FULL PRESCRIBING INFORMATION: CONTENTS*

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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:

<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>

* indicates information is not applicable.
† 0.2 mL indicated for intranasal administration by a healthcare provider.

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 to 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).

3 WARNINGS AND PRECAUTIONS

3.1 Risks of Hospitalization and Wheezing in Children Younger than 24 Months of Age

3.2 Asthma, Recurrent Wheezing, and Active Wheezing

3.3 Guillain-Barré Syndrome

3.4 Allergic Immune Response

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5.4 Concomitant Administration with Other Live Vaccines

5.5 Intranasal Products

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7.2 Patient Counseling Information

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

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

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**HIGHLIGHTS OF 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.

Flumist® Quadrivalent (Influenza Vaccine Live, Intranasal) Intranasal Spray

2023-2024 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 subtype viruses and type B viruses contained in the vaccine. Flumist Quadrivalent is approved for use in persons 2 through 49 years of age.

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**DOSAGE AND ADMINISTRATION**

For intranasal administration by a healthcare provider.

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
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</tr>
<tr>
<td>9 years through 49 years</td>
<td>1 dose, 0.2 mL†</td>
<td>-</td>
</tr>
</tbody>
</table>

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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 may be at increased risk of wheezing following the administration of Flumist Quadrivalent, (5.2)
- Guillain-Barré syndrome has occurred within 4 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, less than 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 less than 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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**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)

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**USE IN SPECIFIC POPULATIONS**

- In clinical trials, 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: 08/2023

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**REFERENCES**

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**HOW SUPPLIED/STORAGE AND HANDLING**

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**PATIENT COUNSELING INFORMATION**

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

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**INFORMATION FOR PATIENTS AND THEIR CAREGIVERS**

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**Figure 1**

1. Check expiration date. Product must not be used after the date on sprayer label.
2. Remove rubber tip protector. Do not remove dose-divider clip at the other end of the sprayer.
3. Place the tip just inside the nostril and with a slight motion depress plunger as rapidly as possible to deliver remaining vaccine.
This treatment is not available 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 Allergic Immunocompromise
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 123 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 viral-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 other 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 9597 children and adolescents 1 through 17 years of age and 3941 adults 18 through 64 years of age received FluMist in randomized, placebo-controlled studies D153-P501, AV006, D153-P526, AV019, and AV009 (3 used Adjuvanted Inactivated Influenza Vaccine [FluMist Quadrivalent]; 2 used Inactivated Influenza Vaccine, [FluMist]; placebo). For purposes of safety analysis, children and adolescents were pooled into one age group (younger than 17 years of age).

A total of 1382 children and adolescents 2 through 17 years of age and 1198 adults 18 through 69 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 MI-CP111, AV006, D153-P526, AV019, and AV009, subjects were White (71%), Hispanic (11%), Asian (7%), Black (6%), and Other (5%), with all others identified as Asian. A total of 1382 children and adolescents 2 through 17 years of age and 1198 adults 18 through 69 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 MI-CP111, AV006, D153-P526, AV019, and AV009, subjects were White (71%), Hispanic (11%), Asian (7%), Black (6%), and Other (5%), with all others identified as Hispanic or Latino.

Flulistent in Children and Adolescents
The safety of FluMist was evaluated in an AF-SPS placebo-controlled Study (AV019) conducted in a Health Maintenance Organization (HMO) in children 1 through 17 years of age (Flumist = 6472, placebo = 3216). 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 3.33, 90% CI: 1.1, 10.7).

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 to 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* | Adverse Reaction | Age Group | FluMist‡ | Active Control† | p value |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations‡</td>
<td>6-23 months</td>
<td>4.2% (24/579)</td>
<td>3.2% (63/1975)</td>
<td>0.632</td>
</tr>
<tr>
<td></td>
<td>24-59 months</td>
<td>2.1% (46/2187)</td>
<td>2.5% (56/2198)</td>
<td>0.632</td>
</tr>
<tr>
<td>Wheezing§</td>
<td>6-23 months</td>
<td>5.5% (17/319)</td>
<td>3.2% (75/1975)</td>
<td>0.340</td>
</tr>
<tr>
<td></td>
<td>24-59 months</td>
<td>2.1% (45/2187)</td>
<td>2.6% (56/2198)</td>
<td>0.632</td>
</tr>
</tbody>
</table>

*NC100132187; see www.clinicaltrials.gov
†Inactivated Influenza Virus Vaccine manufactured by Sanofi Pasteur Inc., administered intramuscularly.
‡Hospitalization due to any cause from randomization through 180 days post last vaccination.
§Wheezing during the 42 days post last vaccination.

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

Table 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>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>70% (50)</td>
<td>70% (50)</td>
<td>70% (50)</td>
</tr>
<tr>
<td>Headache</td>
<td>14% (11)</td>
<td>14% (11)</td>
<td>14% (11)</td>
</tr>
<tr>
<td>Muscle Aches</td>
<td>14% (11)</td>
<td>14% (11)</td>
<td>14% (11)</td>
</tr>
<tr>
<td>Chills</td>
<td>4% (3)</td>
<td>4% (3)</td>
<td>4% (3)</td>
</tr>
</tbody>
</table>

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 Mectizan, Mumps, and Pneumococcus Vaccine Live (MMR, manufactured by Merck & Co., Inc.) and Varicella Virus Vaccine Live (manufactured by Merck & Co., Inc.) to children 12 through 15 months of age, adverse reactions were similar to those seen in other clinical trials of FluMist.
for Gastrointestinal aches (urticaria).

Cough

Sore Throat

Decreased Appetite

Muscle Aches

Fever

> 100°F by any route

> 100 - < 101°F by any route

> 101 - < 102°F by any route

Number of 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.

FluMist in Adults

In adults 18 through 49 years of age in Study AV009, solicited adverse reactions occurring in at least 1% of FluMist recipients and at a higher rate (≥1% difference after rounding) compared to AF-SPG placebo include runny nose (44% FluMist vs. 27% placebo), headache (40% FluMist vs. 36% placebo), sore throat (28% FluMist vs. 17% placebo), tiredness/weakness (25% FluMist vs. 22% placebo), muscle aches (17% FluMist vs. 15% placebo), cough (14% FluMist vs. 11% placebo), and chills (8% FluMist vs. 6% placebo).

In Study AV009, unsolicited adverse reactions occurring in at least 1% of FluMist recipients and at a higher rate (≥1% difference after rounding) compared to placebo were nasal congestion (5% FluMist vs. 2% placebo) and sinusitis (4% FluMist vs. 2% placebo).

FluMist Quadrivalent in Adults

In the randomized, active-controlled Study Mi-CP185 that compared FluMist Quadrivalent and FluMist in adults 18 through 49 years of age, the rates of solicited adverse reactions reported were generally similar between subjects who received FluMist Quadrivalent and FluMist. Table 4 presents solicited adverse reactions that either occurred at a higher rate (≥1% 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-CP185 in Adults 18 through 49 Years of Age

<table>
<thead>
<tr>
<th>Event</th>
<th>FluMist Quadrivalent</th>
<th>FluMist</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 1198</td>
<td>N = 597</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Runny Nose/Nasal Congestion</td>
<td>44</td>
<td>26</td>
</tr>
<tr>
<td>Headache</td>
<td>26</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>

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

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 vaccine within two weeks of enrollment.

7.4 Concomitant Administration with Live Other 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 preparations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.2 Lactation

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 placebo recipients and influenza vaccine recipients [see Clinical Studies (14.1)].

FluMist Quadrivalent is not approved for use in children younger than 24 months of age because use of FluMist in children 6 through 23 months has been associated with increased risks of hospitalization and wheezing in clinical trials [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].

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 determined 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 vaccine quadrivalent for administration by intranasal spray. FluMist Quadrivalent contains four vaccine virus strains: an A/H1N1 strain, an A/H3N2 strain and two B strains. FluMist Quadrivalent contains B strains from both the B/Yamagata/16/88 and the B/Victoria/3/87 images. 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 22°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 34°C [Type A strains], temperatures at which many wild-type influenza viruses grow efficiently; and (c) attenuated (at), i.e., they do not produce classic influenza-like illness in the ferret model of human influenza infection.

No evidence of reversion has been observed in the recovered vaccine strains that have been tested [136 (possibly 250 recovered isolates)] using FluMist [see Clinical Pharmacology (12.3)], for each of the four reassortant strains in FluMist Quadrivalent, the six internal gene segments responsible for ca, ts, and at 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 the wild-type viruses MDV 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 at phenotypes. For the Type B MDV, at least three genetic loci in two different internal gene segments contribute to both the ts and at phenotypes; 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 2005-2006 influenza season. Three of the viruses (A/UK/1/99, 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 inoculated to allow the flavin adenine nucleotide virus replication. The allantoic fluid of these eggs is harvested, pooled, and then clarified by filtration. The virus is concentrated by ultracentrifugation and dialyzed with stabilizing buffer to contain the final sucrose and potassium phosphate concentrations. The viral harvests are then sterile filtered to produce the monovalent batches. Each lot is tested for ca, ts, and at phenotypes and is also tested extensively by in vitro and in vivo methods to detect adventitious agents. Monovalent lots from the four stains are subsequently blended and diluted as required to attain the desired potency with stabilizing

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. If 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

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

Clinical Considerations

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

Data

Animal Data: In a developmental and reproductive toxicity study, female rats were administered FluMist Quadrivalent either three times (during the period of organogenesis) or six times (prior to gestation and during the period of organogenesis), 200 micrograms per gestational (approximately 150 human dose equivalents), by intranasal instillation revealing no evidence of impaired fertility or harm to the fetus due to FluMist treatment.
buffers to produce the quadrivalent bulk vaccine. The bulk vaccine is then filled directly into the nasal spray for nasal administration.

Each pre-filled refrigerated FluMist Quadrivalent sprayer contains a single 0.2 ml dose. Each 0.2 ml dose contains 10^8-10^9 FFU (fluorescent focus units) of live attenuated influenza virus reagents of each of the four strains: A/Wyoming/3694/2002 (H1N1) (an A/Victoria/48/2002 (H1N1)pdm09-like virus), A/VI/68/2021 (H3N2) (an A/Adarwini/2021 (H3N2)-like virus), B/Phakt/2023/2013 (B/Yamanagata lineage), and B/Strain/159/2017 (B/Victoria lineage). Each 0.2 ml dose also contains 50 mg of mannitol, 2.9 mg of disodium hydrogen phosphate, 0.24 mg of disodium edetate, 13.6 mg sucrose, 2.26 mg of disodium citrate phosphate, and 0.96 mg of monobasic potassium phosphate. Each dose contains residual amounts of ovomucin (<0.024 mg/dose), and may also contain residual amounts of gentamicin sulfate (<0.015 mg/ml), and ethylenediaminetetraacetic acid (EDTA) (<2.25 mg/dose).

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 Clinical Pharmacology (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-CP29, which enrolled healthy individuals 6 through 59 months of age (N = 2001), and (2) multi-center Study FM026 which enrolled healthy individuals 5 through 49 years of age (N = 3448). In each study, nasal secretions were obtained daily for the first 7 days and every other day thereafter for Day 28 and on Day 28 or Day 28 in Study MI-CP29, Individuals with a positive shedding sample at Day 25 or Day 26 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: Characteristics of Shedding with FluMist in Specified Age Groups by Frequency, Amount, and Duration (Study MI-CP29) and Study FM026.*

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of Subjects</th>
<th>% Shedding</th>
<th>% Shedding After Day 11</th>
<th>% Shedding After Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-22 months</td>
<td>98</td>
<td>89%</td>
<td>7.0%</td>
<td>1.4%</td>
</tr>
<tr>
<td>24-59 months</td>
<td>100</td>
<td>69%</td>
<td>1.0%</td>
<td>0.2%</td>
</tr>
<tr>
<td>5-17 years</td>
<td>102</td>
<td>50%</td>
<td>1.0%</td>
<td>0.5%</td>
</tr>
<tr>
<td>18-48 years</td>
<td>115</td>
<td>95%</td>
<td>0.9%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

A single subject who did not shed previously on Days 1-3, TCD50/ml was less than 1.5 log_10 on Day 23.

*Tables 5 and 6 represent data from clinical studies performed in multi-center trials. FluMist Quadrivalent and FluMist are not approved for use in children younger than 24 months of age [see Adverse Reactions (6.1)].

Safety and shedding of vaccine viruses following FluMist administration were evaluated in 28 HI-vaccinated individuals (median CD4 count of 541 cells/mm³) and 27 HI-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 HI-vaccinated subjects on Day 5 only, and in none of the HI-negative FluMist recipients.

Safety and shedding of vaccine viruses following FluMist administration were also evaluated in children in an open-label, randomized, double-blind, placebo-controlled trial in 24 HI-vaccinated children (median CD4 count of 1013 cells/mm³) and 25 HI-negative children 1 through 7 years of age, and in a randomized (1:1), open-label, inactivated influenza vaccine-controlled trial in 243 HI-vaccinated children and adolescents 5 through 17 years of age receiving stable antiretroviral therapy. Frequency and duration of vaccine virus shedding in HI-inoculated individuals were comparable to that seen in healthy individuals. No adverse effects on HIV viral load or CD4 counts were identified following FluMist administration. In the 5 through 17 year old group, one inactivated influenza vaccine recipient and one FluMist recipient experienced pneumonia within 28 days of vaccination (days 17 and 13, respectively). The effectiveness of FluMist and FluMist Quadrivalent in preventing influenza illness in HI-inoculated individuals has not been evaluated.

Transmission Study

A prospective, randomized, double-blind, placebo-controlled trial was performed in a daycare setting in children younger than 3 years of age to assess the transmission of vaccine viruses from a vaccinated individual to a non-vaccinated individual. A total of 197 children 8 through 36 months of age were randomized to receive one dose of FluMist (N = 99) or AI-SPS placebo (N = 99). Virus shedding was evaluated for 21 days by culture of nasal swab specimens. Wild-type A (H1N2) influenza virus was documented to have circulated in the community and in the study population during the trial, whereas Types A (H1N1) and B (H3N2) strains did not.

At least one vaccine strain was isolated from 83% of FluMist recipients; strains were recovered from 1-2 days post vaccination (mean duration of 7.6 days ± 3.4 days). The ca and np proteins were preserved in 135 tested of 250 strains isolated at the local laboratory. Ten influenza isolates (9 influenza A, 1 influenza B) were cultured from a total of seven placebo subjects. One placebo subject had two isolates of wild-type B virus infection confirmed as a transmitted vaccine virus by a FluMist recipient in the same playgroup. This type B isolate retained the ca, ns, and afp genes of the vaccine virus 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 A isolates were confirmed as wild-type A/H1N1. The remaining isolates could not be further characterized.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

FluMist Quadrivalent has not been evaluated for its carcinogenic or mutagenic potential or its potential to impair fertility.

13.2 Clinical Studies

The clinical effects of FluMist Quadrivalent are 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 (HAI) 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 (1)].

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 effectiveness of FluMist administered, inactivated influenza Virus Vaccine 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 3916 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 with 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, 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 (study MI-CP111).
14.4 Immune Response Study of FluMist Quadrivalent in Adults

A multi-center, randomized, double-blind, active-controlled, and non-inferiority study (MI-CP158) 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 4:1 ratio to receive either 1 dose of FluMist Quadrivalent or 1 dose of one of two formulations of comparator vaccine, FluMist, each containing a 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-CP158 was evaluated by comparing the 4 strain-specific serum HAI antibody GMTs post dosing and provided evidence that the addition of the second B strain did not result in immune interference to other strains included in the vaccine.

15. REFERENCES

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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

Carton containing 10 intranasal sprays: NDC 66019-310-10

Single intranasal spray: NDC 66019-310-01

16.2 Storage and Handling

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

FLUMIST QUADRIVALENT SHOULD BE STORED IN A REFRIGERATOR BETWEEN 2-8°C (35-46°F) UPON RECEIPT. THE PRODUCT MUST NOT BE USED AFTER 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 (i.e., sharp's 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).

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

17.1 Asthma and Recurrent Wheezing
Ask the vaccinee or their parent/guardian if the vaccinee has asthma. For children younger than 5 years of age, ask also if the vaccinee has recurrent wheezing since this may be an asthma equivalent in this age group. Inform the vaccinee or their parent/guardian that there may be an increased risk of wheezing in children vaccinated with FluMist Quadrivalent in persons younger than 8 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.

FluMist® is a registered trademark of MedImmune, LLC.

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

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Issue Date: August 2023 US-77756 77/3

RFL-LUGV110
FluMist® Quadrivalent

Information for Patients and Their Caregivers

FluMist® Quadrivalent (pronounced FLEW-mist Kwâ-dre-Vâ-lent)
(Influenza Vaccine Live, Intranasal)

Please read this Patient Information carefully before you or your child is vaccinated with FluMist Quadrivalent.
This is a summary of information about FluMist Quadrivalent. It does not take the place of talking with your healthcare provider about influenza vaccination. If you have questions or would like more information, please talk with your healthcare provider.

What is FluMist Quadrivalent?

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

Who should not get FluMist Quadrivalent?

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

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

Children under 2 years old have an increased risk of wheezing (difficulty with breathing) after getting FluMist Quadrivalent.

Who may not be able to get FluMist Quadrivalent?

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

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

How is FluMist Quadrivalent given?

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

What are the possible side effects of FluMist Quadrivalent?

The most common side effects are:
- runny or stuffy nose
- sore throat
- fever over 100°F

Other possible side effects include:
- decreased appetite
- headache
- irritability
- muscle ache
- tiredness
- chills
- cough

Call your healthcare provider or go to the emergency department right away if you or your child experience:
- hives or a bad rash
- trouble breathing
- swelling of the face, tongue, or throat

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

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

What are the ingredients in FluMist Quadrivalent?

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

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

FluMist Quadrivalent does not contain preservatives.

How is FluMist Quadrivalent Stored?

FluMist Quadrivalent is stored in a refrigerator (not the freezer) between 35-46°F (2-8°C) upon receipt. FluMist Quadrivalent sprayer must be kept in the carton until use in order to protect from light. FluMist Quadrivalent must not be used after 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 2023 US-77756 7/23

RAL-FLUQV12