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 FORMS AND STRENGTHS**

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

**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)
- Concomitant use of antiviral agents 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)
- In clinical trials, children under 6 months of age who received FluMist were associated with an increased risk of hospitalization and wheezing. (8.4)

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

**USE IN SPECIFIC POPULATIONS**

- 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)

**WARNINGS AND PRECAUTIONS**

- The most common solicited adverse reactions (> 10% in vaccine recipients and at least 5% greater than 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.

**REFERENCES**

- Asthma, Recurrent Wheezing, and Active Wheezing
- Guillain-Barré Syndrome
- Medical Conditions Predisposing to Influenza Complications
- Management of Acute Allergic Reactions
- Allergic Reactions
- Severe Anaphylaxis
- Concomitant Aspirin Therapy and Reye’s Syndrome in Children and Adolescents
- Risks of Hospitalization and Wheezing in Children Younger than 24 Months of Age
- Asthma, Recurrent Wheezing, and Active Wheezing
- Guillain-Barré Syndrome
- Altered Immunocompetence
- Medical Conditions Predisposing to Influenza Complications
- Management of Acute Allergic Reactions
- Limitations of Vaccine Effectiveness
- Adverse Reactions
- Clinical Trials Experience
- Postmarketing Experience
- Drug Interactions
- Aspirin Therapy
- Antiviral Agents Against Influenza A and/or B
- Concomitant Administration with Inactivated Vaccines
- Concomitant Administration with Other Live Vaccines
- Intranasal Products
- Pregnancy
- Lactation
- Pediatric Use
- Geriatric Use
- Pregnancy
- Lactation
- Pediatric Use
- Geriatric Use
- Efficacy Studies of FluMist in Children and Adolescents
- Immune Response Study of FluMist Quadrivalent in Children and Adolescents
- Effectiveness Study of FluMist in Adults
- Immune Response Study of FluMist Quadrivalent in Adults
- Concomitantly Administered Live Virus Vaccines

**FULL PRESCRIBING INFORMATION: CONTENTS**

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.**

<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*, 0.2 mL 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*</td>
<td>-</td>
</tr>
</tbody>
</table>

* 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.

**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. The sprayer must be used before the date on the sprayer label.
2. With a single motion, depress plunger as rapidly as possible until the dose-divider clip prevents you from going further.
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. Pinch and remove dose-divider clip at the other end of the sprayer.
5. Remove rubber tip protector. Do not remove dose-divider clip at the other end of the sprayer.
6. Place the tip just inside the other nostril and with a single motion, depress plunger as rapidly as possible to deliver remaining vaccine.

**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)

**ADVERSE REACTIONS**

The most common solicited adverse reactions (> 10% in vaccine recipients and at least 5% greater than 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.

**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)

**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: 8/2022
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</th>
<th>Active Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6-23 months</td>
<td>24-59 months</td>
<td>6-23 months</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>4% (42/1049)</td>
<td>2.1% (46/2187)</td>
<td>3.2% (32/997)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>5.9% (117/1992)</td>
<td>2.1% (47/2187)</td>
<td>3.8% (75/1997)</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 N = 676-1758</th>
<th>Placebo N = 424-1034</th>
<th>Active Control N = 2170</th>
<th>N &lt; 2155</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 100°F Oral</td>
<td>16/11</td>
<td>13/11</td>
<td>11/11</td>
<td></td>
</tr>
<tr>
<td>&gt; 100 - &lt; 101°F Oral</td>
<td>9/6</td>
<td>6/8</td>
<td>8/3</td>
<td></td>
</tr>
<tr>
<td>&gt; 101 - &lt; 102°F Oral</td>
<td>4/3</td>
<td>4/3</td>
<td>4/3</td>
<td></td>
</tr>
</tbody>
</table>

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 Reyè'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 Reyè's syndrome with aspirin and wide-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. 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 wide-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 AV003 [3 used Alternate FluMist 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 42 months of age, 50% were female; in the study of adults, 55% were female. In MI-CP111, AV006, D153-P526, AV019, and AV003, subjects were White (71%), Hispanic (11%), Asian (7%), Black (6%), and Other (5%); 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 American-African (15%), and Other (7%); overall, 22% were Hispanic or Latino.

FluMist® Quadrivalent

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. Inchildren with 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.

Adverse events from randomized, active-controlled studies MI-CP208 that either occurred at a higher rate (≥1% rate difference after rounding) compared to placebo or at a lower rate (≥1% rate difference after rounding) compared to placebo were as follows: FEVER: 1% rate difference after rounding)

Adverse events from randomized, active-controlled studies MI-CP185 that either occurred at a higher rate (≥1% rate difference after rounding) compared to placebo or at a lower rate (≥1% rate difference after rounding) were:

- FEVER: 1% rate difference after rounding)

Adverse events from randomized, active-controlled studies MI-CP111 that either occurred at a higher rate (≥1% rate difference after rounding) compared to placebo or at a lower rate (≥1% rate difference after rounding) were:

- FEVER: 1% rate difference after rounding)

Adverse events from randomized, active-controlled studies MI-CP111 that either occurred at a higher rate (≥1% rate difference after rounding) compared to placebo or at a lower rate (≥1% rate difference after rounding) were:

- FEVER: 1% rate difference after rounding)

Adverse events from randomized, active-controlled studies MI-CP111 that either occurred at a higher rate (≥1% rate difference after rounding) compared to placebo or at a lower rate (≥1% rate difference after rounding) were:

- FEVER: 1% rate difference after rounding)
FluMist® Quadrivalent

3

Table 3: Summary of Solicited Adverse Reactions* Observed Within 14 Days after Dose 1 for FluMist Quadrivalent and FluMist Recipients in Study MI-CP208 b in Children and Adolescents 2 through 17 Years of Age

<table>
<thead>
<tr>
<th>Event</th>
<th>FluMist Quadrivalent</th>
<th>FluMist b</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1341-1377</td>
<td>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></td>
<td></td>
</tr>
<tr>
<td>&gt; 110°F by any route</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>100°F – &lt; 110°F by any route</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>&lt; 100°F by any route</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

* 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).

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 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 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 influenza vaccination 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 women. Pregnant women with influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

Data

Oropharyngeal 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/rat/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.

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 worsening 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 quadrivalent vaccine administered by intranasal spray. FluMist Quadrivalent contains four virus vaccine 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/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 29°C, a temperature that is restrictive for replication of many wild-type influenza viruses); (b) temperature-sensitive (ts) (i.e., they are restricted in replication at 37°C [Type B strains] or 39°C [Type A strains], temperatures at which many wild-type influenza viruses grow efficiently); and (c) attenuated (att) (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 (12.5)]. For each of the four recombinant influenza A virus segments 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 MDV as well as of wild-type viruses. For the Type A MDV, at least five genetic loci in three different internal gene segments contribute to both the ca and att phenotypes. For the Type B MDV, at least three genetic loci in two different internal gene segments contribute to both the ca 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 2002-2003 influenza season. Three of the viruses (A/H1N1, A/H3N2 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 replication. The allantoic fluid of these eggs is harvested, pooled, and then clarified by filtration. The virus is concentrated by ultracentrifugation and diluted with stabilizing buffer to obtain the final sucrose and potassium phosphate concentrations. 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 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 10^6.75 FFU (fluorescent focus units) of live attenuated virus vaccine reagents of each of the four strains: A/Victoria/1/2002 (H1N1) (an A/Victoria/250/2019 (H1N1)pdm09 - like virus), A/Norway/16608/2021 (H3N2) (an A/Darwin/B/2021 (H3N2) - like virus), B/Panama/4320/2010 (B/Victoria) lineage, and B/Lean/1534/2021 (B/Victoria lineage). Each 0.2 mL dose also contains 0.188 mg/moide monosodium glutamate, 2.00 mg/moide hydroxylated porcine gelatin, 2.42 mg/moide arginine, 13.68 mg/moide sucrose, 2.26 mg/moide d Jabatic potassium phosphate, and 0.96 mg/moide monobasic potassium phosphate. Each dose contains residual amounts of ovalbumin (< 0.024 mg/moide), and may also contain residual amounts of gentamicin sulfate (< 0.015 mcg/mL), and ethylenediaminetetraacetic acid (EDTA) (≤ 2.3 mg/moide) FluMist Quadrivalent sprayer does not contain any preservatives.

The tip attached to the sprayer is equipped with a nozzle that produces a fine mist that is primarily colorless to pale yellow suspension and is clear to slightly cloudy.

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) a multi-center Study MI-CP129 which enrolled healthy individuals 6 through 59 years of age (N = 200); and (2) multi-center 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 through either Day 25 and Day 28 or Day 25 and Day 28 in Study MI-CP129, individuals with a positive shedding sample at Day 25 or Day 28 were to have additional nasal swab collections 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 Child/Adult</th>
<th>Number of Subjects</th>
<th>% Shedding</th>
<th>Peak Titer</th>
<th>% Shedding After Day 11</th>
<th>Day of Last Positive Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-23 months</td>
<td>99</td>
<td>89</td>
<td>&lt; 10^10</td>
<td>7.0</td>
<td>Day 23^2</td>
</tr>
<tr>
<td>24-59 months</td>
<td>100</td>
<td>69</td>
<td>&lt; 10^10</td>
<td>6.0</td>
<td>Day 25^1</td>
</tr>
<tr>
<td>5-8 years</td>
<td>102</td>
<td>50</td>
<td>&lt; 10^10</td>
<td>3.0</td>
<td>Day 29^1</td>
</tr>
<tr>
<td>9-12 years</td>
<td>102</td>
<td>28</td>
<td>&lt; 10^10</td>
<td>1.6</td>
<td>Day 22^1</td>
</tr>
<tr>
<td>13-18 years</td>
<td>115</td>
<td>20</td>
<td>&lt; 10^10</td>
<td>0.9</td>
<td>Day 17</td>
</tr>
</tbody>
</table>

^a NTCTest044365; see www.clinicaltrials.gov
^b NTCTest019140; see www.clinicaltrials.gov
^c Proportion of subjects with detectable virus at any time point during the 28-day shedding period.
^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 (1.1)].

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 TCID50/mL.

Study MI-CP129

Safety and shedding of vaccine virus following FluMist administration were evaluated in 28 HIV-infected adult subjects [median CD4 cell count of 451 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 Study MI-CP129. At the end of Study MI-CP129, 128 vaccinated children aged 6 months through 5 years of age were enrolled. Children aged 6 months through 5 years of age were randomized to receive one dose of FluMist (N = 38) or AF-SPS placebo (N = 99). Virus shedding was evaluated for 21 days by culture of nasal swab specimens. Wild-type A (A/H3N2) influenza virus was documented to have circulated 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 80% of FluMist recipients. Ten vaccine strains isolated at the local laboratory. Ten influenza isolates (5 influenza A, 1 influenza B) were cultured from a total of seven placebo subjects. One influenza B virus strain had Type B influenza virus confirmed as a transmitted vaccine virus by a FluMist recipient in the same playgroup. This Type B isolate retained the ca ts, and art 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/ Paname (H3N2). The remaining isolates could not be further characterized.

A single transmission event (isolation of the Type B vaccine strain), the probability of a young child acquiring vaccine virus following close contact with a FluMist vaccinee in this daily setting was 0.58% (95% CI: 0.1, 1.7) based on the Reed-Frost model. With documented transmission of one Type B in one placebo subject and possible transmission of Type A viruses in four placebo subjects, the probability of acquiring a transmitted vaccine virus was estimated to be 2.4% (95% CI: 0.13, 4.6) using the Reed-Frost model.

13 NONCLINICAL TOXICITY

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 STUDY

The clinical 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 Description (11)].

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 immune response and safety of one dose of vaccine administered to children 6 through 59 months of age (n = 3916) and children aged 6 through 17 years of age (n = 3936) in two trials. Both of the trials were randomized, placebo-controlled, double-blind clinical trials. Vaccine Virus Vaccine was manufactured by Sanofi Pasteur Inc. (active control) in children 6 months to less than 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 3906 were randomized to active control. Children who previously received any 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 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.

In the primary efficacy analysis, FluMist demonstrated a 44.5% (95% CI: 22.4, 66.0) 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 antigenically similar.

Table 6: Comparative Efficacy Against Culture-Confirmed Modified CDC-ILI* Caused by Wild-Type Strains (Study MI-CP111)¹

<table>
<thead>
<tr>
<th>Strain</th>
<th>Matching Strains</th>
<th>unmatched strains</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/H1N1</td>
<td>576</td>
<td>102</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>576</td>
<td>102</td>
</tr>
<tr>
<td>A/H1N1</td>
<td>3916</td>
<td>1825</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>576</td>
<td>102</td>
</tr>
</tbody>
</table>

¹ 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 or consecutive days.

The vaccine candidates were based on the seasonal antigenic strains that were expected to circulate in the upcoming influenza season. The vaccine candidates were based on the seasonal antigenic strains that were expected to circulate in the upcoming influenza season.
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 (1996-1997 and 1997-1998). The primary endpoint of the trial was the prevention of culture-confirmed influenza 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), cough, sore throat, change in mental status, irritability, decreased activity, or vomiting. During the first year of the study, 1623 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 Due to Antigenically Matched Wild-Type Strains (Studies D153-PS01 & AV006, Year 1)

<table>
<thead>
<tr>
<th>Strain</th>
<th>FluMist n (%)</th>
<th>Placebo n (%)</th>
<th>% Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/H1N1</td>
<td>23 (1.4%)</td>
<td>81 (7.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>4 (0.2%)</td>
<td>27 (2.4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>B</td>
<td>29 (1.8%)</td>
<td>35 (3.2%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

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

b) Container containing 10 intranasal sprayers: NDC 66019-309-10

The single-use intranasal sprayer is not made with natural rubber latex.

DO NOT FREEZE.

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.

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.

Carton containing 10 intranasal sprayers: NDC 66019-309-10

Single intranasal sprayer: NDC 66019-309-01

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.

A single temperature excursion up to 25°C (77°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 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 vaccinee 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

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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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.
• have a weakened immune system or live with someone who has a weakened immune system
• have Guillain-Barré syndrome
• have a history of wheezing if under 5
• are currently wheezing
• 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.

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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Gaithersburg, MD 20878
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