AUSTRALIAN PRODUCT INFORMATION

FLUMIST®
(influenza virus vaccine) nasal spray

1 NAME OF THE MEDICINE

FLUMIST influenza virus vaccine (live attenuated)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.2mL dose of FLUMIST contains $10^{7.0\pm0.5}$ FFU (fluorescent focus units) of each of three live attenuated influenza virus reassortant strains propagated in specific pathogen-free (SPF) eggs from SPF chicken flocks.

The three strains used for the 20XX season are:

- A/XXX/XX/XXXX (H1N1)
- A/XXX/XX/XXXX (H3N2)
- B/XXX/XX/XXXX (Victoria lineage)

This influenza vaccine complies with the World Health Organization (WHO) and Australian Influenza Vaccine Committee (AIVC) recommendations for the 20XX Southern Hemisphere influenza season.

FLUMIST contains hydrolysed gelatin (porcine Type A). Residual amounts of ovalbumin (<0.24 µg/dose; an egg protein) and also traces of gentamicin sulfate (<0.015 µg/dose; a trace residue) from the manufacturing process may be present. For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Nasal spray.

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Table 1: 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] 0.2mL (administered as 0.1mL per nostril)	If 2 doses, administer at least 4 weeks apart
9 years to less than 18 years of age	1 dose 0.2mL (administered as 0.1mL 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

Method of administration

Do not inject FLUMIST parenterally.

FLUMIST is for nasal use, administered as a divided dose as described in Figure 2: Instructions of FLUMIST administration. Each FLUMIST nasal applicator is for single use, Figure 1 in one patient only.

Figure 1: The FLUMIST nasal applicator

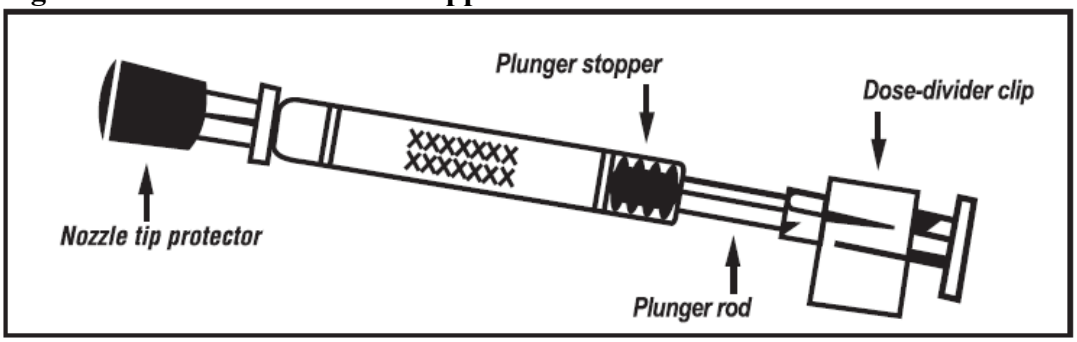
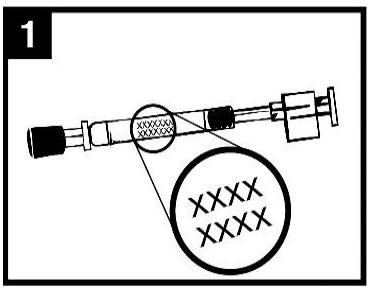
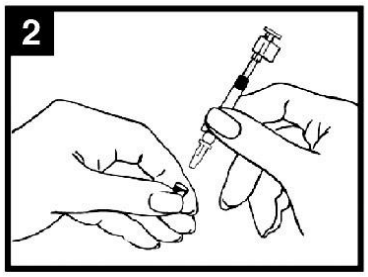


Figure 2: Instructions of FLUMIST administration

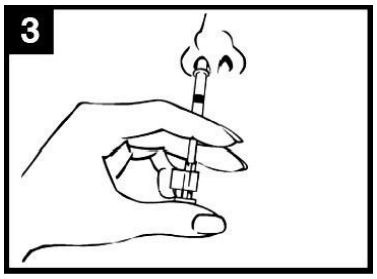


Check expiration date.

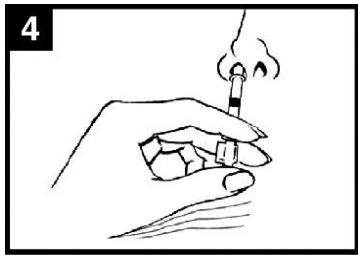
Product must not be used after date on applicator label.



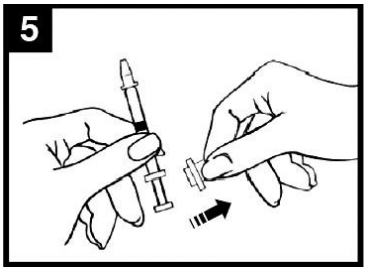
Remove rubber tip protector. Do not remove dose-divider clip at the other end of the applicator.



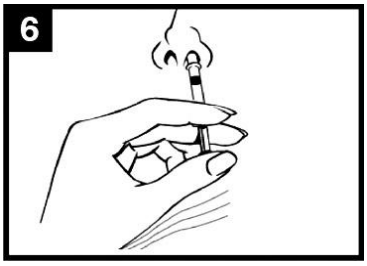
With the patient in an upright position, place the tip just inside the nostril to ensure the vaccine is delivered into the nose.



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



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 (i.e. sniffing) is not required by the patient during vaccine administration.

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

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.

4.3 CONTRAINDICATIONS

Do not administer FLUMIST to:

- Children and adolescents who have had a severe allergic reaction (e.g. anaphylaxis) to the active substances, any of the excipients (e.g. gelatin), gentamicin (a trace residue), eggs or egg proteins (e.g. ovalbumin). See Section 2 Qualitative and quantitative composition and Section 6.1 List of excipients.
- 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 Section 4.4 Special warnings and precautions for use).
- 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 Section 4.5 Interactions with other medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

FLUMIST may not protect all individuals receiving the vaccine.

Risk in children <24 months of age

Do not administer FLUMIST 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 FLUMIST. It is not recommended to administer FLUMIST 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 FLUMIST (see Section 4.8 Adverse effects (Undesirable 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 has not been studied in immunocompromised individuals. Data on the safety and shedding of FLUMIST in immunocompromised individuals are limited (see Section 0 5.1 Pharmacodynamic properties/Clinical trials). FLUMIST administration to immunocompromised individuals should be based on careful consideration of potential benefits and risks (see also Section 4.3 Contraindications). FLUMIST is not contraindicated for use in individuals with asymptomatic HIV infection (see Section 0 5.1 Pharmacodynamic properties/Clinical trials*)*; or individuals who

are receiving topical/inhaled corticosteroids or low-dose systemic corticosteroids or those receiving corticosteroids as replacement therapy e.g. for adrenal insufficiency.

Vaccination with a live vaccine

Vaccine recipients/caregivers should be informed that FLUMIST 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 (e.g. bone marrow transplant recipients requiring isolation) for 1-2 weeks following vaccination.

Guillain Barre Syndrome

If Guillain Barre syndrome (GBS) has occurred within 6 weeks of any prior influenza vaccination, the decision to give FLUMIST should be based on careful consideration of the potential benefits and potential risks.

Use in the elderly

FLUMIST is not recommended in adults.

Paediatric use

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

Effects on laboratory tests

No data available.

Medical Conditions Predisposing to Influenza Complications

The safety of FLUMIST in individuals with underlying medical conditions that may predispose them to complications following wild-type influenza infection has not been established.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Aspirin

Do not administer FLUMIST to children and adolescents (under 18 years of age) receiving salicylate therapy (see Section 4.3 Contraindications). Do not use salicylates in children and adolescents for 4 weeks after vaccination with FLUMIST unless medically indicated as Reye's syndrome has been reported following the use of salicylates during wild-type influenza infection.

Other vaccines

FLUMIST may be given at the same time as other vaccines. Concurrent administration 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 Section 0 5.1 Pharmacodynamic properties/Clinical trials). Adverse events were similar to those seen in other clinical studies with FLUMIST. Studies did not show clinically meaningful changes in immune responses to measles, mumps, rubella, varicella, orally administered poliovirus or FLUMIST.

Antiviral agents

The concurrent use of FLUMIST 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, it is recommended:

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

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

4.6 FERTILITY, PREGNANCY AND LACTATION

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 has not been associated with adverse maternal or fetal outcomes. FLUMIST 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 during pregnancy. Refer to National recommendations as per the current Immunisation Handbook.

There are limited data from the use of FLUMIST in pregnant women. There was no evidence of significant maternal adverse outcomes in 138 pregnant women who had a record of receiving FLUMIST in a US based health insurance claims database. In more than 300 case reports in the AstraZeneca safety database and over 150 case reports from the US Vaccine Adverse Event Reporting System of trivalent and quadrivalent version of FLUMIST administration to pregnant women, no unusual patterns of pregnancy complications or fetal outcomes were observed.

The effects of FLUMIST on embryo-fetal and pre-weaning development were evaluated in developmental toxicity studies in pregnant rats and pregnant ferrets. 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). Ferrets were administered the human dose of FLUMIST intranasally on gestation days 3, 6, 13 and 22. No adverse effects on pregnancy, parturition, lactation or embryo-fetal development were observed in either study and, in addition no adverse effects on pre-weaning development were observed in the rat study. There were no fetal malformations or other evidence of teratogenesis observed.

Use in lactation

Studies in lactating women have not been conducted with FLUMIST. Limited available evidence suggests that FLUMIST is not excreted in human milk. There are some viruses that are excreted in human milk. Caution should be exercised if FLUMIST 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.

4.7 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

Additional experience has occurred with marketed use of trivalent and quadrivalent versions of FLUMIST.

Adverse reactions in clinical studies

Children and adolescents

The safety of FLUMIST was evaluated in an AF-SPG placebo-controlled Study (AV019) conducted in a Health Maintenance Organisation (HMO) in children 1 through 17 years of age (FLUMIST = 6473, 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 3.53, 90% CI: 1.1, 15.7).

In Study MI-CP111, children 6 through 59 months of age were randomised to receive FLUMIST or inactivated Influenza Virus Vaccine. Wheezing requiring bronchodilator therapy or accompanied by respiratory distress or hypoxia was prospectively monitored from randomisation through 42 days post last vaccination. Hospitalisation due to all causes was prospectively monitored from randomisation through 180 days post last vaccination. Increases in wheezing and hospitalisation (for any cause) were observed in children 6 months through 23 months of age who received FLUMIST compared to those who received inactivated Influenza Virus Vaccine, as shown in Table 2.

Table 2: Percentages of Children with Hospitalisations and Wheezing from Study MI-CP111* Percentages of Children with Hospitalisations and Wheezing from Study MI-CP111*

Adverse Reaction	Age Group	FLUMIST (n/N)	Active Control† (n/N)
Hospitalisations‡	6-23 months	4.2% (84/1992)	3.2% (63/1975)
	24-59 months	2.1% (46/2187)	2.5% (56/2198)
Wheezing§	6-23 months	5.9% (117/1992)	3.8% (75/1975)
	24-59 months	2.1% (47/2187)	2.5% (56/2198)

* NCT00128167; see www.clinicaltrials.gov

† Inactivated Influenza Virus Vaccine administered intramuscularly.

‡ Hospitalisation due to any cause from randomisation through 180 days post last vaccination.

§ Wheezing requiring bronchodilator therapy or accompanied by respiratory distress or hypoxia evaluated from randomisation through 42 days post last vaccination.

Most hospitalisations observed were due to gastrointestinal and respiratory tract infections and occurred more than 6 weeks post vaccination. In post-hoc analysis, rates of hospitalisation 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 3 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 3: 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

	Studies D153-P501* & AV006		Study MI-CP111†	
	FLUMIST N = 876-1759¶	Placebo‡ N = 424-1034¶	FLUMIST N = 2170¶	Active Control§ N = 2165¶
Event	%	%	%	%
Runny Nose/ Nasal Congestion	58	50	51	42
Decreased Appetite	21	17	13	12
Irritability	21	19	12	11
Decreased Activity (Lethargy)	14	11	7	6
Sore Throat	11	9	5	6
Headache	9	7	3	3
Muscle Aches	6	3	2	2
Chills	4	3	2	2
Fever				
> 100°F Oral	16	11	13	11
> 100 - ≤ 101°F Oral	9	6	6	4
> 101 - ≤ 102°F Oral	4	3	4	3

* NCT00192244; see www.clinicaltrials.gov

† NCT00128167; see www.clinicaltrials.gov

‡ Study D153-P501 used saline placebo; Study AV006 used AF-SPG placebo.

§ Inactivated Influenza Virus Vaccine administered intramuscularly.

¶ Number of evaluable subjects (those who returned diary cards) for each reaction. Range reflects differences in data collection between the 2 pooled studies.

In clinical studies D153-P501 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 (2% FLUMIST vs.1% active control).

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 3. 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.

FLUMIST is not recommended for use in children younger than 24 months, and should not be used in children younger than 12 months (see Section 4.4 Special warnings and precautions for use).

Post marketing experience

The following adverse reactions have been identified during post-approval use 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.

Table 4: Adverse Reactions identified during post-approval use of FLUMIST
Adverse Reactions identified during post-approval use of FLUMIST

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There have been occasional reports of administration of twice the recommended dose of FLUMIST in the post-marketing setting. The adverse reactions reported were similar to those seen with the recommended single dose of FLUMIST.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

FLUMIST is a trivalent vaccine that contains antigens for three influenza virus strains, an A/(H1N1) strain, an A/(H3N2) strain, and a B strain (Victoria lineage). The influenza virus strains in FLUMIST 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 strain) or 39°C (Type A strains), temperatures at which many wildtype influenza viruses grow efficiently); and (c) *attenuated (att)* (i.e. they do not produce classic influenza-like illness in the ferret model of human influenza infection). 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 three viruses contained in FLUMIST maintain the replication characteristics and phenotypic properties of the master donor virus (MDV) and express the haemagglutinin (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 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.

Clinical trials

Studies in children and adolescents

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. The results of these pivotal efficacy and safety studies are discussed in detail below.

Efficacy data in the paediatric population for FLUMIST consists of 9 controlled studies conducted during 7 influenza seasons. Four placebo-controlled studies included second season revaccination. FLUMIST demonstrated superiority in 3 active-controlled studies with injectable trivalent inactivated influenza vaccines (TIV). See Table 5 (placebo controlled) and Table (active controlled) for a summary of FLUMIST efficacy results in children. The pivotal studies are then detailed further within the text below each table.

Table 5: FLUMIST efficacy in placebo-controlled studies in children

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 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 6 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, 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 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 FLUMIST or placebo. See Table 6 for a description of the results.

Table 6: Efficacy[a] 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 n (%)	**Placebo n (%)**	**% Efficacy (95% CI)**	**FLUMIST 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; FLUMIST demonstrated 87.0% (95% CI: 77.0, 92.6) efficacy against culture-confirmed influenza illness.

Table 7: FLUMIST relative efficacy in active-controlled studies in children and adolescents 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 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 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 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 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 ≥38°C oral or equivalent) plus 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 for a description of the overall results and Table for a description of the results by strain and antigenic similarity.

Table 8: Comparative efficacy against culture-confirmed modified CDC-ILIa caused by wild-type strains in children <5 years of age (ATP population)

	FLUMIST			Active control[b]			Reduction in rate - FLUMIST[c]	95% CI
	N	# of cases	Rate (cases/N)	N	# of cases	Rate (cases/N)		
Matched strains								

	FLUMIST			Active control[b]			Reduction in rate - FLUMIST[c]	95% CI
	N	# of cases	Rate (cases/N)	N	# of cases	Rate (cases/N)		
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 ³ 38°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

Studies in immunocompromised individuals

Safety and shedding of vaccine virus following FLUMIST administration were evaluated in children in a randomised (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/mm^3] and 25 HIV-negative children 1-7 years of age, and in a randomised (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 FLUMIST administration. In the 5-17 year old age group, 1 inactivated influenza vaccine recipient and 1 FLUMIST recipient experienced pneumonia within 28 days of vaccination (Days 17 and 13, respectively). The effectiveness of FLUMIST 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 randomised 1:1 to receive 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 FLUMIST 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 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 randomised in a 1:1:1 ratio to MMR, varicella vaccine and placebo (group 1); MMR, varicella vaccine and FLUMIST (group 2); or FLUMIST alone (group 3). 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. Adverse reactions were similar to those seen in other clinical trials with FLUMIST (see Section 4.8 Adverse effects (Undesirable effects)). No evidence of interference with immune response to measles, mumps, rubella, varicella and FLUMIST vaccines was observed (see Section 4.5 Interactions with other medicines and other forms of interactions).

In Study D153-P511 (Breiman et al 2009) concomitant administration of FLUMIST and oral poliovirus (OPV) was studied in 2,503 subjects 6-35 months of age. Subjects were randomised 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 Section 4.5 Interactions with other medicines and other forms of interactions).

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).

5.2 PHARMACOKINETIC PROPERTIES

Not applicable.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

FLUMIST contains the following as inactive ingredients: sucrose, dibasic potassium phosphate, monobasic potassium phosphate, hydrolysed gelatin (porcine Type A), arginine hydrochloride, monosodium glutamate monohydrate 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 contains no preservatives (i.e. no thiomersal).

See also Section 2 Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

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

See also Section 4.5 Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2ºC to 8ºC (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.

6.5 NATURE AND CONTENTS OF CONTAINER

FLUMIST nasal spray is a 0.2mL 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.

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Not applicable for vaccines

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
66 Talavera Road
MACQUARIE PARK NSW 2113

Telephone: 1800 805 342

9 DATE OF FIRST APPROVAL

18 November 2025

10 DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
N/A	New product (trivalent version of FLUMIST QUADRIVALENT)

VV-RIM-10046707 v2.0