adults 50 through 64 years of age [see Clinical Studies (14.3)]. In this study, solicited events among individuals 50 through 64 years of age were similar in type and frequency to those reported in younger adults. In a clinical study of FluMist in persons 65 years of age and older, 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.

11. DESCRIPTION

FluMist Quadrivalent (Influenza Vaccine Live, Intranasal) is a live, attenuated influenza vaccine for administration by intranasal spray. FluMist Quadrivalent contains four vaccine virus strains: an A/H1N1 strain, an A/H3N2 strain and two B strains. FluMist Quadrivalent contains B strains from both the B/Yamagata/16/88 and the B/Victoria/3/87 antigenic groups [see Antigenic Properties (6.1)]. FluMist Quadrivalent is not approved for use in children younger than 24 months of age because use of FluMist in children 6 through 23 months has been associated with increased risks of hospitalization and wheezing in clinical trials [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].

Specific pathogen-free (SPF) eggs are inoculated with each of the reassortant strains and incubated to control the final sucrose and potassium phosphate concentrations. The viral harvests are then sterile filtered in vitro tests; five genetic loci in three gene segments (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 (at) (i.e., they do not produce classic influenza-like illness in the ferret model of human influenza infection).
Day 115: 20
Day 126: 29
102: 50
100: 69

A prospective, randomized, double-blind, placebo-controlled trial was performed in a daycare setting in children 6 through 24 months of age receiving stable anti-retroviral therapy. Four of the influenza Type A isolates were confirmed as wild-type A/Panama (H3N2). The remaining isolates could not be further characterized.

The clinical significance of these findings is unknown.

13.3.2.1 Pharmacokinetics

Biodistribution

A randomization trial of intranasally administered radiolabeled placebo was conducted in 7 healthy adult volunteers. The mean percentages 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.

14.1. Efficacy Studies of FluMist in Children and Adolescents

A multinational, randomized, double-blind, active-controlled trial (MI-CP111) was performed to assess the clinical experience with FluMist Quadrivalent because both vaccines are manufactured by Sanofi Pasteur Inc. (active control) in children 6 through 18 years of age. A total number of 3916 children without severe asthma, without use of bronchodilator or steroids, and without wheezing within the prior 6 weeks were randomized to FluMist and 3906 were randomized to active control. Children who previously received any influenza vaccine were excluded from the study.

A single subject who did not shed previously; TCID50/mL

Inactivated Influenza Virus Vaccine manufactured by Sanofi Pasteur Inc., administered intramuscularly. In children 6 through 18 years of age.

Children who previously received any influenza vaccine (or had an unknown history of influenza vaccination) received two doses. 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) with cough, sore throat, or runny nose/nasal congestion on the same or consecutive days.

The highest proportion of subjects in each group shed one or more vaccine strains on Days 2-3 post vaccination. After Day 11 among individuals 2 through 49 years of age (n = 443), virus titers did not exceed 1.5 log10/mL.

A single subject who did not shed previously; TCID50/mL was less than 1.5 log10.

Neither the safety of FluMist nor FluMist Quadrivalent were for use in children younger than 18 years of age (See Adverse Reactions (1.4)).

Studies in Immunocompromised Individuals

Safety and shedding of vaccine virus following FluMist administration were evaluated in 28 HIV-infected adults [median CD4 cell count of 541 cells/mm3] and 27 HIV-negative adults 18 through 58 years of age. 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 in none of the HIV-negative FluMist recipients.

Safety and shedding of vaccine virus following FluMist administration were also evaluated in children in a randomized (1:1), cross-over, double-blind, AF-SPG placebo-controlled trial in 24 HIV-infected children [median CD4 cell count of 1031 cells/mm3] and 25 HIV-negative children 1 through 7 years of age, and in a randomized (1:1), open-label, inactivated influenza vaccine-controlled trial in 24 HIV-infected children and adolescents 5 through 17 years of age receiving stable anti-retroviral therapy. Frequency and duration of vaccine virus shedding in HIV-infected individuals were comparable to that seen in healthy individuals. No adverse effects on HIV viral load or CD4 counts were identified following FluMist administration. In the 5 through 17 year old age group, one inactivated influenza vaccine recipient and one FluMist vaccine recipient developed pneumonia within 28 days of vaccination (days 17 and 15, respectively). The effectiveness of FluMist and FluMist Quadrivalent in preventing influenza illness in HIV-infected individuals has not been evaluated.

Twenty mild to moderately immunocompromised children and adolescents 5 through 17 years of age (receiving chemotherapy and/or radiation therapy or who had received chemotherapy in the 12 weeks prior to enrollment) were randomized to receive placebo, FluMist, andduration of vaccine virus shedding in these immunocompromised children and adolescents were comparable to that seen in healthy children and adolescents. The effectiveness of FluMist and FluMist Quadrivalent in preventing influenza illness in immunocompromised individuals has not been evaluated.

Transmission Study

A prospective, randomized, double-blind, placebo-controlled trial was performed in a daycare setting in children younger than 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 through 36 months of age were randomized to receive one dose of FluMist (N = 98) or AF-SPG placebo (N = 99). Virus shedding was evaluated for 21 days by culture of nasal swab specimens. Wild-type A (A/H1N1) influenza virus was distributed to children in the community and in the study population during the trial, whereas Type A (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 ts 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 influenza following close contact with a single FluMist vaccinee was 0.58% (95% CI 0.1, 1.7) based on the Reed-Frost model. With documentation of transmission of one Type B in one placebo subject and transmission of three 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.

12.3 Pharmacokinetics

Safety and shedding of vaccine virus following FluMist administration were evaluated in children 5 through 17 years of age (N = 200) and (2) multicenter study FM026 which enrolled healthy individuals 5 through 49 years of age (N = 344). In each study, nasal secretions were obtained daily for the first 7 days and every other day during either Day 1 and on Day 28 or through Day 28. In study MI-CP129, individuals with a positive shedding sample at Day 25 or Day 28 were to have additional shedding samples collected every 7 days until culture negative on 2 consecutive samples. Results of these studies are presented in Table 5.

Table 5: Characterization of Shedding with FluMist in Specified Age Groups by Frequency, Amount, and Duration (Study MI-CP129 and Study FM026)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>% Shedding</th>
<th>Peak Titer</th>
<th>Shedding After Day 1</th>
<th>Day of Last Positive Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-23 months</td>
<td>90%</td>
<td>&lt; 5 log10</td>
<td>7.0</td>
<td>Day 23</td>
</tr>
<tr>
<td>24-59 months</td>
<td>10%</td>
<td>&lt; 5 log10</td>
<td>1.0</td>
<td>Day 23</td>
</tr>
<tr>
<td>5-8 years</td>
<td>12%</td>
<td>&lt; 5 log10</td>
<td>2.9</td>
<td>Day 23</td>
</tr>
<tr>
<td>8-14 years</td>
<td>16%</td>
<td>&lt; 4 log10</td>
<td>1.6</td>
<td>Day 28</td>
</tr>
<tr>
<td>25-49 years</td>
<td>11%</td>
<td>&lt; 3 log10</td>
<td>0.9</td>
<td>Day 21</td>
</tr>
</tbody>
</table>

FluMist and FluMist Quadrivalent contain 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 (shedding) [see Pharmacodynamics (12.2)].
Study AV006 was a second multi-center, randomized, double-blind, AF-SPG placebo-controlled trial performed in U.S. children without high-risk medical conditions to evaluate the efficacy of FluMist against culture-confirmed influenza during two successive seasons (1996-1997 and 1997-1998). 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. Respiratory illness only that prompted an influenza culture was defined as at least one of the following: fever (>101°F rectal or oral; or >100.4°F axillary), wheezing, shortness of breath, pulmonary congestion, pneumonia, or otitis media; or two of the following: runny nose/nasal congestion, sore throat, cough, muscle aches, chills, headache, irritability, decreased activity, or vomiting. During the first year of the study, 1602 children 15 through 71 months of age were randomized 2:1 (vaccine: placebo). See Table 7 for a description of the results.

### Table 7: Efficacy of FluMist vs. Placebo Against Culture-Confirmed Influenza Illness Due to Antigenically Matched Wild-Type Strains (Studies D153-PS01 and AV006, Year 1)

<table>
<thead>
<tr>
<th>Strain</th>
<th>FluMist Placebo % Efficacy (95% CI)</th>
<th>Placebo % Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any strain</td>
<td>51.9% (63.4%)</td>
<td>57.1% (69.3%)</td>
</tr>
<tr>
<td>A/H1N1</td>
<td>79.9% (86.2, 95.5)</td>
<td>86.2% (92.3, 98.6)</td>
</tr>
<tr>
<td>A/H1N2</td>
<td>90.0% (88.1, 97.5)</td>
<td>88.1% (97.5, 100.0)</td>
</tr>
<tr>
<td>B</td>
<td>43.3% (36.1, 62.7)</td>
<td>46.5% (28.0, 69.0)</td>
</tr>
</tbody>
</table>

a D153-PS01 and AV006 data are for subjects who received two doses of study vaccine.

b Numbers of evaluable subjects (92.7% and 93.0% of FluMist and placebo recipients, respectively).

### Efficacy of FluMist Quadrivalent in Adults

A multicenter, randomized, double-blind, active-controlled, and non-inferiority study (MI-CP185) was performed to assess the immunogenicity of FluMist Quadrivalent compared to FluMist (active control) in children and adolescents 2 through 17 years of age. A total of 2312 subjects were randomized by site at a 3:1 ratio to receive either FluMist Quadrivalent or one of two formulations of comparator vaccine FluMist, each containing a B strain that corresponded to one of the two B strains in FluMist Quadrivalent (a B strain of the Yamagata lineage and a B strain of the Victoria lineage).

In immunogenicity study MI-CP185 was evaluated by comparing the 4 strain-specific serum hemagglutination inhibition (HAI) antibody geometric mean titers (GMTs) post dosing and provided evidence that the addition of the second B strain did not result in immune interference to other strains included in the vaccine.

### 15. REFERENCES


### 16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

FluMist Quadrivalent is supplied in a package of 10 pre-filled, single-dose (0.2 mL) intranasal sprays. The single-use intranasal spray is not made with natural rubber latex. Carton containing 10 intranasal sprayers: NDC 66019-303-10

Single intranasal spray: NDC 66019-303-01

16.2 Storage and Handling

The cold chain [2-8°C (35-46°F)] must be maintained when transporting FluMist Quadrivalent.

**FLUMIST QUADRIVALENT SHOULD BE STORED IN A REFRIGERATOR BETWEEN 2-8°C (35-46°F) UNTIL RECEIVED. THE PRODUCT MUST BE USED BEFORE THE EXPIRATION DATE ON THE SPRAYER LABEL. DO NOT FREEZE.**

Keep FluMist Quadrivalent in outer carton in order to protect from light.

A single temperature excursion up to 75°C (167°F) for 12 hours has been shown to have no adverse impact on the vaccine. After a temperature excursion, the vaccine should be returned immediately to the recommended storage condition (2°C – 8°C) and used as soon as feasible. Subsequent excursions are not permitted.

Once FluMist Quadrivalent has been administered or has expired, the sprayer should be disposed of according to the standard procedures for medical waste (e.g., sharps container or biohazard container).

### 17. PATIENT COUNSELING INFORMATION

Advise the vaccine recipient or their caregiver to read the FDA-approved patient labeling (Information for Patients and Their Caregivers).

Informed vaccine recipients or their parents/guardians of the need for two doses at least 1 month apart in children 2 through 8 years of age, depending on vaccination history. Provide the Vaccine Information Statements (VIS) which are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization.

17.1 Asthma and Recurrent Wheezing

Ask the vaccinee or their parent/guardian if the vaccinee has asthma. For children younger than 5 years of age, ask also if the vaccinee has recurrent wheezing since this may be an asthma equivalent in this age group. Inform the vaccinee or their parent/guardian that there may be an increased risk of wheezing associated with FluMist Quadrivalent in persons younger than 5 years of age with recurrent wheezing and persons of any age with asthma [see Warnings and Precautions (5.2)].

17.2 Vaccination with a Live Virus Vaccine

Inform vaccine recipients or their parents/guardians that FluMist Quadrivalent is an attenuated live virus vaccine and has the potential for transmission to immunocompromised household contacts.

17.3 Adverse Event Reporting

Instruct the vaccine recipient or their parent/guardian to report adverse reactions to their healthcare provider.

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Manufactured by: MedImmune, LLC

Gathersburg, MD 20878

1-877-033-4411

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**RAL-FLUV5**
Information for Patients and Their Caregivers

FluMist® Quadrivalent (pronounced FLEW-mist Kwä-drí-lá-vent)
(Influenza Vaccine Live, Intranasal)

Please read this Patient Information carefully before you or your child is vaccinated with FluMist Quadrivalent.

This is a summary of information about FluMist Quadrivalent. It does not take the place of talking with your healthcare provider about influenza vaccination. If you have questions or would like more information, please talk with your healthcare provider.

What is FluMist Quadrivalent?

FluMist Quadrivalent is a vaccine that is sprayed into the nose to help protect against influenza. It can be used in children, adolescents, and adults ages 2 through 49. FluMist Quadrivalent is similar to MedImmune's trivalent Influenza Vaccine Live, Intranasal (Flumist) except FluMist Quadrivalent provides protection against an additional influenza strain. FluMist Quadrivalent may not prevent influenza in everyone who gets vaccinated.

Who should not get FluMist Quadrivalent?

You should not get FluMist Quadrivalent if you:

• have a severe allergy to eggs or to any inactive ingredient in the vaccine (see "What are the ingredients in FluMist Quadrivalent?")
• have ever had a life-threatening reaction to influenza vaccinations
• are 2 through 17 years old and take aspirin or medicines containing aspirin. Children or adolescents should not be given aspirin for 4 weeks after getting FluMist or FluMist Quadrivalent unless your healthcare provider tells you otherwise.

Please talk to your healthcare provider if you are not sure if the items listed above apply to you or your child.

Children 2 through 8 years old may need 2 doses of FluMist Quadrivalent, depending on their history of previous influenza vaccination. Your healthcare provider will decide if your child needs to come back for a second dose.

Who may not be able to get FluMist Quadrivalent?

Tell your healthcare provider if you or your child:

• are currently wheezing
• have a history of wheezing if under 5 years old
• have had Guillain-Barré syndrome
• have a weakened immune system or live with someone who has a severely weakened immune system
• have problems with your heart, kidneys, or lungs
• have diabetes
• are pregnant or nursing
• are taking Tamiflu®, Relenza®, amantadine, or rimantadine

If you or your child cannot take FluMist Quadrivalent, you may still be able to get an influenza shot. Talk to your healthcare provider about this.

How is FluMist Quadrivalent given?

• FluMist Quadrivalent is a liquid that is sprayed into the nose.
• You can breathe normally while getting FluMist Quadrivalent. There is no need to inhale or "sniff" it.
• People 9 years of age and older need one dose of FluMist Quadrivalent each year.
• Children 2 through 8 years old may need 2 doses of FluMist Quadrivalent, depending on their history of previous influenza vaccination. Your healthcare provider will decide if your child needs to come back for a second dose.

What are the possible side effects of FluMist Quadrivalent?

The most common side effects are:

• runny or stuffy nose
• sore throat
• fever over 100 degrees F

Other possible side effects include:

• decreased appetite
• headache
• irritability
• muscle ache
• tiredness
• chills
• cough

Call your healthcare provider or go to the emergency department right away if you or your child experience:

• hives or a bad rash
• trouble breathing
• swelling of the face, tongue, or throat

These are not all the possible side effects of FluMist Quadrivalent. You can ask your healthcare provider for a complete list of side effects that is available to healthcare professionals.

Call your healthcare provider for medical advice about side effects. You may report side effects to VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

What are the ingredients in FluMist Quadrivalent?

Active Ingredient: FluMist Quadrivalent contains 4 influenza virus strains that are weakened (A(H1N1), A(H3N2), B Yamagata lineage, and B Victoria lineage).

Inactive Ingredients: monosodium glutamate, gelatin, arginine, sucrose, dibasic potassium phosphate, monobasic potassium phosphate, and gentamicin.

FluMist Quadrivalent does not contain preservatives.

How is FluMist Quadrivalent Stored?

FluMist Quadrivalent is stored in a refrigerator (not the freezer) between 35-46 degrees F (2-8 degrees C) upon receipt. FluMist Quadrivalent sprayer must be kept in the carton until use in order to protect from light. FluMist Quadrivalent must be used before the expiration date on the sprayer label.

If you would like more information, talk to your healthcare provider or visit www.flumistquadrivalent.com or call 1-877-633-4411.

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MedImmune

Manufactured by:
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