FLUMIST® QUADRIVALENT is a vaccine indicated for active immunization for the prevention of influenza 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)

DOSE 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 dosesa, 0.2 mLb 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 mLb</td>
<td>-</td>
</tr>
</tbody>
</table>

a 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.
b Administer as 0.1 mL per nostril.
-" indicates information is not applicable.

ADVERSE REACTIONS

Among adults 18 through 49 years, 1.6% reported local reactant symptoms of nasal congestion, runny nose, or sneezing. Among children ages 2 years through 6 years, 44% reported runny nose or nasal congestion and 19% reported sore throat. (6.1)

FluMist Quadrivalent has not been studied in immunocompromised persons. (5.4)

If Guillain-Barré syndrome 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 risks. (5.3)

FluMist Quadrivalent has not been studied in immunocompromised persons. (5.4)

USE IN SPECIFIC POPULATIONS

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.

Revised: 8/2020
**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 Quadrivalent (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 one additional case per 1 million persons vaccinated. 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

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

This safety experience with FluMist is relevant to FluMist Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions [see Description (11)].

A total of 9537 children and adolescents 1 through 17 years of age and 3041 adults 18 through 64 years of age received FluMist in randomized, placebo-controlled Studies D153-P501, AV006, D153-P526, AV019, and AV009 [3 used Allantoic Fluid containing Sucrose-Phosphate-Glutamate (AF-SPG) placebo, and 2 used saline placebo] described below. In addition, 4179 children 6 through 59 months of age received FluMist in Study MI-CP111, a randomized, active-controlled trial. Among pediatric FluMist recipients 6 months through 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 (3%), while in D153-P501, 96% of subjects were Asian.

A total of 1382 children and adolescents 2 through 17 years of age and 1198 adults 18 through 49 years of age received FluMist Quadrivalent in randomized, active-controlled Studies MI-CP208 and MI-CP185. Among pediatric FluMist Quadrivalent recipients 2 through 17 years of age, 51% were female; in the study of adults, 55% were female. In Studies MI-CP208 and MI-CP185, subjects were White (73%), Asian (1%), Black or African-American (19%), and Other (7%); overall, 22% were Hispanic or Latino.

**FluMist in Children and Adolescents**

The safety of FluMist was evaluated in an AF-SPG placebo-controlled study (AV019) conducted in a Health Maintenance Organization (HMO) in children 1 through 17 years of age (FluMist = 673, placebo = 6216). An increase in asthma events, captured by review of diagnostic codes, was observed in children younger than 5 years of age who received FluMist compared to those who received placebo (Relative Risk 3.53, 90% CI 1.1, 15.7).

In Study MI-CP111, children 6 through 59 months of age were randomized to receive FluMist or inactivated Influenza Virus Vaccine manufactured by Sanofi Pasteur Inc. Wheezing requiring bronchodilator therapy or accompanied by respiratory distress or hypoxia was prospectively monitored from randomization through 42 days post last vaccination. Hospitalization due to all causes was prospectively monitored from randomization through 42 days post last vaccination. Increases in wheezing and hospitalization (for any cause) were observed in children 6 months through 23 months of age who received FluMist compared to those who received inactivated Influenza Virus Vaccine, as shown in Table 1.

**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% (84/2012)</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>

**Table 2: Summary of Solicited Adverse Reactions Observed Within 10 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>FluMist Placebo</th>
<th>FluMist Active Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>876-1756</td>
<td>424-1034</td>
</tr>
<tr>
<td></td>
<td>2108</td>
<td>2170</td>
</tr>
<tr>
<td></td>
<td>2165</td>
<td>2165</td>
</tr>
<tr>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Fever</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>18 &gt; 10°F Oral</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>&gt; 18 &gt; 10°F Oral</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>&gt; 101 &gt; 10°F Oral</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>&lt; 101 &gt; 10°F Oral</td>
<td>4</td>
</tr>
</tbody>
</table>

**Table 2: Summary of Solicited Adverse Reactions Observed Within 10 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>Study D153-P501 &amp; AV006</th>
<th>Study MI-CP111</th>
</tr>
</thead>
<tbody>
<tr>
<td>FluMist Placebo</td>
<td>FluMist Active Control</td>
</tr>
<tr>
<td>N</td>
<td>876-1756</td>
</tr>
<tr>
<td></td>
<td>424-1034</td>
</tr>
<tr>
<td>headquartered</td>
<td>2108</td>
</tr>
<tr>
<td>FluMist Active Control</td>
<td>2170</td>
</tr>
<tr>
<td></td>
<td>2165</td>
</tr>
</tbody>
</table>

**Event**

**FluMist® Quadrivalent 2**

In clinical studies D153-P501 and AV006, unsolicited adverse reactions in children occurring in at least 1% of FluMist recipients and at a higher rate (≥ 1% rate difference after rounding) compared to placebo were abdominal pain (2% FluMist vs. 0% placebo) and otitis media (3% FluMist vs. 1% placebo). An additional adverse reaction identified in the active-controlled trial MI-CP111 occurring in at least 1% of FluMist recipients and at a higher rate (≥ 1% rate difference after rounding) compared to active control was sneezing (2% FluMist vs. 1% active control).

In a separate saline placebo-controlled trial (D153-P526) in a subset of older children and adolescents 9 through 17 years of age who received one dose of FluMist, the solicited adverse reactions as well as unsolicited adverse reactions reported were generally consistent with observations from the trials in Table 2. Abdominal pain was reported in 12% of FluMist recipients compared to 4% of placebo recipients and decreased activity was reported in 6% of FluMist recipients compared to 0% of placebo recipients. In Study AV018, in which FluMist was concomitantly administered with Measles, Mumps, and Rubella Virus Vaccine Live (MMR, manufactured by Merck & Co., Inc.) and Varicella Virus Vaccine Live (manufactured by Merck & Co., Inc.) to children 12 through 15 months of age, adverse reactions were similar to those seen in other clinical trials of FluMist.

**FluMist Quadrivalent in Children and Adolescents**

In the randomized, active-controlled Study MI-CP208 that compared FluMist Quadrivalent and FluMist in children and adolescents 2 through 17 years of age, the rates of solicited adverse reaction events were similar between subjects who received FluMist Quadrivalent and FluMist. Table 3 includes solicited adverse reactions post Dose 1 from Study MI-CP208 that either occurred at a higher rate (≥ 1% rate difference after rounding) in FluMist Quadrivalent recipients compared to FluMist recipients or were identified in previous FluMist clinical studies (see Table 2). In this study, solicited adverse reactions were documented for 14 days post vaccination. Solicited adverse reactions post-Dose 2 were observed at a lower frequency compared to those post Dose 1 for FluMist Quadrivalent and were similar between subjects who received FluMist Quadrivalent and FluMist.
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. 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 enrolment.

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

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

8. USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
FluMist Quadrivalent is not absorbed systemically following intranasal administration and maternal use is not expected to result in fetal exposure to the drug.

Clinical Considerations
Disease-Associated Maternal and/or Embryo/Fetal Risk: Pregnant women infected with seasonal influenza are at increased risk of severe illness associated with influenza infection compared with non-pregnant adults. Pregnant women who develop influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

Data
Animal Data: In a developmental and reproductive toxicity study, female rats were administered FluMist Quadrivalent either three times (during the period of organogenesis) or six times (prior to gestation and during the period of organogenesis), 200 microliter/occasion (approximately 150 human dose equivalents), by intranasal instillation revealing no evidence of impaired fertility or harm to the fetus due to FluMist Quadrivalent.

8.2 Lactation
Risk Summary
FluMist is not absorbed systemically by the mother following intranasal administration and breastfeeding is not expected to result in exposure of the child to FluMist Quadrivalent.

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 (14.1, 14.2)]. FluMist Quadrivalent is not approved for use in children younger than 24 months of age because use of FluMist in children under 24 months of age is 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 adverse events at a higher rate (≥ 1% rate difference after rounding) compared to nasal congestion (8% FluMist vs. 2% placebo) and sinusitis (4% FluMist vs. 2% placebo).

FluMist Quadrivalent in Adults
In the randomized, active-controlled Study MI-CP185 that compared FluMist Quadrivalent and FluMist in adults 18 through 49 years of age, the rates of solicited adverse reactions reported were generally similar between subjects who received FluMist Quadrivalent and FluMist. Table 4 presents solicited adverse reactions that either occurred at a higher rate (≥ 1% rate difference after rounding) in FluMist Quadrivalent recipients compared to FluMist recipients or were identified in Study MI-CP208.

8.9 Pregnancy
FluMist Quadrivalent is not absorbed systemically following intranasal administration and maternal use is not expected to result in fetal exposure to the drug.

**Table 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</th>
<th>FluMist Recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 1341-1377</td>
<td>N = 901-920</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>&gt; 100°F by any route</td>
<td>7</td>
</tr>
<tr>
<td>&gt; 100 - 101°F by any route</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 101 - 102°F by any route</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

8.10 Pediatric Use
FluMist Quadrivalent is not approved for use in children younger than 12 months of age because use of FluMist in children under 12 months of age is associated with increased risks of hospitalization and wheezing in clinical trials [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].

**Table 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</th>
<th>FluMist Recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 1197</td>
<td>N = 597</td>
</tr>
<tr>
<td>Runny Nose/Nasal Congestion</td>
<td>44</td>
<td>40</td>
</tr>
<tr>
<td>Headache</td>
<td>28</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>

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 (14.3)].

d Number of evaluable subjects for each event.

In Study MI-CP185, no unsolicited adverse reactions occurred at a higher rate (1% or greater) in FluMist Quadrivalent recipients compared to FluMist recipients.

**FluMist in Adults**
In adults 18 through 49 years of age in Study AV009, solicited adverse reactions occurring in at least 1% of FluMist recipients and at a higher rate (≥ 1% rate difference after rounding) compared to AF-SPG placebo include runny nose (44% FluMist vs. 2% AF-SPG), headache (40% FluMist vs. 38% placebo), sore throat (28% FluMist vs. 17% placebo), tiredness/weariness (26% FluMist vs. 22% placebo), muscle aches (17% FluMist vs. 15% placebo), cough (14 FluMist vs. 11% placebo), and chills (9% FluMist vs. 6% placebo).

In Study AV009, unsolicited adverse reactions occurring in at least 1% of FluMist recipients and at a higher rate (≥ 1% rate difference after rounding) compared to placebo were nasal congestion (8% FluMist vs. 2% placebo) and sinusitis (4% FluMist vs. 2% placebo).

**FluMist Quadrivalent in Adults**
In the randomized, active-controlled Study MI-CP185 that compared FluMist Quadrivalent and FluMist in adults 18 through 49 years of age, the rates of solicited adverse reactions reported were generally similar between subjects who received FluMist Quadrivalent and FluMist. Table 4 presents solicited adverse reactions that either occurred at a higher rate (≥ 1% rate difference after rounding) in FluMist Quadrivalent recipients compared to FluMist recipients or were identified in Study MI-CP208.
strains are subsequently blended and diluted as required to attain the desired potency with stabilizing buffers to produce the quadrivalent bulk vaccine. The bulk vaccine is then filled directly into individual sprayers for nasal administration.

Each pre-filled refrigerated FluMist Quadrivalent sprayer contains a single 0.2 mL dose. Each 0.2 mL dose contains 10<sup>6.0-7.2</sup> EID<sub>50</sub> (fluorescent focus units) of live attenuated influenza virus reagents of each of the four strains: A/Hawaii/68/2019 (H1N1) (an A/Guangdong-Moanxian/SWL1530/2019 (H1N1)pdm09-like virus), A/Switzerland/97/2011 (H3N2), B/Panama/2007/2011 (B/Yamagata lineage), and B/Massachusetts/02/2019 (B/Victoria lineage). Each 0.2 mL dose also contains 0.188 mg/mL monosodium glutamate, 2.00 mg/mL hydrolyzed porcine gelatin, 2.42 mg/mL ascorbic acid, 13.68 mg/mL sucrose, 2.26 mg/mL dibasic potassium phosphate, and 0.96 mg/mL monobasic potassium phosphate. Each dose contains residual amounts of sodium (≤ 0.024 mg/dose), and may also contain residual amounts of gentamicin sulfate (< 0.015 mcg/mL), and ethylenediaminetetraacetic acid (EDTA) (< 2.3 mcg/mL). FluMist Quadrivalent contains no preservatives.

The tip attached to the sprayer is equipped with a nozzle that produces a fine mist that is primarily of gentamicin sulfate (< 0.015 mcg/mL), and ethylenediaminetetraacetic acid (EDTA) (< 2.3 mcg/mL). FluMist Quadrivalent contains no preservatives.

The tip attached to the sprayer is equipped with a nozzle that produces a fine mist that is primarily of gentamicin sulfate (< 0.015 mcg/mL), and ethylenediaminetetraacetic acid (EDTA) (< 2.3 mcg/mL). FluMist Quadrivalent contains no preservatives.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Immune mechanisms conferring protection against influenza following receipt of FluMist Quadrivalent vaccine are not fully understood; serum antibodies, mucosal antibodies, and influenza-specific T cells may play a role.

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)].

12.2 Pharmacodynamics

Shedding Studies
Shedding of vaccine viruses within 28 days of vaccination with FluMist was evaluated in (1) multi-center Study MI-CP129 which enrolled healthy individuals 6 through 59 months of age (N = 200); and (2) multi-center Study FM026 which enrolled healthy individuals 5 through 49 years of age (N = 544). In each study, nasal wash specimens were collected daily for the first 7 days and every other day thereafter until Day 25 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>
<thead>
<tr>
<th>Age Group</th>
<th>Number of Subjects</th>
<th>% Shedding</th>
<th>Peak Titer</th>
<th>% Shedding After Day 11</th>
<th>Last Day of Positive Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-23 months&lt;sup&gt;a&lt;/sup&gt;</td>
<td>99</td>
<td>89</td>
<td>&lt;5 log&lt;sub&gt;10&lt;/sub&gt;</td>
<td>7.0</td>
<td>Day 23&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>24-59 months</td>
<td>100</td>
<td>69</td>
<td>&lt;1 log&lt;sub&gt;10&lt;/sub&gt;</td>
<td>1.0</td>
<td>Day 25&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5-8 years</td>
<td>102</td>
<td>50</td>
<td>&lt;2 log&lt;sub&gt;10&lt;/sub&gt;</td>
<td>2.9</td>
<td>Day 23&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>9-17 years</td>
<td>126</td>
<td>29</td>
<td>&lt;4 log&lt;sub&gt;10&lt;/sub&gt;</td>
<td>1.6</td>
<td>Day 28&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>18-49 years</td>
<td>115</td>
<td>20</td>
<td>&lt;3 log&lt;sub&gt;10&lt;/sub&gt;</td>
<td>0.9</td>
<td>Day 17&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> NCT00344036; see www.clinicaltrials.gov
<sup>b</sup> NCT01021432; see www.clinicaltrials.gov
<sup>c</sup> Proportion of subjects with detectable virus at any time point during the 28 days.

Frequency and duration of vaccine virus shedding in HIV-infected individuals were comparable to that seen in healthy children and adolescents 5 through 17 years of age in a randomized (1:1), cross-over, double-blind, AF-SPG placebo-controlled trial in 24 children and the effectiveness of FluMist in adults, and a comparison of post vaccination geometric mean titers (GMTs) of hemagglutination inhibition (HI) antibodies between individuals receiving FluMist and FluMist Quadrivalent. The clinical experience with FluMist is relevant to FluMist Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions [see Observations (12.2)].

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
FluMist Quadrivalent has not been evaluated for its carcinogenic or mutagenic potential or its potential to impair fertility.

14 CLINICAL STUDIES
The effectiveness of FluMist Quadrivalent is based on data demonstrating the clinical efficacy of FluMist in children and the effectiveness of FluMist in adults, and a comparison of post vaccination geometric mean titers (GMTs) of hemagglutination inhibition (HI) antibodies between individuals receiving FluMist and FluMist Quadrivalent. The clinical experience with FluMist is relevant to FluMist Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions [see Observations (12.2)].

14.1 Efficacy Studies of FluMist in Children and Adolescents
A multi-national, randomized, double-blind, active-controlled trial (MI-CP111) was performed to assess the efficacy of FluMist compared to an intramuscularly administered, inactivated Influenza Virus Vaccine manufactured by Sanofi Pasteur Inc. (active control) in children 6 months to 5 years of age during the 2004-2005 influenza season. 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 3936 were randomized to active control. Children who previously received an influenza vaccine received a single dose of study vaccine, while those who never previously received an influenza vaccination (or had an unknown history of influenza vaccination) received two doses. Participants were then followed through the influenza season to determine if they were infected 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 day.

In the primary efficacy analysis, FluMist demonstrated a 44.5% (95% CI: 22.4, 60.6) reduction in influenza rate compared to active control as measured by culture-confirmed modified CDC-ILI caused by wild-type strains antigenically similar to those contained in the vaccine. See Table 6 for a description of the results by strain and antigenic similarity.

<table>
<thead>
<tr>
<th>Strain</th>
<th># of Cases</th>
<th>Rate (cases/N)</th>
<th># of Cases</th>
<th>Rate (cases/N)</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matched Strains</td>
<td>3916</td>
<td>53</td>
<td>1.4%</td>
<td>3936</td>
<td>93</td>
</tr>
<tr>
<td>A/H1N1</td>
<td>3916</td>
<td>0</td>
<td>0.0%</td>
<td>3936</td>
<td>0</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>3916</td>
<td>0</td>
<td>0.0%</td>
<td>3936</td>
<td>7</td>
</tr>
<tr>
<td>B</td>
<td>3916</td>
<td>50</td>
<td>1.3%</td>
<td>3936</td>
<td>67</td>
</tr>
<tr>
<td>A/H1N1</td>
<td>3916</td>
<td>102</td>
<td>2.6%</td>
<td>3936</td>
<td>245</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>3916</td>
<td>0</td>
<td>0.0%</td>
<td>3936</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>3916</td>
<td>37</td>
<td>0.9%</td>
<td>3936</td>
<td>178</td>
</tr>
<tr>
<td>A/H1N1</td>
<td>3916</td>
<td>66</td>
<td>1.7%</td>
<td>3936</td>
<td>71</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>3916</td>
<td>0.3%</td>
<td>3936</td>
<td>0.8%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

In the primary efficacy analysis, FluMist demonstrated a 44.5% (95% CI: 22.4, 60.6) reduction in influenza rate compared to active control as measured by culture-confirmed modified CDC-ILI caused by wild-type strains antigenically similar to those contained in the vaccine. See Table 6 for a description of the results by strain and antigenic similarity.

14.2 Efficacy Studies of FluMist in Adults
A modified CDC-ILI was defined as fever (temperature ≥100°F oral or equivalent) plus cough, sore throat, or runny nose/nasal congestion on the same day.

In the primary efficacy analysis, FluMist demonstrated a 44.5% (95% CI: 22.4, 60.6) reduction in influenza rate compared to active control as measured by culture-confirmed modified CDC-ILI caused by wild-type strains antigenically similar to those contained in the vaccine. See Table 6 for a description of the results by strain and antigenic similarity.

A single dose of study vaccine was given to each participant. 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 3936 were randomized to active control. Children who previously received an influenza vaccine received a single dose of study vaccine, while those who never previously received an influenza vaccination (or had an unknown history of influenza vaccination) received two doses. Participants were then followed through the influenza season to determine if they were infected 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 day.

In the primary efficacy analysis, FluMist demonstrated a 44.5% (95% CI: 22.4, 60.6) reduction in influenza rate compared to active control as measured by culture-confirmed modified CDC-ILI caused by wild-type strains antigenically similar to those contained in the vaccine. See Table 6 for a description of the results by strain and antigenic similarity.
Study AV006 was a multicenter, randomized, double-blind, AF-SPG placebo-controlled trial performed in U.S. children <18 years of age with high-risk medical conditions to evaluate the effectiveness of FluMist against culture-confirmed influenza virus during the 7-Week Site-Specific Outbreak Period (Study AV009). Effective protection was not demonstrated in a single dose of vaccine. During the second year, the primary circulating strain was the A/Sydney/05/97 H3N2 strain, which was antigenically dissimilar from the H3N2 strain represented in AV006 and received a single dose of FluMist or placebo. During the second year, the primary circulating strain was the A/Sydney/05/97 (H3N2), an antigenic variant not in the vaccine. A multi-center, randomized, double-blind, active-controlled, non-inferiority study (MI-CP185) was performed to assess the safety and immunogenicity of FluMist Quadrivalent compared to those of FluMist (active control) in adults 18 through 49 years of age. A total of 1800 subjects were randomized by site at a 1:1 ratio to receive either 1 dose of FluMist Quadrivalent or 1 dose of 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). Immunogenicity in Study MI-CP185 was evaluated by comparing the 3 strain-specific serum hemagglutination inhibition (HAI) antibody geometric mean titers (GMTs) post dosing and providing evidence that the addition of the second B strain did not result in immune interference to other strains included in the vaccine.

### Table 7: Efficacy of FluMist vs. Placebo Against Culture-Confirmed Influenza Illness Due to Antigenically Matched Wild-Type Strains (Studies D153-P501 & AV006, Year 1)

<table>
<thead>
<tr>
<th>Strain</th>
<th>FluMist Placebo</th>
<th>% Efficacy (95% CI)</th>
<th>FluMist Placebo</th>
<th>% Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any strain</td>
<td>N = 1653</td>
<td>N = 1111</td>
<td>N = 849</td>
<td>N = 410</td>
</tr>
<tr>
<td>Total</td>
<td>56 (3.4%)</td>
<td>139 (12.5%)</td>
<td>10 (1%)</td>
<td>73 (18%)</td>
</tr>
<tr>
<td>A/H1N1</td>
<td>23 (1.4%)</td>
<td>81 (7.3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>4 (0.2%)</td>
<td>27 (2.4%)</td>
<td>4 (0.5%)</td>
<td>48 (12%)</td>
</tr>
<tr>
<td>B</td>
<td>29 (1.8%)</td>
<td>35 (3.2%)</td>
<td>6 (0.7%)</td>
<td>31 (7%)</td>
</tr>
</tbody>
</table>

\* D153-P501 and AV006 data are for subjects who received two doses of vaccine. 

\*a In children 12 through 15 months of age. 

\*b In children 15 through 71 months of age. 

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

### 14.2 Immune Response Study of FluMist Quadrivalent in Children and Adolescents

A multicenter, randomized, double-blind, active-controlled, non-inferiority study (MI-CP208) 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). Children 2 through 8 years of age received 2 doses of vaccine approximately 30 days apart; children 9 years of age and older received 1 dose. For children 2 through 8 years of age with a history of influenza vaccination, immunogenicity assessments were performed prior to vaccination and at 28 days after the second dose. For children 9 years of age and older, immunogenicity assessments were performed prior to vaccination and at 28 days post vaccination. Immunogenicity was evaluated by comparing the 3 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.

### Table 8: Effectiveness of FluMist to Prevent Febrile Illness in Adults 18 through 49 Years of Age During the 7-Week Site-Specific Outbreak Period (Study AV009)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>FluMist Placebo</th>
<th>% Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any febrile illness</td>
<td>331 (13.73)</td>
<td>189 (15.42)</td>
</tr>
<tr>
<td>Secondary Endpoints:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe febrile illness</td>
<td>250 (10.37)</td>
<td>158 (12.89)</td>
</tr>
<tr>
<td>Febrile upper respiratory illness</td>
<td>213 (8.83)</td>
<td>142 (11.58)</td>
</tr>
</tbody>
</table>

\*a Number of evaluable subjects (92.7% and 93.0% of FluMist and placebo recipients, respectively). 

\*b The predominantly circulating virus during the trial period was A/Sydney/05/97 (H3N2), an antigenic variant not included in the vaccine.
FluMist® Quadrivalent

Information for Patients and Their Caregivers

FluMist® Quadrivalent (pronounced FLEW-mist Kwä-drä-VÄ-lent)
(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 under 2 years old have an increased risk of wheezing (difficulty with breathing) after getting FluMist Quadrivalent.

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°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°F (2-8°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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Manufactured by:
MedImmune, LLC
Gaithersburg, MD 20878

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