FluMist® Quadrivalent (Influenza Vaccine Live, Intranasal)

Intranasal Spray

2019-2020 Formula
Initial U.S. Approval: 2003

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INDICATIONS AND USAGE

FluMist Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtypes 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)

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DOSAGE AND ADMINISTRATION

For intranasal administration by a healthcare provider. (2)

Age | Dose | Schedule
--- | --- | ---
2 years through 8 years | 1 or 2 doses<sup>a</sup>, 0.2 mL<sup>b</sup> each | If 2 doses, administer at least 1 month apart
9 years through 49 years | 1 dose, 0.2 mL<sup>b</sup> | -

<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.

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DOSE FORMS AND STRENGTHS

Each 0.2 mL dose is a suspension supplied in a single-dose pre-filled intranasal sprayer. (3)

- Concomitant aspirin therapy in children and adolescents. (4, 11)

- Concomitant aspirin therapy and Reye's Syndrome in Children and Adolescents

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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, 11)

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WARNINGS AND PRECAUTIONS

- 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). (5.1)

- 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 the administration of FluMist Quadrivalent. (5.2)

- 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)

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ADVERSE REACTIONS

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.

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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. (7.2)

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PATIENT COUNSELING INFORMATION

- 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). (5.1)

- 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 the administration of FluMist Quadrivalent. (5.2)

- 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)

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DRUG INTERACTIONS

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)

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

Revised: 9/2019

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FULL PRESCRIBING INFORMATION

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 (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:

Age | Dose | Schedule
--- | --- | ---
2 years through 8 years | 1 or 2 doses<sup>a</sup>, 0.2 mL<sup>b</sup> each | If 2 doses, administer at least 1 month apart
9 years through 49 years | 1 dose, 0.2 mL<sup>b</sup> | -

<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).

Figure 1

1. Check expiration date. Product must be used before the date on sprayer label.

2. Remove rubber tip protector. Do not remove dose-divider clip at the other end of the sprayer.

3. With the patient in an upright position, place the tip just inside the nostril to ensure the vaccine is delivered into the nose.

4. Place the tip just inside the other nostril and with a single motion, depress plunger as rapidly as possible to deliver remaining vaccine.

5. With a single motion, depress plunger as rapidly as possible until the dose-divider clip prevents you from going further.

6. Pinch and remove the dose-divider clip from plunger.

7. Remove rubber tip protector. Do not remove dose-divider clip at the other end of the sprayer.

8. Do not inject. Do not use a needle.

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

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REFERENCES

14.1 Efficacy Studies of FluMist in Children and Adolescents

14.2 Immune Response Study of FluMist Quadrivalent in Children and Adolescents

14.3 Effectiveness Study of FluMist in Adults

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FULL PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FLUMIST® QUADRIVALENT safely and effectively. See full prescribing information for FLUMIST® QUADRIVALENT.
3 DOSE 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 Reye’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 Reye’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 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 Immune Competence
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 7 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 Adult FluMist containing Sucrose-Phosphate-Glutamate (AP-SG) 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 through 23 months of age, 50% were female; in the study of adults, 55% were female. In MI-CP111, AV006, D153-P526, AV019, and AV009, subjects were White (71%), Hispanic (11%), Asian (7%), Black (6%), and Other (5%), while in D153-P501, 99% of subjects were Asian.

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 (71%), Hispanic (11%), Asian (7%), Black (6%), and Other (5%); 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 = 6473, 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 180 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>Hospitalizations¹</td>
<td>6-23 months</td>
<td>4.2% (84/2002)</td>
<td>3.2% (63/1975)</td>
</tr>
<tr>
<td></td>
<td>24-59 months</td>
<td>2.1% (46/2187)</td>
<td>2.5% (56/2198)</td>
</tr>
<tr>
<td>Wheezing²</td>
<td>6-23 months</td>
<td>5.9% (117/1992)</td>
<td>3.8% (75/1975)</td>
</tr>
<tr>
<td></td>
<td>24-59 months</td>
<td>2.1% (47/2187)</td>
<td>2.5% (56/2198)</td>
</tr>
</tbody>
</table>

¹ NCT0128167; see www.clinicaltrials.gov
² Inactivated Influenza Virus Vaccine manufactured by Sanofi Pasteur Inc., administered intramuscularly.
³ Hospitalization due to any cause from randomization through 180 days post last vaccination.
⁴ Wheezing requiring bronchodilator therapy or accompanied by respiratory distress or hypoxia evaluated from randomization through 42 days post last vaccination.

Most hospitalizations observed were due to gastrointestinal and respiratory tract infections and occurred mainly in children 6 through 23 months of age. In children younger than 2 months 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 2 shows pooled solicited adverse reactions occurring in at least 1% of FluMist recipients and at a higher rate (>1% rate difference after rounding) compared to placebo post Dose 1 for Studies D153-P501 and AV006, and solicited adverse reactions post Dose 1 for Study MI-CP111. Solicited adverse reactions were those about which parents/guardians were specifically queried after receipt of FluMist, placebo, or control vaccine. In these studies, solicited reactions were documented for 10 days post vaccination. Solicited reactions following the second dose of FluMist were similar to those following the first dose and were generally observed at a lower frequency.

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</th>
<th>Placebo</th>
<th>Active Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>FluMist Placebo</td>
<td>N = 876-1758a</td>
<td>N = 424-1034a</td>
<td>N = 2170b</td>
</tr>
<tr>
<td>FluMist Active Control</td>
<td>N = 2165c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FluMist Placebo</td>
<td>FluMist</td>
<td>Placebo</td>
<td>Active Control</td>
</tr>
<tr>
<td>Fever</td>
<td>1.0%</td>
<td>0.6%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Sore Throat</td>
<td>2.1%</td>
<td>2.0%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Muscle Aches</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Chills</td>
<td>0.3%</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Weekend Fever</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Zero days Fever</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Fever</td>
<td>100°F Oral</td>
<td>101°F Oral</td>
<td>102°F Oral</td>
</tr>
<tr>
<td>Fever</td>
<td>100°F Oral</td>
<td>101°F Oral</td>
<td>102°F Oral</td>
</tr>
</tbody>
</table>

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 of 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 recipients.

FluMist Quadrivalent in Children and Adolescents

In the randomized, active-controlled 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.
Table 3: Summary of Solicited Adverse Reactionsa Observed Within 14 Days after Dose 1 for FluMist Quadrivalent and FluMist Recipients in Study MI-CP208b in Children and Adolescents 2 through 17 Years of Age

<table>
<thead>
<tr>
<th>Event</th>
<th>FluMist Quadrivalent</th>
<th>FluMistc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 1341-1377a</td>
<td>N = 901-920b</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 - ≤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>

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 Reproduced or adopted from the FluMist study arms (see Clinical Studies [14.2]).

d Number of evaluable subjects for each event.

In Study MI-CP208, no unsolicited adverse reactions occurred at a higher rate (1% or greater) in FluMist Quadrivalent recipients compared to FluMist recipients.

Table 4: Summary of Solicited Adverse Reactionsa Observed Within 14 Days after Dose 1 for FluMist Quadrivalent and FluMist Recipients in Study MI-CP185b in Adults 18 through 49 Years of Age

<table>
<thead>
<tr>
<th>Event</th>
<th>FluMist Quadrivalent</th>
<th>FluMistc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 1197a</td>
<td>N = 597b</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 Study MI-CP09. 

b NCT00880067; see www.clinicaltrials.gov

c Reproduced or adopted from the FluMist study arms (see Clinical Studies [14.4]).

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.

### 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: Péricarditis

Congenital, familial, and genetic disorders: Exacerbation of symptoms of mitochondrial encephalomyopathy (Leigh syndrome)

Gastrointestinal disorders: Nausea, vomiting, diarrhea

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

Nervous system disorders: Guillain–Barré syndrome, Bell’s Palsy, meningitis, eosinophilic meningitis, vaccine-associated encephalitis

Respiratory, thoracic, and mediastinal disorders: Epistaxis

Skin and subcutaneous tissue disorders: Rash

### 7 DRUG INTERACTIONS

#### 7.1 Aspirin Therapy

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 [4.2]). 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 enrolment.

#### 7.4 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.

### 7.5 Intranasal Products

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

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

### 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.

#### 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 of use of FluMist in children 24 through 59 months of age who received FluMist Quadrivalent during the 2017-2018 influenza season and had increased rates 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 occurred in 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 vaccine vaccine for administration by intranasal spray. FluMist Quadrivalent contains four virus vaccine strains: an A/CA/Strain, an H3N2 strain and two B strains. FluMist Quadrivalent contains B strains from both the B/Yamagata/16/88 and the B/Victoria/2/87 lineages. FluMist Quadrivalent is manufactured according to the same process as FluMist. The influenza virus strains in FluMist Quadrivalent 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 30°C (Type B strains) or 35°C (Type A strains), temperatures at which many wild-type influenza viruses grow efficiently); and (c) attenuated (att) (i.e., they do not produce classic influenza-like illness in the ferret model of human influenza infection).

No evidence of reversion has been observed in the recovered vaccine strains that have been tested (135 of possible 250 recovered isolates) using FluMist (see Clinical Pharmacology [12.2]). For each of the four representative strains in FluMist Quadrivalent, 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. Thus, the four viruses contained in FluMist Quadrivalent maintain the replication characteristics and phenotypic properties of the MDVs and express the HA and NA of wild-type viruses. For the Type A MDV, at least five genetic loci in three different internal gene segments contribute to the ha and na phenotype. For the Type B MDV, at least three genetic loci in two different internal gene segments contribute to both the ts and att properties; five genetic loci in three gene segments control the ca property.

Each of the reassortant strains in FluMist Quadrivalent express the HA and NA of wild-type viruses that are related to strains expected to circulate during the 2019-2020 influenza season. Three of the viruses (A/H1N1, A/CA/Strain, and one B strain) have been recommended by the United States Public Health Service (USPHS) for inclusion in the annual trivalent and quadrivalent influenza vaccine formulations. An additional B strain has been recommended by the USPHS for inclusion in the quadrivalent influenza vaccine formulation.

Specific pathogen-free (SPF) eggs are inoculated with each of the reassortant strains and incubated to allow virus vaccine replication. The allantoic fluid of these eggs is harvested, pooled, and then clarified by filtration. The virus is concentrated by ultra centrifugation and diluted with stabilizing buffer to contain the final sucrose and potassium phosphate concentrations. 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 four...
Day 100 69

FluMist recipients. 

is clear to slightly cloudy. The tip attached to the sprayer is equipped with a nozzle that produces a fine mist that is primarily gentamicin sulfate (< 0.015 mcg/mL), and ethylenediaminetetraacetic acid (EDTA) (< 2.3 mcg/dose). FluMist 2.00 mg/dose hydrolyzed porcine gelatin, 2.42 mg/dose arginine, 13.68 mg/dose sucrose, 2.26 mg/dose dibasic potassium phosphate, and 0.96 mg/dose monobasic potassium phosphate. Each dose contains residual amounts of ovalbumin (< 0.024 mcg/dose), and may also contain residual amounts of gentamicin sulfate (< 0.015 mcg/mL), and ethylenediaminetetraacetic acid (EDTA) (< 2.5 mcg/dose). FluMist Quadrivalent contains no preservatives.

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

A single subject who did not shed previously; TCID50

A single subject who shed previously on Days 1-3; TCID50

a NCT00344305; see www.clinicaltrials.gov

b NCT01201421; see www.clinicaltrials.gov

c Proportion of subjects with detectable virus at any time point during the 28 days.

d Peak titer at any time point during the 28 days among samples positive for a single vaccine virus.

e FluMist and FluMist Quadrivalent are not approved for use in children younger than 24 months of age [see Adverse Reactions (6.1)].

f 100.4°F rectal or 99.5°F axillary), wheezing, shortness of breath, pulmonary congestion, pneumonia, or otitis media; or two of the following: runny nose/nasal congestion, muscle aches, chills, headache, irritability, decreased activity, or vomiting. 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 7 for a description of the results.

The antibody response was calculated using the following formula:

\[ 	ext{Peak Titer} = \frac{\text{Log}_{10} \text{TCID}_{50} \text{mL}^{-1}}{2} \]
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 over two successive seasons (1999-1997 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 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, 1629 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 DI13-P501a & AV006, Year 1)

<table>
<thead>
<tr>
<th>Strain</th>
<th>FluMist n (%)</th>
<th>Placebo n (%)</th>
<th>% Efficacy (95% CI)</th>
<th>FluMist n (%)</th>
<th>Placebo n (%)</th>
<th>% Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any strain</td>
<td>1563</td>
<td>1111</td>
<td>110</td>
<td>1101</td>
<td>849</td>
<td>110</td>
</tr>
<tr>
<td>A/H1N1</td>
<td>139 (12.5%)</td>
<td>101 (11%)</td>
<td>72.9%</td>
<td>82 (8.0%)</td>
<td>69 (8.5%)</td>
<td>93.4%</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>81 (7.3%)</td>
<td>56 (6.4%)</td>
<td>23.1%</td>
<td>78 (9.0%)</td>
<td>66 (8.4%)</td>
<td>78.6%</td>
</tr>
<tr>
<td>B</td>
<td>43 (3.8%)</td>
<td>36 (4.1%)</td>
<td>36.9%</td>
<td>45 (5.2%)</td>
<td>36 (4.1%)</td>
<td>25.0%</td>
</tr>
</tbody>
</table>

* a DI13-P501 and AV006 data are for subjects who received two doses of vaccine. 

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 1:1 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 and 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 4 strain-specific serum hemagglutination inhibition (HAI) antibody geometric mean titers (GMTs) post dose and providing evidence that the addition of the second B strain did not result in immune interference to other strains included in the vaccine.

14.3 Effectiveness Study of FluMist in Adults

AV009 was a U.S. multi-center, randomized, double-blind, AF-SPG placebo-controlled trial to evaluate effectiveness of FluMist in adults 18 through 64 years of age without high-risk medical conditions over the 1997-1998 influenza season. Participants were randomized 2:1 (vaccine:placebo). Cultures for influenza virus were not obtained from subjects in the trial, thus efficacy against culture-confirmed influenza was not assessed. The A/WSan Francisco/39/97 (H3N2) strain, which was contained in FluMist, was antigenically distinct from the predominant circulating strain of influenza virus during the trial period, A/Sydney/5/97 (H3N2). Type A/Wuhan (H3N2) and Type B strains also circulated in the U.S. during the study period. The primary endpoint of the trial was defined as any febrile illness, and prospective secondary endpoints were severe febrile illness and febrile upper respiratory illness. Effectiveness for any of the three endpoints was not demonstrated in a subgroup of adults 50 through 64 years of age. Primary and secondary effectiveness endpoints from the age group 18 through 49 years are presented in Table 8. Effectiveness was not demonstrated for the primary endpoint in adults 18 through 49 years of age.

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 N = 2111</th>
<th>Placebo N = 2126</th>
<th>Percent Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any febrile illness</td>
<td>331 (15.7%)</td>
<td>189 (11.1%)</td>
<td>53.3% (-5.1, 75.8)</td>
</tr>
<tr>
<td>Severe febrile illness</td>
<td>250 (10.3%)</td>
<td>158 (7.5%)</td>
<td>26.3% (6.6, 45.0)</td>
</tr>
<tr>
<td>Febrile upper respiratory illness</td>
<td>213 (8.8%)</td>
<td>145 (6.8%)</td>
<td>32.9% (5.7, 50.1)</td>
</tr>
</tbody>
</table>

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

14.4 Immune Response Study of FluMist Quadrivalent in Adults

A multicenter, randomized, double-blind, active-controlled, and 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 3:1 ratio to receive 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 4 strain-specific serum hemagglutination inhibition (HAI) antibody geometric mean titers (GMTs) post dose and providing evidence that the addition of the second B strain did not result in immune interference to other strains included in the vaccine.

14.5 Concomitantly Administered Live Virus Vaccines

In Study AV108, concomitant administration of FluMist, MMR (manufactured by Merck & Co., Inc.) and Varicella Virus Vaccine Live (manufactured by Merck & Co., Inc.) was studied in 1245 subjects 12 through 18 years of age. Subjects were randomized in a 1:1:1 ratio to MMR, Varicella vaccine and FluMist (group 1); FluMist alone (group 2). Immunogenic responses to MMR and Varicella vaccines were evaluated 6 weeks post-vaccination while the immune responses to FluMist were evaluated 4 weeks after the second dose. No evidence of interference with immune response to measles, mumps, rubella, varicella and FluMist vaccines was observed.

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 sprayer is not made with natural rubber latex.

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) UPON RECEIPT. THE PRODUCT MUST BE USED BEFORE THE EXPIRATION DATE ON THE SPRAYER LABEL. DO NOT FREEZE.

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

17 PATIENT COUNSELING INFORMATION

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

Inform 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 vaccine or their parent/guardian if the vaccinee has asthma. For children younger than 5 years of age, also ask 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

Advise 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.

FluMist® is a registered trademark of MedImmune, LLC.

Manufactured by: MedImmune, LLC
Galtersburg, MD 20878
1-877-633-4411

U.S. Government License No. 1799
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RAL-FLUQV8
Information for Patients and Their Caregivers

FluMist® Quadrivalent (pronounced FLEW-mist Kwä-drə-VĀ-lənt) (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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MedImmune

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