FluMist® Quadrivalent is an intranasal live, intranasal vaccine. It 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. (1.1, 11)

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

**DOSE FORMS AND STRENGTHS**

Each sprayer contains a single dose (0.2 mL) of FluMist Quadrivalent, including egg protein, or after a previous dose of any influenza vaccine. (4.1, 11)

**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)

**ADVERSE REACTIONS**

In clinical trials, in children 6 through 23 years of age who received FluMist Quadrivalent, 44% reported runny nose or nasal congestion and 19% reported sore throat. (5.2, 6.1)

In clinical trials, in children 6 through 23 years of age who received FluMist Quadrivalent, 44% reported runny nose or nasal congestion and 19% reported sore throat. (5.2, 6.1)

**USE IN SPECIFIC POPULATIONS**

- Safety and effectiveness of FluMist Quadrivalent have not been established in pregnant women, nursing mothers, geriatric adults, or children less than 2 years of age. (8.1, 8.3, 8.4, 8.5)

- In clinical trials, in children 6 through 23 months of age, FluMist was associated with an increased risk of hospitalization and wheezing. (8.4)

**CONTRIBUTING INFORMATION**

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

**Figure 1**

- Check expiration date. (Product must be used before the date on sprayer label)
- Remove rubber tip protector. Do not remove dose-divider clip at the other end of the sprayer
- Place the tip just inside the nostril (with the patient in an upright position, place the tip just inside the nostril to ensure the vaccine is delivered into the nose)
- With a single motion, depress plunger as rapidly as possible until the dose-divider clip prevents you from going further
- Pinch and remove the dose-divider clip from plunger

**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)
An increase in asthma events, captured by review of diagnostic codes, was observed in children younger through 42 months of age who received FluMist compared to those who received placebo (Relative Risk ≥2.5). This is consistent with previous observations that mild-to-moderate 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

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)].

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)].

In Study MI-CP111, children 6 through 59 months of age and 1198 study participants were randomized to receive FluMist or inactivated Vaccine Live (MMR, manufactured by Merck & Co., Inc.) and Varicella Virus Vaccine Live (manufactured by Merck & Co., Inc.). In this study, solicited adverse reactions were documented for 14 children aged 42 to 103 months.

### 6.2 Adverse Reactions

#### Table 2: Summary of 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/N)</th>
<th>Placebo (n/N)</th>
<th>FluMist (n/N)</th>
<th>Active Control (n/N)</th>
</tr>
</thead>
</table>

In studies D153-PS01 and AV006, solicited adverse reactions occurring in at least 1% of FluMist recipients and at a higher rate (≥1% rate difference after rounding) compared to placebo were abdominal pain (2% FluMist vs 0% placebo) and otitis media (3% FluMist vs 1% placebo). An additional adverse reaction identified in the active-controlled trial MI-CP111 occurring in at least 1% of FluMist recipients and at a higher rate (≥1% rate difference after rounding) compared to active control was sneezing (in 2% FluMist vs 1% active control). In a separate saline placebo-controlled trial (D153-PS26) in a subset of older children and adolescents 9 through 17 years of age who received one dose of FluMist, the solicited adverse reactions as well as unsolicited adverse reactions reported were generally consistent with observations from the trials in Table 2. Abdominal pain was reported in 12% of FluMist recipients compared to 4% of placebo recipients and decreased activity was reported in 6% of FluMist recipients compared to 0% of placebo recipients.

In Study AV018, in which FluMist was concomitantly administered with Measles, Mumps, and Rubella Virus Vaccine Live (MMR, manufactured by Merck & Co., Inc.) and Varicella Virus Vaccine Live (manufactured by Merck & Co., Inc.) to children 12 through 15 months of age, adverse reactions were similar to those seen in other clinical trials of FluMist.

#### 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% (84/1992)</td>
<td>3.9% (63/1675)</td>
</tr>
<tr>
<td>24-59 months</td>
<td>2.1% (46/2187)</td>
<td>2.5% (56/2188)</td>
<td></td>
</tr>
<tr>
<td>Wheezing</td>
<td>6-23 months</td>
<td>5.9% (117/1992)</td>
<td>3.8% (75/1975)</td>
</tr>
<tr>
<td>24-59 months</td>
<td>2.1% (47/2187)</td>
<td>2.5% (56/2188)</td>
<td></td>
</tr>
</tbody>
</table>

* CT001281677; www.clinicaltrials.gov

** Intrinsically Influenza Virus Vaccine manufactured by Sanofi Pasteur Inc., administered intramuscularly.

** Intrinsically Influenza Virus Vaccine manufactured by Sanofi Pasteur Inc., administered intramuscularly.

** Hospitalization due to any cause from randomization through 180 days post last vaccination.

** Welching requiring bronchodilator therapy or accompanied by respiratory distress or hypoxia evaluated from randomization through 42 days post last vaccination.

** 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)].

### 5.8 Allergic 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)].

### 5.9 Guillain-Barré Syndrome

The 1976 swine influenza vaccine (inactivated) was associated with an elevated risk of Guillain-Barré syndrome (GBS). Evidence for causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, based on data for inactivated influenza vaccines, it is probably slightly more than 1 additional case per million persons vaccinated [1]. 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.

### 5.10 Most Commonly Requested Questions (FAQs)

#### 5.10.1 How do I store FluMist Quadrivalent?

FluMist Quadrivalent is shipped in an AF-SPG placebo-controlled study (AV019) conducted in a Health Maintenance Organization (HMO) in children 1 through 17 years of age who received one dose of FluMist, the solicited adverse reactions as well as unsolicited adverse reactions reported were generally consistent with observations from the trials in Table 2. Abdominal pain was reported in 12% of FluMist recipients compared to 4% of placebo recipients and decreased activity was reported in 6% of FluMist recipients compared to 0% of placebo recipients.

In Study AV018, in which FluMist was concomitantly administered with Measles, Mumps, and Rubella Virus Vaccine Live (MMR, manufactured by Merck & Co., Inc.) and Varicella Virus Vaccine Live (manufactured by Merck & Co., Inc.) to children 12 through 15 months of age, adverse reactions were similar to those seen in other clinical trials of FluMist.

#### 5.10.2 Adverse Reactions

In clinical studies D153-PS01 and AV006, unsolicited adverse reactions in children occurring in at least 1% of FluMist recipients and at a higher rate (≥1% rate difference after rounding) compared to placebo were abdominal pain (2% FluMist vs 0% placebo) and otitis media (3% FluMist vs 1% placebo). An additional adverse reaction identified in the active-controlled trial MI-CP111 occurring in at least 1% of FluMist recipients and at a higher rate (≥1% rate difference after rounding) compared to active control was sneezing (in 2% FluMist vs 1% active control). In a separate saline placebo-controlled trial (D153-PS26) in a subset of older children and adolescents 9 through 17 years of age who received one dose of FluMist, the solicited adverse reactions as well as unsolicited adverse reactions reported were generally consistent with observations from the trials in Table 2. Abdominal pain was reported in 12% of FluMist recipients compared to 4% of placebo recipients and decreased activity was reported in 6% of FluMist recipients compared to 0% of placebo recipients.

In Study AV018, in which FluMist was concomitantly administered with Measles, Mumps, and Rubella Virus Vaccine Live (MMR, manufactured by Merck & Co., Inc.) and Varicella Virus Vaccine Live (manufactured by Merck & Co., Inc.) to children 12 through 15 months of age, adverse reactions were similar to those seen in other clinical trials of FluMist.

#### 5.10.3 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 reactions reported were similar between subjects who received FluMist Quadrivalent and FluMist. Table 3 includes solicited adverse reactions post Dose 1 from Study MI-CP208 that either occurred at a higher rate (≥1% rate difference after rounding) in FluMist Quadrivalent recipients compared to FluMist recipients or were identified in previous FluMist clinical studies (see Table 2). In this study, solicited adverse reactions were documented for 14 days post vaccination. Solicited adverse reactions post Dose 2 were observed at a lower frequency compared to those post Dose 1 for FluMist Quadrivalent and were similar between subjects who received FluMist Quadrivalent and FluMist.
7.2 Antiviral Agents Against Influenza A and/or B
Antiviral drugs that are active against influenza A and/or B viruses may reduce the effectiveness of FluMist Quadrivalent if administered within 48 hours before, or within 2 weeks after vaccination. The concurrent use of FluMist Quadrivalent with antiviral agents that are active against influenza A and/or B viruses has not been evaluated. If antiviral agents and FluMist Quadrivalent are administered concomitantly, revaccination should be considered when appropriate.

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category B
A developmental and reproductive toxicity study has been performed in female rats administered FluMist Quadrivalent either three times (during the period of organogenesis) or six times (prior to gestation and during the period of organogenesis). No microstructural or functional (approximately 150 human dose equivalent) implantation and has revealed no evidence of impaired fertility or harm to the fetus due to FluMist Quadrivalent. There are however, no adequate and well controlled studies in pregnant women. Because animal studies are not always predictive of human response FluMist Quadrivalent should be administered during pregnancy only if clearly needed.

8.2 Nursing Mothers
It is not known whether FluMist Quadrivalent is excreted in human milk. Because some viruses are excreted in human milk, caution should be exercised when FluMist Quadrivalent is administered to a nursing woman.

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 [14.4]). 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 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 vaccine 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 lineages. The four influenza virus strains contained in FluMist Quadrivalent are derived from a master donor virus (MDV), and the two segments that encode the two antigenically relevant wild-type influenza viruses. Thus, the four viruses contained in FluMist Quadrivalent were inactivated, propagated and an influenza vaccine formulation.

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 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 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 possible 250 recovered isolates) using FluMist [see Clinical Pharmacology (12.2)]. For each of the four reassortant strains in FluMist Quadrivalent, the six internal gene segments responsible for ca, ts and att phenotypes are derived from a master donor virus (MDV), and the two segments that encode the two surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA), are derived from the corresponding antigenically relevant wild-type influenza viruses. Thus, the four viruses contained in FluMist Quadrivalent maintain the replication characteristics and phenotypic properties of the 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 ca and ts 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 expresses the HA and NA of wild-type viruses that are related to strains expected to circulate during the 2017-2018 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 virus vaccine formulation.

Specific pathogen-free (SPF) eggs are inoculated with each of the reassortant strains and incubated to produce vaccine virus replication. The allotypic 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 preparations are then sterile filtered to produce the monovalent bulks. Each lot is tested for ca, ts and att phenotypes and 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 spray devices for nasal administration.

Each pre-filled refrigerated FluMist Quadrivalent sprayer contains a single 0.2 mL dose. Each 0.2 mL dose contains 125 μg of each of the four influenza vaccine virus strains contained in each of the four strains: A/Slovenia/2035/2015 (H1N1) (an A/Michigan/45/2015 (H1N1)pdm09-like virus), A/Perth/16/2010 (H3N2) (an A/Perth/16/2010 (H3N2)), B/Florida/04/2006 (B/Victoria) and B/Florida/04/2006 (B/Yamagata).
Day and shedding of vaccine virus following FluMist administration were also evaluated in children 8 through 36 months of age receiving stable anti-retroviral therapy.

All strains
All children
3916 102 2.6% 3936 245 6.2% 58.2% 47.4, 67.0
A/H1N1
3916 0 0.0% 3936 0 0.0% -- --
A/H5N2
3916 0 0.0% 3936 0 0.0% -- --
A/H3N2
3916 37 0.9% 3936 178 4.5% 79.2% 70.6, 85.7
A/H5N2
3916 68 1.7% 3936 71 1.8% 8.5% -31.6, 59.6

MMR Quadrivalent

At least one vaccine strain was isolated from 80% of FluMist recipients; strains were recovered from 21-21 days post vaccination (mean duration of 7.6 days ± 3.4 days). The cold-adapted (ca) and temperature-sensitive (ts) phenotypes 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 mild symptomatic 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, ts, and att 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/panama (H3N2). The remaining isolates could not be further characterized.

In summary, a single transmission event (isolation of the Type B vaccine strain), the probability of a young child acquiring vaccine virus from a FluMist recipient in the same playgroup was estimated to be 2.4% (95% CI: 0.1, 6.4) using 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: 0.1, 6.4) using the Reed-Frost model.

CLINICAL STUDIES

The effectiveness of FluMist Quadrivalent is based on data demonstrating the clinical efficacy of FluMist in children and the effectiveness of FluMist in adults, and a comparison of post vaccination geometric mean titers (GMTs) of hemagglutination inhibition (HI) antibodies between individuals receiving FluMist and FluMist Quadrivalent. The clinical experience with FluMist is relevant to FluMist Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions [see Description (11)].

14.1 Efficacy Studies of FluMist in Children and Adolescents

A multinational, randomized, double-blind, active-controlled trial (MI-CP111) was performed to assess the safety and immunogenicity of FluMist Quadrivalent in children 6 through 17 years of age and in adolescents 18 through 49 years of age [see Clinical Pharmacology (12.1)].

Shedding Studies

Shedding of vaccine viruses within 28 days of vaccination with FluMist was evaluated in (1) multi-center study MI-CP129 which enrolled healthy individuals 6 through 59 years of age (N = 200); and (2) multi-center study FM026 which enrolled healthy individuals 5 through 49 years of age (N = 244). In each study, nasal secretions were obtained daily for the first 7 days and every other day thereafter through Day 13 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.

Detection of vaccine virus from nasal secretions of vaccine recipients (shedding) [see Pharmacodynamics (12.2)]

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 = 98) or AS-PE placebo (N = 99). Virus shedding was evaluated for 21 days by culture of nasal swab specimens. Wild-type A (A/CA/9/91) influenza virus was documented to have circulated in the community and in the study population during the trial, whereas Type B A/Aachen1 and Type B strains did not.

At least one vaccine strain was isolated from 80% of FluMist recipients; strains were recovered from 21-21 days post vaccination (mean duration of 7.6 days ± 3.4 days). The cold-adapted (ca) and temperature-sensitive (ts) phenotypes 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
Table 7: Effect of FluMist vs. Placebo Against Culture-Confirmed Influenza Illness Due to Antigenically Matched Wild-Type Strains (Studies D153-P501* & AV006*, Year 1)

<table>
<thead>
<tr>
<th>Strain</th>
<th>Placebo N (%)</th>
<th>FluMist N (%)</th>
<th>Placebo % Efficacy (95% CI)</th>
<th>FluMist % Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/SA1*</td>
<td>150 (21.3%)</td>
<td>100 (14.3%)</td>
<td>39.0% (84.5, 73.5)</td>
<td>90.5% (97.5, 93.5)</td>
</tr>
<tr>
<td>A/H1N1</td>
<td>23 (31.7%)</td>
<td>18 (25.0%)</td>
<td>26.8% (90.5, 87.4)</td>
<td>90.5% (97.5, 93.5)</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>4 (0.5%)</td>
<td>0 (0.0%)</td>
<td>0.0% (--</td>
<td>90.5% (97.5, 93.5)</td>
</tr>
<tr>
<td>B</td>
<td>29 (3.2%)</td>
<td>7 (1.0%)</td>
<td>9.6% (19.9, 1.3)</td>
<td>84.4% (94, 98)</td>
</tr>
</tbody>
</table>

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

** Immune Response Study of FluMist Quadrivalent in Children and Adolescents

A multicenter, randomized, double-blind, active-controlled, non-inferiority study (MI-CP208) was performed to assess the immunogenicity of FluMist Quadrivalent compared to FluMist (active control) in children and adolescents 2 through 17 years of age. A total of 2312 subjects were randomized by site at a 3:1:1 ratio to receive either FluMist Quadrivalent or one of two formulations of comparator vaccine FluMist, each containing a B strain that corresponded to one of the two B strains in FluMist Quadrivalent (a B strain of the Yamagata lineage or a B strain of the Victoria lineage). Children 2 through 8 years of age received 2 doses of vaccine approximately 30 days apart; children 9 years of age and older received 1 dose. For children 2 through 8 years of age with a history of influenza vaccination, immunogenicity assessments were performed prior to vaccination and at 28 days after the first dose. For children 2 through 8 years of age without a history of influenza vaccination, immunogenicity assessments were performed prior to vaccination and 28 days after the second dose. For children 9 years of age and older, immunogenicity assessments were performed prior to vaccination and at 28 days post vaccination.

Immunogenicity was evaluated by comparing the 4 strain-specific serum hemagglutination inhibition (HAI) antibody geometric mean titers (GMTs) post 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.

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 4:1:1 ratio to receive either 1 dose of FluMist Quadrivalent or 1 dose of one of two formulations of comparator vaccine FluMist, each containing a B strain that corresponded to one of the two B strains in FluMist Quadrivalent (a B strain of the Yamagata lineage and a B strain of the Victoria lineage). Immune responses to MMR and Varicella vaccines were evaluated 6 weeks post-vaccination while the immune responses to FluMist were evaluated 4 weeks after the second dose. No evidence of interference with immune response to measles, mumps, rubella, varicella and FluMist vaccines was observed.

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

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>FluMist N = 2411*</th>
<th>Placebo N = 1126*</th>
<th>Percent Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any febrile illness</td>
<td>331 (13.7)</td>
<td>185 (15.4)</td>
<td>10.9 (-5.1, 24.4)</td>
</tr>
<tr>
<td>Severe febrile illness</td>
<td>250 (10.37)</td>
<td>158 (12.89)</td>
<td>19.5 (3.0, 33.2)</td>
</tr>
<tr>
<td>Febrile upper respiratory illness</td>
<td>213 (8.83)</td>
<td>142 (11.58)</td>
<td>23.7 (6.7, 37.5)</td>
</tr>
</tbody>
</table>

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

** The predominantly circulating virus during the trial period was A/Sydney/05/97 (H3N2), an antigenic variant not included in the vaccine.
Information for Patients and Their Caregivers

FluMist® Quadrivalent (pronounced FLEW-mist Kwá-dre-VÁ-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 degrees 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 degrees F (2-8 degrees 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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