

FluMist[®] Quadrivalent

Influenza virus vaccine nasal spray

PRODUCT INFORMATION

NAME OF THE MEDICINE

Quadrivalent influenza virus vaccine (live attenuated)

DESCRIPTION¹

FluMist Quadrivalent contains the following 4 live attenuated influenza virus reassortant strains, propagated in specific pathogen-free (SPF) eggs from SPF chicken flocks.

- A/South Dakota/6/2007 (H1N1)
- A/Uruguay/716/2007 (H3N2)
- B/Malaysia/2506/2004 (Victoria lineage)
- B/Florida/4/2006 (Yamagata lineage)

This influenza vaccine complies with the World Health Organisation (WHO) and Australian Influenza Vaccine Committee (AIVC) recommendations for the 2009 Southern Hemisphere influenza season.

FluMist Quadrivalent nasal spray

FluMist Quadrivalent nasal spray is a colourless to pale yellow, clear to opalescent suspension. Small white particles may be present.

Each 200 µL dose of FluMist Quadrivalent contains $10^{7.0\pm 0.5}$ FFU (fluorescent focus units) of each of the 4 influenza virus strains. The nasal spray also contains the following as inactive ingredients: sucrose, dibasic potassium phosphate, monobasic potassium phosphate, gelatin (porcine Type A), arginine hydrochloride, monosodium glutamate and water for injections. Residual amounts of ovalbumin (<0.24 µg/dose and also traces of gentamicin sulfate (<0.015 µg/dose) from the manufacturing process may be present. FluMist Quadrivalent contains no preservatives (ie no thiomersal).

PHARMACOLOGY

Since 1985, 2 distinct lineages of influenza B viruses (Victoria and Yamagata) have circulated worldwide. FluMist Quadrivalent is a quadrivalent (also known as tetravalent) vaccine that contains antigens for 4 influenza virus strains, an A/(H1N1) strain, an A/(H3N2) strain, and 2 B strains (one from each lineage). The

¹ Template section to be updated annually for strain changes. This may also mean modifications to the WHO and AIVC statement if there are differences between the two one year

influenza virus strains in FluMist Quadrivalent are (a) *cold-adapted (ca)* (ie they replicate efficiently at 25°C, a temperature that is restrictive for replication of many wild-type influenza viruses); (b) *temperature-sensitive (ts)* (ie they are restricted in replication at 37°C (Type B strains) or 39°C (Type A strains), temperatures at which many wildtype influenza viruses grow efficiently); and (c) *attenuated (att)* (ie they do not produce classic influenza-like illness in the ferret model of human influenza infection). The cumulative effect of the antigenic properties and the *ca*, *ts*, and *att* phenotypes is that the attenuated vaccine viruses replicate in the nasopharynx and induce protective immunity.

No evidence of reversion has been observed in the recovered vaccine strains that have been tested (135 of possible 250 recovered isolates). The 4 viruses contained in FluMist Quadrivalent maintain the replication characteristics and phenotypic properties of the master donor virus (MDV) and express the hemagglutinin (HA) and neuraminidase (NA) of wild-type viruses that are related to strains expected to circulate during the influenza season. For each strain, at least five genetic loci contribute to the *ca/ts/att* phenotype.

Mechanism of action

Immune mechanisms conferring protection against influenza following receipt of FluMist Quadrivalent vaccine are not fully understood. Likewise, naturally acquired immunity to wild-type influenza has not been completely elucidated. Serum antibodies, mucosal antibodies and influenza-specific T cells may play a role in prevention of infection and in recovery from infection.

Pharmacokinetics

Not applicable.

CLINICAL TRIALS

The efficacy of FluMist Quadrivalent in children and adolescents is based on data demonstrating laboratory-confirmed efficacy of trivalent version of FluMist and a comparison of post vaccination geometric mean titers (GMTs) of hemagglutination inhibition (HAI) antibodies between individuals receiving trivalent version of FluMist and FluMist Quadrivalent. Clinical experience with trivalent version of FluMist is relevant to FluMist Quadrivalent because trivalent version of FluMist is identical to FluMist Quadrivalent with the only difference being the addition of a fourth strain (a second B strain) to FluMist Quadrivalent.

Trivalent version of FluMist has been administered to over 20 000 children and adolescents in controlled clinical studies over multiple years, in various regions and using different vaccine strains. FluMist Quadrivalent has been administered to 1382 children and adolescents within a controlled clinical study. The results of these pivotal efficacy and safety studies are discussed in detail below.

Studies of trivalent version of FluMist

Efficacy data in the paediatric population for trivalent version of FluMist consists of 9 controlled studies conducted during 7 influenza seasons. Four placebo-controlled studies included second season revaccination. The trivalent version of

FluMist demonstrated superiority in 3 active-controlled studies with injectable trivalent inactivated influenza vaccines (TIV). See Table 1 (placebo controlled) and Table 3 (active controlled) for a summary of trivalent version of FluMist efficacy results in children. The pivotal studies are then detailed further within the text below each table.

Table 1 Trivalent version of FluMist efficacy in placebo-controlled paediatric studies

Study number	Region	Age (months)	N	Influenza season	Efficacy ^a (95% CI)	
					Matched strains	All strains regardless of match
D153-P502 (Vesikari et al 2006)	Europe	6-35	1616	2000-2001	85.4%; (74.3, 92.2)	85.9% (76.3, 92.0)
				2001-2002	88.7% (82.0, 93.2)	85.8% (78.6, 90.9)
D153-P504 (Bracco Neto et al 2009)	Africa, Latin America	6-35	1886	2001	73.5% (63.6, 81.0) ^b	72.0% (61.9, 79.8) ^b
				2002	73.6% (33.3, 91.2)	46.6% (14.9, 67.2)
D153-P513 (Forest et al 2008)	Asia/Oceania	6-35	1041	2002	62.2% (43.6, 75.2)	48.6% (28.8, 63.3)
D153-P522 (Lum et al 2010)	Europe, Asia/Oceania, Latin America	11-24	1150	2002-2003	78.4% (50.9, 91.3)	63.8% (36.2, 79.8)
D153-P501 (Tam et al 2007)	Asia/Oceania	12-35	2764	2000-2001	72.9% (62.8, 80.5)	70.1% (60.9, 77.3)
				2001-2002	84.3% (70.1, 92.4) ^c	64.2% (44.2, 77.3) ^c
AV006 (Belshe et al 1998, Belshe et al 2000)	USA	15-71	1259	1996-1997	93.4% (87.5, 96.5)	93.4% (87.5, 96.5)
				1997-1998	100% (63.1, 100)	87.1% (77.7, 92.6) ^d

N - Number of study participants for year 1 efficacy analysis; CI – confidence intervals

^a Reduction in culture-confirmed influenza illness relative to placebo

^b Data presented for clinical trial D153-P504 are for children who received 2 doses of study vaccine. In previously unvaccinated children who received one dose in Year 1, efficacy was 57.7% (95% CI: 44.7, 67.9) and 56.3% (95% CI: 43.1, 66.7), respectively, thus supporting the need for 2 doses of vaccine in previously unvaccinated children

^c In children who received 2 doses in Year 1 and placebo in Year 2, efficacy in Year 2 was 56.2% (95% CI: 30.5, 72.7) and 44.8% (95% CI: 18.2, 62.9), respectively, in D153-P501, thus supporting the need for second-season revaccination

^d The primary circulating strain was antigenically dissimilar from the H3N2 strain represented in the vaccine; efficacy against the mismatched A/H3N2 strain was 85.9% (95% CI: 75.3, 91.9).

Study D153-P501: Paediatric study

A randomised, double-blind, placebo-controlled trial (D153-P501) was performed to evaluate the efficacy of trivalent version of FluMist in children 12-35 months of age without high-risk medical conditions against culture-confirmed influenza illness. The primary endpoint of the trial was the prevention of culture-confirmed influenza illness due to antigenically matched wild-type influenza. A total of 3174 children were randomised 3:2 (vaccine: placebo) to receive 2 doses of study vaccine or placebo at least 28 days apart in Year 1. See Table 2 for a description of the results.

During the second year of Study D153-P501, for children who received two doses in Year 1 and one dose in Year 2, trivalent version of FluMist demonstrated 84.3% (95% CI: 70.1, 92.4) efficacy against culture-confirmed influenza illness due to antigenically matched wild-type influenza.

Study AV006: Paediatric study

AV006 was a multi-centre, randomised, double-blind, placebo-controlled trial performed in US children without high-risk medical conditions to evaluate the efficacy of trivalent version of FluMist against culture-confirmed influenza over 2 successive seasons. 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. During the first year of the study, 1602 children 15-71 months of age were randomised 2:1 (vaccine: placebo). In Year 2, children remained in the same treatment group as in year one and received a single dose of trivalent version of FluMist or placebo. See Table 2 for a description of the results.

Table 2 Efficacy^a of trivalent version of FluMist vs placebo against culture confirmed influenza illness due to antigenically matched wild-type strains (D153-P501 & AV006, Year 1)

	D153-P501			AV006		
	FluMist (trivalent) n (%)	Placebo n (%)	% Efficacy (95% CI)	FluMist (trivalent) n (%)	Placebo n (%)	% Efficacy (95% CI)
N	1653	1111		849	410	
Any strain	56 (3.4%)	139 (12.5%)	72.9% ^b (62.8, 80.5)	10 (1%)	73 (18%)	93.4% (87.5, 96.5)
A/H1N1	23 (1.4%)	81 (7.3%)	80.9% (69.4, 88.5) ^c	0	0	--
A/H3N2	4 (0.2%)	27 (2.4%)	90.0% (71.4, 97.5)	4 (0.5%)	48 (12%)	96.0% (89.4, 98.5)
B	29 (1.8%)	35 (3.2%)	44.3% (6.2, 67.2)	6 (0.7%)	31 (7%)	90.5% (78.0, 95.9)

N - Number of subjects in per-protocol efficacy analysis population of each treatment group of each study for the "any strain" analysis

n - Number and percent of subjects in per-protocol efficacy analysis population with culture-confirmed influenza illness

CI - confidence intervals

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

^b For D153-P501, influenza circulated through 12 months following vaccination.

^c Estimate includes A/H1N1 and A/H1N2 strains. Both were considered antigenically similar to the vaccine.

During the second year of Study AV006, the primary circulating strain was the A/Sydney/05/97 H3N2 strain, which was antigenically dissimilar from the H3N2 strain represented in the vaccine, A/Wuhan/359/95; trivalent version of FluMist demonstrated 87.0% (95% CI: 77.0, 92.6) efficacy against culture-confirmed influenza illness.

Table 3 Trivalent version of FluMist relative efficacy in active-controlled paediatric studies with injectable trivalent inactivated influenza vaccine (TIV)

Study number	Region	Age range	N	Influenza season	Improved efficacy ^a (95% CI)	
					Matched strains	All strains regardless of match
MI-CP111 (Belshe et al 2007)	USA, Europe, Asia/Oceania	6-59 M	7852	2004-2005	44.5% (22.4, 60.6) fewer cases than injectable	54.9% (45.4, 62.9) ^b fewer cases than injectable
D153-P514 (Ashkenazi et al 2006)	Europe	6-71 M	2085	2002-2003	52.7% (21.6, 72.2) fewer cases than injectable	52.4% (24.6, 70.5) ^c fewer cases than injectable
D153-P515 (Fleming et al 2006)	Europe	6-17 Y	2211	2002-2003	34.7% (3.9, 56.0) fewer cases than injectable	31.9% (1.1, 53.5) fewer cases than injectable

M – months; Y - years. Age range as described in the protocol for the study.

N – Number of study participants (per protocol); CI – confidence intervals

^a Reduction in culture-confirmed influenza illness relative to injectable influenza vaccine

^b FluMist (trivalent) demonstrated 55.7% (39.9, 67.6) fewer cases than injectable influenza vaccine in 3686 children 6-23 months of age and 54.4% (41.8, 64.5) fewer cases in 4166 children 24-59 months of age

^c FluMist (trivalent) demonstrated 64.4% (1.4, 88.8) fewer cases than injectable influenza vaccine in 476 children 6-23 months of age and 48.2% (12.7, 70.0) fewer cases in 1609 children 24-71 months of age

Study MI-CP111: Paediatric comparative study

A multinational, randomised, double-blind, active-controlled trial (MI-CP111) was performed to assess the efficacy and safety of trivalent version of FluMist compared to an injectable trivalent inactivated influenza vaccine (TIV) (active control) in children <5 years of age.

During the 2004-2005 influenza season, a total number of 3916 children <5 years of age and without severe asthma, without use of bronchodilator or steroids and without wheezing within the prior 6 weeks were randomised to trivalent version of FluMist and 3936 were randomised to active control. Participants were then followed through the influenza season to identify illness caused by influenza virus. As the primary endpoint, culture-confirmed modified CDC-ILI (Centers for Disease Control and Prevention [CDC]-defined influenza-like illness) was defined as a positive culture for a wild-type influenza virus associated within ± 7 days of modified CDC-ILI. Modified CDC-ILI was defined as fever (temperature $\geq 38^{\circ}\text{C}$ oral or equivalent) plus cough, sore throat or runny nose/nasal congestion on the same or consecutive days.

In the primary efficacy analysis, trivalent version of 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 3 for a description of the overall results and Table 4 for a description of the results by strain and antigenic similarity.

Table 4 Comparative efficacy against culture-confirmed modified CDC-ILI^a caused by wild-type strains in children <5 years of age (ATP population)

	FluMist (trivalent)			Active control ^b			Reduction in rate - FluMist (trivalent) ^c	95% CI
	N	# of cases	Rate (cases/N)	N	# of cases	Rate (cases/N)		
Matched Strains								
All strains	3916	53	1.4%	3936	93	2.4%	44.5%	22.4, 60.6
A/H1N1	3916	3	0.1%	3936	27	0.7%	89.2%	67.7, 97.4
A/H3N2	3916	0	0.0%	3936	0	0.0%	--	--
B	3916	50	1.3%	3936	67	1.7%	27.3%	-4.8, 49.9
Mismatched Strains								
All strains	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/H3N2	3916	37	0.9%	3936	178	4.5%	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	3	0.1%	3936	27	0.7%	89.2%	67.7, 97.4
A/H3N2	3916	37	0.9%	3936	178	4.5%	79.2%	70.6, 85.7
B	3916	115	2.9%	3936	136	3.5%	16.1%	-7.7, 34.7

CI – confidence intervals

^a Modified CDC-ILI was defined as fever (temperature $\geq 38^{\circ}\text{C}$ oral or equivalent) plus cough, sore throat, or runny nose/nasal congestion on the same or consecutive days

^b Injectable trivalent inactivated influenza vaccine (TIV)

^c Reduction in rate was adjusted for country, age, prior influenza vaccination status and wheezing history status

FluMist Quadrivalent - Immune response study in children and adolescents

A multicentre, randomised, double-blind, active-controlled, non-inferiority study (MI-CP208; Block et al 2012) was performed to assess the immunogenicity of FluMist Quadrivalent compared to trivalent version of FluMist (active control) in children and adolescents 2 through 17 years of age. A total of 2312 subjects were randomized at a 3:1:1 ratio to receive either FluMist Quadrivalent or 1 of 2 formulations of comparator vaccine trivalent version of FluMist, each containing a B strain that corresponded to one of the two B strains in FluMist Quadrivalent.

Immunogenicity was evaluated by comparing the 4 strain-specific serum HAI antibody GMTs post-dosing. FluMist Quadrivalent demonstrated immunologic non-inferiority to the 2 formulations of trivalent version of FluMist, as the upper bound for each of the four 95% CIs for the post-dose strain specific GMT HAI antibody ratios was less than the pre-specified non-inferiority criterion of 1.5. These data provide evidence that the addition of the second B strain did not result in immune interference to other strains included in the vaccine.

Studies in immunocompromised individuals

Safety and shedding of vaccine virus following trivalent version of FluMist administration were also evaluated in children in a randomized (1:1), cross-over, double-blind, placebo-controlled trial (Study DMID 99-012; King et al, 2001) in 24 HIV-infected children [median CD4 cell count of 1013 cells/mm³] and

25 HIV-negative children 1-7 years of age, and in a randomized (1:1), open-label, inactivated influenza vaccine-controlled trial (Study PACTG 1057; Levin et al, 2008) in 243 HIV-infected children and adolescents 5-17 years of age receiving stable anti-retroviral therapy. Frequency and duration of vaccine virus shedding in HIV-infected individuals were comparable to that seen in healthy individuals. No adverse effects on HIV viral load or CD4 counts were identified following trivalent version of FluMist administration. In the 5-17 year old age group, 1 inactivated influenza vaccine recipient and 1 trivalent version of FluMist recipient experienced pneumonia within 28 days of vaccination (Days 17 and 13, respectively). The effectiveness of trivalent version of FluMist and FluMist Quadrivalent in preventing influenza illness in HIV-infected individuals has not been evaluated.

Twenty mild to moderately immunocompromised children and adolescents 5-17 years of age (receiving chemotherapy and/or radiation therapy or who had received chemotherapy in the 12 weeks prior to enrolment) were randomized 1:1 to receive trivalent version of FluMist or placebo (Study MI-CP114; Halasa et al 2011). Frequency and duration of vaccine virus shedding in these immunocompromised children and adolescents were comparable to that seen in healthy children and adolescents. The effectiveness of trivalent version of FluMist and FluMist Quadrivalent in preventing influenza illness in immunocompromised individuals has not been evaluated.

Studies with concomitant live vaccines

In Study AV018 (Nolan et al 2008), concomitant administration of trivalent version of FluMist, measles, mumps & rubella virus vaccine live (MMR) and varicella virus vaccine live was studied in 1245 subjects 12-15 months of age. Subjects were randomized in a 1:1:1 ratio to MMR, varicella vaccine and placebo (group 1); MMR, varicella vaccine and trivalent version of FluMist (group 2); or trivalent version of FluMist alone (group 3). Immune responses to MMR and varicella vaccines were evaluated 6 weeks post-vaccination while the immune responses to trivalent version of FluMist were evaluated 4 weeks after the second dose. Adverse reactions were similar to those seen in other clinical trials with trivalent version of FluMist (see *Adverse Effects*). No evidence of interference with immune response to measles, mumps, rubella, varicella and trivalent version of FluMist vaccines was observed (see *Interactions with other medicines*).

In Study D153-P511 (Breiman et al 2009) concomitant administration of trivalent FluMist and oral poliovirus (OPV) was studied in 2,503 subjects 6-35 months of age. Subjects were randomized in a 1:1:1 ratio to 1 of 3 study groups: FluMist + OPV; placebo + OPV; or FluMist alone. The rate of reactogenicity events reported by vaccine recipients in study D153-P511 was similar to that observed in previous trials with FluMist. Immune responses after concomitant vaccination were non-inferior to those elicited when the vaccines were administered independently of one another (see *Interactions with other medicines*).

Duration of efficacy

Analyses that examined the impact of time on the efficacy of LAIV in young children compared with placebo, demonstrated comparable efficacy through 12 months post-vaccination; two studies have shown that LAIV efficacy can persist at a lower but clinically meaningful level through the following influenza season

without revaccination (Study D153-P501, Tam et al, 2007; Study D153-P504, Bracco Neto et al 2009).

Vaccine effectiveness

Data from observational effectiveness studies have confirmed a protective effect of LAIV, although there does appear to be variation in vaccine effectiveness estimates from different studies. Due to the limitations in observational studies it is difficult to compare the results of one study to another. The reasons for low vaccine effectiveness observed in occasional vaccine effectiveness studies are not always understood and may warrant further assessment.

INDICATIONS

FluMist Quadrivalent is indicated for the prevention of influenza in children and adolescents from 24 months to less than 18 years of age.

CONTRAINDICATIONS

- Do not administer FluMist Quadrivalent to persons who have had a severe allergic reaction (eg anaphylaxis) to the active substances, any of the excipients (eg gelatin; see *Description*), gentamicin (a trace residual), eggs or egg proteins (eg ovalbumin; see *Description*).
- Children and adolescents with clinical immunodeficiency due to conditions or immunosuppressive therapy such as: acute & chronic leukaemias; lymphoma; symptomatic HIV infection; cellular immune deficiencies; and high-dose corticosteroids (see also *Precautions*).
- Children and adolescents less than 18 years of age receiving salicylate therapy because of the association of Reye's syndrome with salicylates and wild-type influenza infection (see *Interactions with other medicines*).

PRECAUTIONS

Clinical data presented in this section includes studies conducted with the trivalent version of FluMist. These data are relevant to FluMist Quadrivalent because FluMist Quadrivalent is identical to trivalent version of FluMist with the only difference being the addition of a fourth strain (a second B strain) to FluMist Quadrivalent.

Risk in children <24 months of age

Do not administer FluMist Quadrivalent to children younger than 12 months. In a clinical study, an increase in hospitalisations was observed in children younger than 12 months after vaccination with trivalent version of FluMist. It is not recommended to administer FluMist Quadrivalent to children 12-23 months of age. In a clinical study, an increased rate of wheezing was observed in children 12-23 months of age after vaccination with trivalent version of FluMist (see *Adverse effects*).

Severe asthma or active wheezing

Individuals with severe asthma or active wheezing have not been adequately studied in clinical studies.

Management of acute allergic reactions

As with all vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.

Altered immunocompetence

FluMist Quadrivalent has not been studied in immunocompromised individuals. Data on the safety and shedding of trivalent version of FluMist in immunocompromised individuals are limited (see *Clinical trials*). FluMist Quadrivalent administration to immunocompromised individuals should be based on careful consideration of potential benefits and risks (see also *Contraindications*). FluMist Quadrivalent is not contraindicated for use in individuals with asymptomatic HIV infection (see *Clinical trials*); or individuals who are receiving topical/inhaled corticosteroids or low-dose systemic corticosteroids or those receiving corticosteroids as replacement therapy eg for adrenal insufficiency.

Vaccine recipients/caregivers should be informed that FluMist Quadrivalent is an attenuated live virus vaccine and has the potential for transmission to immunocompromised contacts. Vaccine recipients should attempt, whenever possible, to avoid close association with severely immunocompromised individuals (eg bone marrow transplant recipients requiring isolation) for 1-2 weeks following vaccination.

Effects on fertility

FluMist Quadrivalent has not been evaluated for its potential to impair human fertility. However a reproductive and developmental toxicity study in which rats were intranasally administered the human dose of FluMist Quadrivalent 3 times in the 2 weeks prior to mating, and 3 times during gestation, showed no adverse effects on female fertility.

Use in pregnancy – Category B1

Available data, including post-marketing reports, suggest that FluMist Quadrivalent has not been associated with adverse maternal or fetal outcomes. FluMist Quadrivalent is not recommended during pregnancy as these reports do not adequately inform the presence or absence of drug-associated risk with the use of FluMist Quadrivalent during pregnancy. Refer to National recommendations as per the current Immunisation Handbook.

There are limited data from the use of FluMist Quadrivalent in pregnant women. There was no evidence of significant maternal adverse outcomes in 138 pregnant women who had a record of receiving trivalent version of FluMist in a US based health insurance claims database. In 27 reports of trivalent version of FluMist administration to pregnant women from the US Vaccine Adverse Event Reporting

System, no unusual patterns of pregnancy complications or fetal outcomes were observed.

The effects of FluMist Quadrivalent on embryo-fetal and pre-weaning development were evaluated in a developmental toxicity study of pregnant rats. Rats were intranasally administered the human dose of FluMist Quadrivalent on gestation days 6, 13 and 20 (and in some groups also 3 times in the 2 weeks prior to mating). No adverse effects on pregnancy, parturition, lactation or embryo-fetal development were observed and, in addition no adverse effects on pre-weaning development were observed. There were no fetal malformations or other evidence of teratogenesis observed. A lack of adverse effects was also seen in developmental toxicity studies with the trivalent vaccine in rats and ferrets.

Use in lactation

Studies in lactating women have not been conducted with FluMist Quadrivalent. It is not known whether FluMist Quadrivalent is excreted in human milk. Therefore, as some viruses are excreted in human milk, caution should be exercised if FluMist Quadrivalent is administered to nursing mothers.

Vaccine antigen-specific antibodies were transferred to rat pups via milk from dams administered FluMist Quadrivalent during gestation and lactation, with no adverse effects.

Paediatric use

FluMist Quadrivalent is not recommended in children below the age of 24 months.

Genotoxicity

FluMist Quadrivalent has not been tested for its genotoxic potential.

Carcinogenicity

FluMist Quadrivalent has not been tested for its carcinogenetic potential.

Effects on ability to drive and use machines

The vaccine is not expected to have an effect on the ability to drive and use machines.

INTERACTIONS WITH OTHER MEDICINES

Clinical data presented in this section includes studies conducted with the trivalent version of FluMist. These data are relevant to FluMist Quadrivalent because FluMist Quadrivalent is identical to trivalent version of FluMist with the only difference being the addition of a fourth strain (a second B strain) to FluMist Quadrivalent.

Aspirin

Do not administer FluMist Quadrivalent to children and adolescents (under 18 years of age) receiving salicylate therapy t (see *Contraindications*). Do not use salicylates in children and adolescents for 4 weeks after vaccination with FluMist

Quadrivalent unless medically indicated as Reye's syndrome has been reported following the use of salicylates during wild-type influenza infection.

Other vaccines

FluMist Quadrivalent may be given at the same time as other vaccines. Concurrent administration of trivalent version of FluMist with the MMR vaccine (1233 children 11-23 months of age), the MMR and varicella vaccine (1245 children 12-15 months of age), and the orally administered poliovirus vaccine (2503 children 6-35 months of age) has been studied (see *Clinical trials*). Adverse events were similar to those seen in other clinical studies with trivalent version of FluMist Quadrivalent. Studies did not show clinically meaningful changes in immune responses to measles, mumps, rubella, varicella, orally administered poliovirus or trivalent version of FluMist.

Antiviral agents

The concurrent use of FluMist Quadrivalent with antiviral agents that are active against influenza A and/or B viruses has not been evaluated. However, based upon the potential for influenza antiviral agents to reduce the effectiveness of FluMist Quadrivalent, it is recommended:

- not to administer FluMist Quadrivalent until 48 hours after the cessation of influenza antiviral therapy.
- not to administer influenza antiviral agents until two weeks after administration of FluMist Quadrivalent unless medically indicated.

If influenza antiviral agents and FluMist Quadrivalent are administered concomitantly, revaccination should be considered when appropriate.

ADVERSE EFFECTS

The safety experience with trivalent version of FluMist is relevant to the use of FluMist Quadrivalent because trivalent version of FluMist is identical to FluMist Quadrivalent with the only difference being the addition of a fourth strain (a second B strain) to FluMist.

The safety of trivalent version of FluMist was analysed in a total of over 29 000 children and adolescents 2-17 years of age. In addition, the safety of FluMist Quadrivalent in this population has been assessed in 1382 children and adolescents in the comparative immune response study (MI-CP208; see *Clinical Trials*). In clinical studies, the safety profile of FluMist Quadrivalent was similar to the safety profile of the trivalent version of FluMist.

Additional experience has occurred with marketed use of FluMist Quadrivalent and trivalent version of FluMist.

Adverse reactions in clinical studies (children and adolescents)

Seven placebo-controlled studies (3245 trivalent version of FluMist recipients and 1994 placebo recipients) and four active-controlled studies (4108 trivalent version of FluMist recipients and 4118 active-control recipients) were pooled to evaluate

solicited events occurring in children and adolescents 2-17 years of age. Table 5 presents an analysis of solicited events post dose 1 occurring in trivalent version of FluMist recipients with at least 2% higher rate compared to placebo and includes rates for these solicited events from active controlled studies.

Table 5 Summary of solicited events* observed within 10 days after dose 1 for the trivalent version of FluMist and either placebo or active-control recipients; children and adolescents 2-17 years of age

Solicited Event	System Organ Class ^c	Placebo-controlled studies ^a		Active-controlled studies ^b	
		FluMist (trivalent) n/N (%)	Placebo n/N (%)	FluMist (trivalent) n/N (%)	Inj. influenza vaccine n/N (%)
Nasal congestion/ rhinorrhoea	<i>Respiratory, thoracic & mediastinal disorders</i>	2065/3241 (63.7%)	1134/1992 (56.9%)	2327/4101 (56.7%)	1847/4108 (45.0%)
Decreased appetite	<i>Metabolism & nutrition disorders</i>	596/2474 (24.1%)	353/1629 (21.7%)	650/4100 (15.9%)	623/4107 (15.2%)
Malaise	<i>General disorders & administration site conditions</i>	447/3239 (13.8%)	232/1991 (11.7%)	536/4100 (13.1%)	485/4107 (11.8%)
Headache	<i>Nervous system disorders</i>	36/268 (13.4%)	13/200 (6.5%)	541/3933 (13.8%)	489/3985 (12.3%)
Pyrexia ^d	<i>General disorders & administration site conditions</i>	361/3229 (11.2%)	191/1979 (9.7%)	379/4073 (9.3%)	350/4082 (8.6%)
Myalgia	<i>Musculoskeletal & connective tissue disorders</i>	21/259 (8.1%)	10/191 (5.2%)	226/3931 (5.7%)	275/3983 (6.9%)

N - Number of subjects evaluated for the specific solicited event

^a Includes Studies D153-P002, D153-P501 (Year 1), D153-P502 (Year 1), D153-P504 (Year 1), D153-P511, D153-P513 and D153-P526. Follow-up time for Study D153-P526 was Days 0-6 post dose

^b Includes Studies MI-CP111, D153-P002, D153-P514 and D153-P515

^c MedDRA v 8.0

^d Pyrexia collected as a solicited event did not occur at a 2% higher rate compared with placebo. Pyrexia did occur at a 2% higher rate compared with placebo based on a pooled analysis of adverse events of the same placebo-controlled studies (9.6% trivalent version of FluMist versus 7.5% placebo)

In an active-controlled clinical study (MI-CP111; Belshe et al 2007), an increased rate of hospitalisations (for any cause) through 180 days after final vaccination dose was observed in children 6-11 months of age [6.1% (42/684) trivalent version of FluMist versus 2.6% (18/683) injectable influenza vaccine]. The rate of hospitalisations was not increased in trivalent version of FluMist recipients 12 months and older. In the same study an increased rate of wheezing through 42 days was observed in children 6-23 months of age [5.9% (117/1992) trivalent version of FluMist versus 3.8% (75/1975) injectable influenza vaccine]. The rate of wheezing was not increased in trivalent version of FluMist recipients 24 months and older. FluMist Quadrivalent is not recommended for use in children younger than 24 months, and should not be used in children younger than 12 months (see *Precautions*).

Post marketing experience

The following adverse reactions have been identified during post-approval use of FluMist Quadrivalent or trivalent version of FluMist. Because these reactions 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.

System Organ Class	Event
<i>Immune system disorders</i>	Hypersensitivity reactions (including anaphylactic reaction, facial oedema & urticaria)
<i>Nervous system disorders</i>	Guillain-Barré syndrome
<i>Respiratory, thoracic & mediastinal disorders</i>	Epistaxis
<i>Skin and subcutaneous tissue disorders</i>	Rash
<i>Congenital, familial & genetic disorders</i>	Exacerbation of symptoms of Leigh syndrome (mitochondrial encephalomyopathy)

DOSAGE AND ADMINISTRATION

Children and adolescents (24 months to less than 18 years of age)

Age	Dose	Schedule
24 months to 8 years of age	1 or 2 doses ^a 200 µL (administered as 100 µL per nostril)	If 2 doses, administer at least 4 weeks apart
9 years to less than 18 years of age	1 dose 200 µL (administered as 100 µL per nostril)	N/A

^a - For children 24 months to 8 years of age who have not previously been vaccinated against seasonal influenza, 2 doses are recommended. For children 24 months to 8 years of age who have been vaccinated against seasonal influenza, one dose is recommended. Refer to the national recommendations as per the current Immunisation Handbook; N/A – not applicable

Administration

Do not inject FluMist Quadrivalent parenterally.

FluMist Quadrivalent is for nasal use, administered as a divided dose in both nostrils, as described below. Each FluMist Quadrivalent nasal applicator is for single use in one patient only.

In the absence of compatibility studies, this vaccine must not be mixed with other medicines/vaccines.

After use, any remaining vaccine and container must be disposed of safely, preferably by heat inactivation or incineration, according to locally agreed procedures.

Refer to the following administration diagrams (Figure 1 and Figure 2 below) for step-by-step administration instructions. Detailed administration instructions are also provided within each pack.

Figure 1 The FluMist Quadrivalent nasal applicator

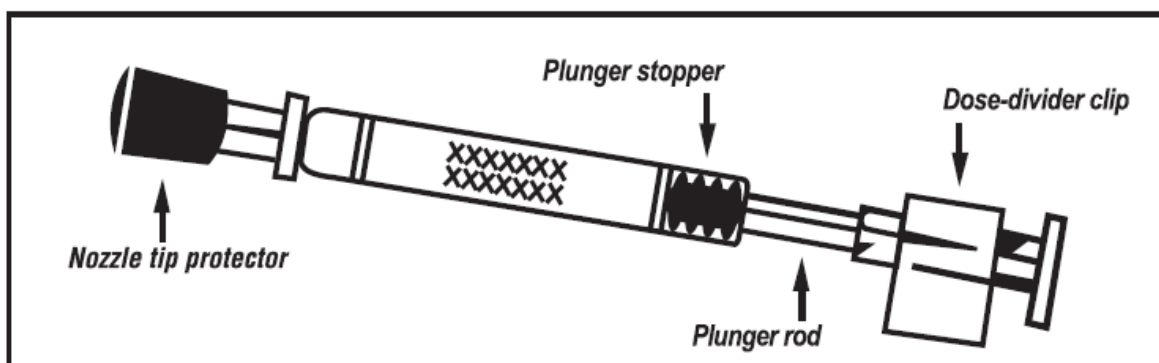
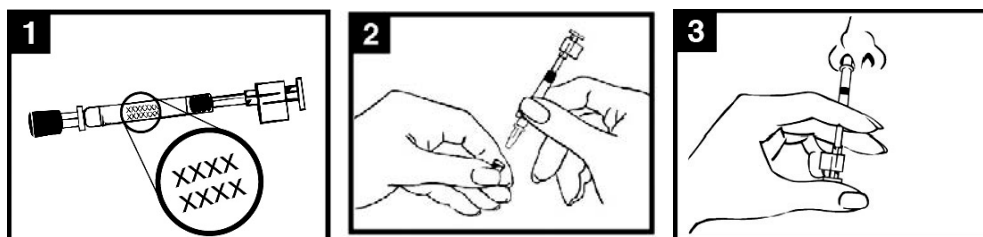


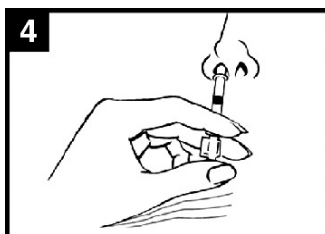
Figure 2 Instructions for FluMist Quadrivalent administration



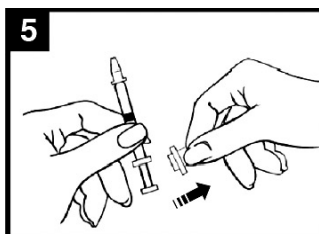
1
Check expiration date.
 Product must be used before date on applicator label.

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

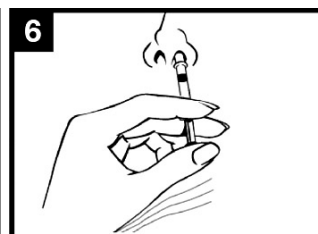
3
 With the patient in an upright position, place the tip just inside the nostril to ensure the vaccine is delivered into the nose.



4
 With a single motion, depress plunger **as rapidly as possible** until the dose-divider clip prevents you from going further.



5
 Pinch and remove the dose-divider clip from plunger.



6
 Place the tip just inside the other nostril and with a single motion, depress plunger **as rapidly as possible** to deliver remaining vaccine.



DO NOT INJECT. DO NOT USE A NEEDLE.

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

Do not use FluMist Quadrivalent if damaged, for example if the plunger is loose or displaced from the sprayer or if there are any signs of leakage.

OVERDOSAGE

There have been occasional reports of administration of twice the recommended dose of FluMist Quadrivalent and trivalent version of FluMist in the post-marketing

Attachment 1: Product information for AusPAR FluMist Quadrivalent live attenuated influenza vaccine AstraZeneca Pty Ltd PM 2015 01533 1-2 Final 6 November 2017. This Product Information was approved at the time this AusPAR was published.

setting. The adverse reactions reported were similar to those seen with the recommended single dose of FluMist Quadrivalent.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

FluMist Quadrivalent nasal spray is a 200 µL suspension in a pre-filled, single-use nasal applicator (Type 1 glass) with a nozzle (polypropylene with polyethylene transfer valve), nozzle tip-protector cap (synthetic rubber), plunger rod, plunger-stopper (butyl rubber) and a dose-divider clip. The nasal applicator contains no latex.

The ingredients of the nasal spray are detailed in the *Description* section above.

Packs of 1 or 10 nasal applicators are registered. Not all pack sizes may be available in Australia.

Storage conditions

Store at 2°C to 8°C (Refrigerate. Do not freeze).

A single temperature excursion up to 25°C 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 to 8°C) and used as soon as feasible. Subsequent excursions are not permitted.

Keep the nasal applicator in the carton in order to protect from light.

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
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MACQUARIE PARK NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

<<TBC>>

DATE OF MOST RECENT AMENDMENT

N/A << draft 12 October 2016>>

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