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FULL PRESCRIBING INFORMATION

Flumist® Quadrivalent (Influenza Vaccine Live, Intranasal) Intrasnasal Spray
2021-2022 Formula Initial U.S. Approval: 2003

INDICATIONS AND USAGE
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. See Description (11).

Flumist Quadrivalent is approved for use in persons 2 through 49 years of age. (1)

DOSAGE AND ADMINISTRATION
For intranasal administration by a healthcare provider. (2)

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)

WARNINGS AND PRECAUTIONS

1. 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)

2. 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)

3. 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)

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

ADVERSE REACTIONS

1. 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 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)

2. To report SUSPECTED ADVERSE REACTIONS, contact MedImmune at 1-877-633-4411 or VAERS at 1-800-822-7967 or http://vaers.hhs.gov

USE IN SPECIFIC POPULATIONS

1. In clinical trials, in children 6 through 23 months of age, Flumist was associated with an increased risk of hospitalization and wheezing. (8.2)

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

Revised: 8/2021

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Figure 1
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 Drug Interactions (7.1)].

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 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 AS-03 Adjuvant containing Sucrose-Phosphate-Gluatamate (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 through 17 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, 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 = 6473, placebo = 2921). 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.

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 reports were similar between subjects who received FluMist Quadrivalent and FluMist. Table 3 includes solicited adverse reaction reports 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.

 FluMist® Quadrivalent

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% (84/2019)</td>
<td>3.3% (63/195)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>6-23 months</td>
<td>2.1% (46/2187)</td>
<td>2.5% (56/2198)</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>Fever</td>
<td>16% (11/67)</td>
<td>13% (11/84)</td>
</tr>
<tr>
<td>Sore Throat</td>
<td>9% (9/121)</td>
<td>7% (7/101)</td>
</tr>
<tr>
<td>Muscle Aches</td>
<td>3% (3/92)</td>
<td>2% (2/102)</td>
</tr>
<tr>
<td>Chills</td>
<td>4% (4/107)</td>
<td>3% (3/105)</td>
</tr>
<tr>
<td>Headache</td>
<td>11% (11/101)</td>
<td>9% (9/99)</td>
</tr>
<tr>
<td>Decreased Activity</td>
<td>14% (11/80)</td>
<td>11% (11/99)</td>
</tr>
<tr>
<td>Irritability</td>
<td>21% (21/101)</td>
<td>19% (19/100)</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>21% (21/101)</td>
<td>19% (19/100)</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>58% (58/101)</td>
<td>51% (51/100)</td>
</tr>
<tr>
<td>Runny Nose</td>
<td>50% (50/100)</td>
<td>42% (42/100)</td>
</tr>
<tr>
<td>Throat</td>
<td>11% (11/99)</td>
<td>9% (9/100)</td>
</tr>
<tr>
<td>Oral Temperature</td>
<td>6% (6/101)</td>
<td>4% (4/102)</td>
</tr>
<tr>
<td>Oral Temperature</td>
<td>101°F (101/101)</td>
<td>91°F (91/100)</td>
</tr>
<tr>
<td>Temperature</td>
<td>16% (16/100)</td>
<td>13% (13/100)</td>
</tr>
</tbody>
</table>

**Notes**

- *NCT01231876: see www.clinicaltrials.gov*
- irinotecan (CPT11) Inactivated Influenza Virus Vaccine manufactured by Sanofi Pasteur Inc., administered intramuscularly.
- *NCT00128167: see www.clinicaltrials.gov*
- *NCT00128167: see www.clinicaltrials.gov*
- *NCT01012944: see www.clinicaltrials.gov*
- *NCT01012944: see www.clinicaltrials.gov*
- Study D153-P501 used saline placebo; Study AV006 used AF-SPG placebo.
- *NCT01012944: see www.clinicaltrials.gov*
- *NCT01012944: see www.clinicaltrials.gov*
- *NCT01012944: see www.clinicaltrials.gov*
- *NCT01012944: see www.clinicaltrials.gov*
reactions that either occurred at a higher rate (FluMist Quadrivalent recipients compared to FluMist recipients).

Between subjects who received FluMist Quadrivalent and FluMist. Table 1

receive aspirin therapy or aspirin-containing therapy because of the association of Reye's syndrome with FluMist Quadrivalent recipients compared to FluMist recipients or were identified in Study AV009.

In Study MI-CP208, 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 (t 1% rate difference after rounding) compared to AF-SPG placebo include runny nose (44% FluMist vs. 27% placebo), headache (40% FluMist vs. 38% placebo), sore throat (28% FluMist vs. 17% placebo), tiredness/fatigue (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 (t 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 (t 1% rate difference after rounding) in FluMist Quadrivalent recipients compared to FluMist recipients or were identified in Study AV009.

Table 4: Summary of Solicited Adverse Reactions Observed Within 14 Days after Dose 1 for FluMist Quadrivalent and FluMist Recipients in Study MI-CP185a

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

a Solicited adverse reactions that occurred at a higher rate (t 1% rate difference after rounding) in FluMist Quadrivalent recipients compared to FluMist recipients or were identified in Study AV009.

b NCT00880667; see www.clinicaltrials.gov.

c Representative of events from the FluMist study arms; see Clinical Studies (14.1).

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: Pericarditis

Congenital, familial, and genetic disorders: Exacerabation of symptoms of mitochondrial encephalopathy (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 B

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

7.3 Concomitant Administration with Inactivated Vaccines

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

7.4 Concomitant Administration with Other Live Vaccines

Concomitant administration of 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 FluMist 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 prepreations.

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 Embryonic/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 an 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/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 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 6 through 23 months has been associated with increased risks of hospitalization and wheezing in clinical trials [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].

8.5 Geriatric Use

FluMist Quadrivalent is not approved for use in persons 65 years of age and older because in a clinical study (AV005), 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 individual subjects 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 for administration 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 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 33°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 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 reassortant strains in FluMist Quadrivalent, the amino acid substitution that contributes to the 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 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 ts and att phenotypes. 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 2021-2022 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 ultrafiltration 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 syringes for nasal administration.

Each pre-filled refrigerated FluMist Quadrivalent sprayer contains a single 0.2 mL dose. Each 0.2 mL dose contains 10^6.5-7.5 FFU (fluorescent focus units) of live attenuated influenza virus reassortants of the four strains: A/Victoria/1/2003 (H1N1) (an A/Victoria/270/1979 (H1N1)pdm09-like - virus), A/Hong Kong/156/2012 (H3N2) (an A/California/02/2009 (H3N2) - like virus), B/Phuket/03/2013 (B/Yamagata lineage), and B/Washington/02/2002 (B/Victoria lineage). Each 0.2 mL dose also contains 0.188 mg/dose monosodium glutamate, 2.00 mg/dose hydrolyzed porcine gelatin, 2.42 mg/dose arginine, 13.88 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 contain residual amounts of gentamicin sulfate (< 0.015 mcg/mL), and ethylenediaminetetraacetic acid (EDTA) (< 2.3 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 deposited in the nose and nasopharynx. FluMist Quadrivalent is a 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) multi-center Study MI-CP129 which enrolled healthy children 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, nasopharyngeal secretions for the detection of vaccine virus were collected daily for the first 7 days and every other day through either 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 5: Characterization of Shedding with FluMist in Specified Age Groups by Frequency, Amount, and Duration (Study MI-CP129 and Study FM026) [a]

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number of Subjects</th>
<th>% Shedding</th>
<th>Peak Titers</th>
<th>% Shedding After 5 Days</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;5 log10</td>
<td>70</td>
<td>Day 23</td>
</tr>
<tr>
<td>24-59 months</td>
<td>100</td>
<td>69</td>
<td>&lt;5 log10</td>
<td>1.0</td>
<td>Day 25</td>
</tr>
<tr>
<td>5-8 years</td>
<td>102</td>
<td>50</td>
<td>&lt;5 log10</td>
<td>2.9</td>
<td>Day 23</td>
</tr>
<tr>
<td>9-17 years</td>
<td>126</td>
<td>29</td>
<td>&lt;4 log10</td>
<td>1.6</td>
<td>Day 28</td>
</tr>
<tr>
<td>18-49 years</td>
<td>115</td>
<td>20</td>
<td>&lt;3 log10</td>
<td>0.9</td>
<td>Day 17</td>
</tr>
</tbody>
</table>

[a] NCT00344305; see www.clinicaltrials.gov

Positive Culture

All strains 3916 153 3.9% 3936 338 8.6% 54.9% 45.4, 62.9
A/H1N1 3916 102 2.6% 3936 245 6.2% 58.2% 47.4, 67.0
A/H1N1 3916 0 0.0% 3936 0 0.0% 79.2% 70.6, 85.7
B 3916 66 1.7% 3936 71 1.8% 6.3% 31.6, 33.3

Regardless of Match
All strains 3916 153 3.9% 3936 338 8.6% 54.9% 45.4, 62.9
A/H1N1 3916 0 0.0% 3936 0 0.0% 79.2% 70.6, 85.7
B 3916 115 2.9% 3936 136 3.5% 16.1% 27.4, 48.9

* 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, 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 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 (1997-1998 and 1998-1999). 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, 1620 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 DIUS-DS5-501® & AV006®; Year 1)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>N=1563</th>
<th>Placebo N=1111</th>
<th>% Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/H1N1</td>
<td>10 (1%)</td>
<td>73 (18%)</td>
<td>93.4% (87.5, 96.5)</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>0 0</td>
<td>4 (5%)</td>
<td>96.0% (89.4, 98.5)</td>
</tr>
<tr>
<td>B</td>
<td>6 (0.7%)</td>
<td>31 (7%)</td>
<td>90.5% (78.5, 93.9)</td>
</tr>
</tbody>
</table>

**DiUS-DS5-501® and AV006® data are for subjects who received two doses of vaccine.**

### Table 8: Effectiveness of FluMist to Prevent Febrile Infections 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=2411</th>
<th>Placebo N=1226</th>
<th>Percent Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any febrile illness</td>
<td>331 (13.73)</td>
<td>189 (15.42)</td>
<td>10.9% (-5.1, 24.4)</td>
</tr>
<tr>
<td>Severe febrile illness</td>
<td>20 (10.37)</td>
<td>15 (12.89)</td>
<td>15.9% (3.0, 33.2)</td>
</tr>
<tr>
<td>Febrile upper respiratory illness</td>
<td>213 (8.33)</td>
<td>142 (11.58)</td>
<td>27.6% (6.7, 37.5)</td>
</tr>
</tbody>
</table>

**Participants with one or more events of:**

- **Any febrile illness:**
  - FluMist: 331 (13.73%)
  - Placebo: 189 (15.42%)
  - Percent Reduction: 10.9% (95% CI: -5.1, 24.4)

- **Severe febrile illness:**
  - FluMist: 20 (10.37%)
  - Placebo: 15 (12.89%)
  - Percent Reduction: 15.9% (95% CI: 3.0, 33.2)

- **Febrile upper respiratory illness:**
  - FluMist: 213 (8.33%)
  - Placebo: 142 (11.58%)
  - Percent Reduction: 27.6% (95% CI: 6.7, 37.5)

Effectiveness was shown in a post-hoc analysis using an endpoint of CDC-ILI in the age group 18 through 49 years of age.

### 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 2:1 ratio to receive either one dose of FluMist Quadrivalent or one 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). Immune response was shown in a post-hoc analysis using the 4-strain-specific serum hemagglutination inhibition (HAI) antibody geometric mean titer (GMT) post dosing and provided evidence that the addition of the second B strain did not result in immune interference to other strains included in the vaccine.

### 15 REFERENCES


### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 16.1 How Supplied

FluMist Quadrivalent is supplied in a package of 10 pre-filled, single-dose (0.2 mL) intranasal sprays. The single-use intranasal sprayer is not made with natural rubber latex.

Carting contains 10 intranasal sprays: NDC 66019-308-10

Single intranasal sprayer: NDC 66019-308-01

### 16.2 Storage and Handling

The cold chain [2°C-8°C (35-46°F)] must be maintained when transporting FluMist Quadrivalent. The product must be used before the expiration date on the sprayer label. Do not freeze.

### 17 PATIENT COUNSELING INFORMATION

#### 17.1 Administration Information

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

#### 17.2 Vaccination with a Live Virus Vaccine

Instruct vaccine recipients or their parents/guardians that FluMist Quadrivalent is an attenuated live virus vaccine (see Warnings and Precautions). Instruct vaccine recipients or their parents/guardians that FluMist Quadrivalent may not be given concomitantly with any other live virus vaccine (see Contraindications). Instruct 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. Instruct vaccine recipients or their parents/guardians to alert their healthcare provider if they have a history of recurrent wheezing since this may be an asthma equivalent in this age group.

#### 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.
FluMist® Quadrivalent

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 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.

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 is vaccinated with FluMist Quadrivalent, your healthcare provider will decide if your child needs to come back for a second dose.

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.

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
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- have problems with your heart, kidneys, or lungs
- have diabetes
- are pregnant or nursing
- are taking Tamiflu®, Relenza®, amantadine, or rimantadine

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.

FluMist® is a registered trademark of MedImmune, LLC.

Other brands listed are registered trademarks of their respective owners and are not trademarks of MedImmune, LLC.

MedImmune
Manufactured by:
MedImmune, LLC
Gaithersburg, MD 20878
Issue date: August 2021   US-55499   7/21
RAL-FLUVQV10

Information for Patients and Their Caregivers

FluMist® Quadrivalent (pronounced FLEW-mist Kwä-dr-î-Î-lant)
(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
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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.

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