Afluria Quad™

WARNING: Afluria Quad™ vaccine is indicated for use only in persons aged 18 years and over. It must not be used in persons under 18 years (see Contraindications).

For season 2017

NAME OF THE MEDICINE

Afluria Quad™ vaccine
Inactivated Quadrivalent Influenza Vaccine (split virion)
Suspension for injection

DESCRIPTION

This is a purified, inactivated, split virion (split virus) vaccine. Each 0.5 mL dose contains antigens for the 2017 influenza season representative of the following types:

A/Singapore/GP1908/2015 (IVR-180) (A/Michigan/45/2015 (H1N1) – like):
15 µg haemagglutinin per dose
A/Hong Kong/4801/2014 (NYMC X-263B) (A/Hong Kong/4801/2014 (H3N2) – like):
15 µg haemagglutinin per dose
B/Phuket/3073/2013 (B/Phuket/3073/2013- like):
15 µg haemagglutinin per dose
B/Brisbane/46/2015 (B/Brisbane/60/2008 - like):
15 µg haemagglutinin per dose

Each 0.5 mL dose also contains, nominally: sodium chloride 4.1 mg, dibasic sodium phosphate anhydrous 0.3 mg, monobasic sodium phosphate 0.08 mg, potassium chloride 0.02 mg, monobasic potassium phosphate 0.02 mg and calcium chloride 0.5 µg.
Trace amounts of the following may also be present in each 0.5 mL dose: sodium taurodeoxycholate, ovalbumin (< 1 µg), sucrose, neomycin sulfate, polymyxin B sulfate and propiolactone.

The type and amount of viral antigens in Afluria Quad™ vaccine conform to the requirements of the Australian Influenza Vaccine Committee for the winter of 2017. The strains chosen for vaccine manufacture are endorsed by the Australian Influenza Vaccine Committee as being antigenically equivalent to the reference virus.

The vaccine is prepared from virus grown in the allantoic cavity of embryonated eggs, purified by zonal centrifugation, inactivated by propiolactone and disrupted by sodium taurodeoxycholate. Afluria Quad™ vaccine conforms in safety and sterility to the requirements of the British Pharmacopoeia.

Afluria Quad™ vaccine is a clear to slightly opaque liquid with some sediment that resuspends upon shaking.
See Administration.

PHARMACOLOGY

Afluria Quad™ vaccine has been shown to induce antibodies to the viral surface glycoprotein, haemagglutinin. These antibodies are important in the prevention of natural infection.

Seroprotection is generally obtained within 2 to 3 weeks. The duration of post-vaccination immunity to homologous strains, or to strains closely related to the vaccine strains, varies but is usually 6 to 12 months.

CLINICAL TRIALS

QIV-01 (NCT02214225, see http://clinicaltrials.gov) was a randomised, double-blind, active comparator-controlled trial conducted in the US in adults aged 18 years and older. Subjects in the per protocol population that was used for the primary immunogenicity analysis received one dose of either Afluria Quad™ vaccine (N=1691) or one of two formulations of comparator trivalent influenza vaccine (TIV-1 N=854 or TIV-2 N=850), each containing an influenza type B virus that corresponded to one of the two B viruses in Afluria Quad™ vaccine (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The mean age of the enrolled population was 58 years. 57% were female, 82% were White and 16% Black/African American. The age sub-groups were 18 to < 65 years and ≥ 65 years with a mean age of 43 years and 73 years, respectively. Post-vaccination immunogenicity was evaluated on sera obtained 21 days after administration of a single dose of Afluria Quad™ vaccine or TIV.

The co-primary endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted for baseline HI titers) and the difference in seroconversion rates for each vaccine strain, 21 days after the vaccination. Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the GMT ratio (TIV/Afluria Quad™ vaccine) did not exceed 1.5 and the upper bound of the 2-sided 95% CI of the seroconversion rate difference (TIV minus Afluria Quad™ vaccine) did not exceed 10% for each strain.

Serum HI antibody responses to Afluria Quad™ vaccine were non-inferior to both TIVs for all influenza strains. Additionally, non-inferiority was demonstrated for both endpoints in both age sub-groups, adults aged 18 to < 65 years and ≥ 65 years (Table 1), for all strains. Antibody responses were lower in adults aged ≥ 65 years.

Superiority of the immune response to each of the influenza B strains contained in Afluria Quad™ vaccine was shown relative to the antibody response after vaccination with TIV formulations not containing that B lineage strain. Superiority against the alternate B strain was also demonstrated for each of the influenza B strains in both age sub-groups; 18 to < 65 years and ≥ 65 years.

Post-hoc analyses of immunogenicity by gender did not demonstrate significant differences between males and females. The study population was not sufficiently diverse to assess differences between races or ethnicities.

Table 1: QIV-01: Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of Non-Inferiority of Afluria Quad™ vaccine Relative to Trivalent Influenza Vaccine (TIV) for each Strain, at 21 Days Post-Vaccination by Age Cohort (Per Protocol Population)

	Post-vaccination GMT [a]		GMT Ratio	Seroconversion % [b]		Difference	Met both pre-defined non-inferiority criteria? [c]
Strain	Afluria Quad™ vaccine	Pooled TIV or TIV-1 (B Yam) or TIV-2 (B Vic)	Pooled TIV or TIV-1 or TIV-2 over Afluria Quad™ vaccine (95% CI)	Afluria Quad™ vaccine	Pooled TIV or TIV-1 (B Yam) or TIV-2 (B Vic)	Pooled TIV or TIV-1 or TIV-2 minus Afluria Quad™ vaccine (95% CI)	
18 to < 65 years	**Afluria Quad™ vaccine N=835, Pooled TIV N=845, TIV-1 N=424, TIV-2 N=421**						
A/H1N1	432.7	402.8	0.93 [d] (0.85, 1.02)	51.3	49.1	-2.1 [g] (-6.9, 2.7)	Yes
A/H3N2	569.1	515.1	0.91 [d] (0.83, 0.99)	56.3	51.7	-4.6 [g] (-9.4, 0.2)	Yes
B/YAM	92.3	79.3	0.86 [e] (0.76, 0.97)	45.7	41.3	-4.5 [h] (-10.3, 1.4)	Yes
B/VIC	110.7	95.2	0.86 [f] (0.76, 0.98)	57.6	53.0	-4.6 [i] (-10.5, 1.2)	Yes
≥ 65 years	**Afluria Quad™ vaccine N=856, Pooled TIV N=859, TIV-1 N=430, TIV-2 N=429**						
A/H1N1	211.4	199.8	0.95 [d] (0.88, 1.02)	26.6	26.4	-0.2 [g] (-5.0, 4.5)	Yes
A/H3N2	419.5	400.0	0.95 [d] (0.89, 1.02)	25.9	27.0	1.1 [g] (-3.7, 5.8)	Yes
B/YAM	43.3	39.1	0.90 [e] (0.84, 0.97)	16.6	14.4	-2.2 [h] (-8.0, 3.6)	Yes
B/VIC	66.1	68.4	1.03 [f] (0.94, 1.14)	23.5	24.7	1.2 [i] (-4.6, 7.0)	Yes

Abbreviations: CI, confidence interval; GMT, geometric mean titer.

[a] GMT results were modelled on a multi-variable adjusted analysis including gender, vaccination history, pre-vaccination HI titers and other factors.

[b] Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer ≥ 1:10 or an increase in titer from < 1:10 to ≥ 1:40.

[c] Non-inferiority (NI) criteria for the GMT ratio: upper bound of 2-sided 95% CI on the ratio of Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria)/ Afluria Quad™ vaccine. GMT should not exceed 1.5. NI criteria for the seroconversion rate (SCR) difference: upper bound of 2-sided 95% CI on the difference between SCR Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria) minus Afluria Quad™ vaccine should not exceed 10%.

[d] Pooled TIV/Afluria Quad™ vaccine

[e] TIV-1 (B Yamagata)/Afluria Quad™vaccine

[f] TIV-2 (B Victoria)/Afluria Quad™ vaccine

[g] Pooled TIV - Afluria Quad™ vaccine

[h] TIV-1 (B Yamagata) - Afluria Quad™ vaccine

[i] TIV-2 (B Victoria) - Afluria Quad™ vaccine

INDICATIONS

For the prevention of influenza caused by Influenza Virus, Types A and B contained in the vaccine. The vaccine is indicated for use only in persons aged 18 years and over.
See Precautions and Dosage and Administration.

For full details regarding recommendations for influenza vaccination, please refer to the relevant national immunisation guidelines.

CONTRAINDICATIONS

Afluria Quad™ vaccine is contraindicated in children < 18 years because the safety and efficacy in this age group has not been established.
Afluria Quad™ vaccine is contraindicated in individuals with history of hypersensitivity to egg protein or any of the constituents or trace residues of this vaccine.
Immunization should generally be postponed in individuals having a febrile illness or acute infection.

PRECAUTIONS

The safety and efficacy of Afluria Quad™ vaccine in children < 18 years has not been established in clinical trials.
Administration of the 2010 Fluvax® TIV was associated with increased rates of fever and febrile convulsions, predominantly in children below the age of 5 years as compared to previous years.

As with other injectable vaccines, appropriate medical treatment and supervision should always be available to manage the rare event of an anaphylactic reaction following administration of the vaccine. Adrenaline should always be ready for immediate use whenever any injection is given.

In immunocompromised patients the antibody response may be lower.

If Guillain-Barré syndrome has occurred within 6 weeks of previous influenza vaccination, the decision to give Afluria Quad™ vaccine should be based on careful consideration of the potential benefits and risks.

Effects on Fertility

Afluria Quad™ vaccine has not been evaluated for possible effect on fertility.

A reproductive study of female rats vaccinated with Fluvax® TIV revealed no impairment of fertility.

Use in Pregnancy: Category B2

The safety and effectiveness of Afluria Quad™ vaccine has not been established in pregnant women. Therefore, careful consideration should be made regarding the benefits and risks prior to administration of Afluria Quad™ vaccine to women who are pregnant, or plan to become pregnant.

No embryofetal development study has been conducted with Afluria Quad™ vaccine. An animal reproduction study has been conducted with Fluvax® TIV. This study did not demonstrate any maternal or developmental toxicity.

Use in Lactation

The safety and effectiveness of Afluria Quad™ vaccine has not been established in nursing mothers.

Paediatric Use

Afluria Quad™ vaccine was not administered in children < 18 years of age in QIV-01.

Use in the Elderly

The safety and immunogenicity of Afluria Quad™ vaccine was evaluated in adults ≥ 65 years in QIV-01 (See **ADVERSE EFFECTS** and **CLINICAL TRIALS**). There were 541 enrolled subjects aged 65 to < 75 years and 329 enrolled subjects ≥ 75 years. Antibody responses to Afluria Quad™ vaccine were non-inferior to comparator trivalent influenza (TIV-1 and TIV-2) responses in adults ≥ 65 years of age, and lower than in younger adults.

Genotoxicity

Afluria Quad™ vaccine has not been evaluated for genotoxic potential.

Carcinogenicity

Afluria Quad™ vaccine has not been evaluated for carcinogenic potential.

Effect on Laboratory Tests

Interference of Afluria Quad™ vaccine with laboratory and/or diagnostic tests has not been studied.

INTERACTIONS WITH OTHER MEDICINES

No interaction studies have been performed on interaction between influenza vaccines in general and other vaccines or medications.

ADVERSE EFFECTS

Clinical trials:

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

In adults 18 to <65 years, the most commonly reported injection-site adverse reaction observed in clinical

studies with Afluria Quad™ vaccine was pain (≥40%). The most common systemic adverse events observed were myalgia and headache (≥20%). In adults ≥ 65 years of age, the most commonly reported injection-site adverse reaction observed in clinical studies with Afluria Quad™ vaccine was pain (≥20%). The most common systemic adverse event observed was myalgia (≥10%). A small number of adults ≥ 65 years of age (n=4) experienced severe injection site swelling.

Adult studies:

QIV-01 (NCT02214225, see http://clinicaltrials.gov) was a randomised, double-blind, active-controlled trial conducted in the US in 3449 subjects aged ≥ 18 years. Subjects in the safety population received one dose of either Afluria Quad™ vaccine (N=1721) or one of two formulations of comparator trivalent influenza vaccine (TIV-1 N=864 or TIV-2 N=864) each containing an influenza type B virus that corresponded to one of the two B viruses in Afluria Quad™ vaccine (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage).

Local (injection-site) adverse reactions and systemic adverse events were solicited for 7 days post-vaccination (Table 2). Unsolicited adverse events were collected for 28 days post-vaccination. Serious adverse events were collected for 180 days post-vaccination. All adverse events are presented regardless of any treatment causality assigned by study investigators.

Table 2: QIV-01: Proportion of Subjects per Age Cohort with Any Solicited Local Adverse Reactions or Systemic Adverse Events within 7 Days after Administration of Afluria Quad™ vaccine or Trivalent Influenza vaccine (TIV-1 or TIV-2), Irrespective of Causality (Safety population)

	Percentage (%) [a] of Subjects in each Age Cohort Reporting an Event											
	Subjects 18 to < 65 years						Subjects ≥ 65 years					
	Afluria Quad™ vaccine N=854 [b]		TIV-1 N=428 [b]		TIV-2 N=430 [b]		Afluria Quad™ vaccine N=867 [b]		TIV-1 N=436 [b]		TIV-2 N=434 [b]	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
Local Adverse Reactions[c]												
Pain	47.9	0.7	43.7	1.4	50.7	1.2	24.6	0.1	22. 7	0	21.0	0.2
Swelling/Lump	3.7	0.1	2.3	0	3.5	0.2	3.2	0.5	1.8	0	1.6	0
Redness	2.9	0	2.8	0	2.8	0	4.2	0.3	2.1	0	2.5	0.2
Systemic Adverse Events[d]												
Myalgia (muscle ache)	25.5	1.9	23.4	1.4	24.2	1.2	12.7	0.3	14.0	0.7	12.2	0.5
Headache	21.7	1.7	15.2	0.9	19.1	1.2	8.4	0	7. 1	0.2	7.8	0.7
Malaise	8.9	0.7	9.1	0	9.3	0.7	4.4	0.5	5.0	0.2	5.1	0.2
Nausea	6.9	0.6	7.7	0.5	6.3	1.2	1.6	0	1.8	0	2.1	0.2
Chills	4.8	0.6	4.4	0.2	4.7	0.5	2.0	0	2.1	0.5	1.4	0.2
Vomiting	1.5	0.4	0.9	0	2.3	0.7	0.5	0.1	0	0	0.7	0.2
Fever	1.1	0.4	0.9	0	0.5	0	0.2	0	0.9	0	0.5	0.2

[a] Proportion of subjects reporting each solicited local adverse reaction or systemic adverse event by study vaccine group, based on the number of subjects contributing any follow up safety information for at least one data value of an individual sign/symptom.

[b] N = number of subjects in the Safety Population Subgroup for each study vaccine group.

[c] Local adverse reactions: Grade 3 pain is that which prevents daily activity; Swelling/Lump and redness: any = ≥ 20 mm diameter, Grade 3 = ≥100 mm diameter

[d] Systemic adverse events: Fever: any = ≥ 38.0°C, Grade 3 = ≥ 39.0°C; Grade 3 for all other adverse events is that which prevents daily activity.

In adults 18 to < 65 years who received Afluria Quad™ vaccine, commonly reported unsolicited adverse events were headache (5.3%), oropharyngeal pain (2.5%), back pain (1.9%), diarrhoea (1.6%), cough (1.3%) and nausea (1.1%). In adults ≥ 65 years who received Afluria Quad™ vaccine, commonly reported unsolicited adverse events were headache (2.3%), rhinorrhoea (1.3%), oropharyngeal pain (1.2%) and back pain (1.2%).

Post-marketing surveillance:

There are no post-marketing data available for Afluria Quad™ vaccine.

As the Afluria Quad™ vaccine formulation is consistent with the currently licensed vaccine (Fluvax® TIV), with the exception of an additional B influenza strain, it is assumed that the adverse events experienced after administration of Fluvax® TIV will generally be predictive of the adverse events experienced after

administration of Afluria Quad™ vaccine during postapproval use.

Blood and Lymphatic System Disorders

Thrombocytopenia.

Immune System Disorders

Allergic or immediate hypersensitivity reactions including anaphylactic shock.

Nervous System Disorders

Neuralgia, paraesthesia and convulsions, encephalomyelitis, neuritis or neuropathy, and Guillain-Barré syndrome.

Vascular Disorders

Vasculitis which may be associated with transient renal involvement.

Skin and Subcutaneous Tissue Disorders

Pruritus, urticaria and rash.

General Disorders and Administration Site Conditions

Cellulitis and large injection site swelling

Influenza-like illness.

DOSAGE AND ADMINISTRATION

Immunisation should be undertaken in anticipation of seasonal outbreaks of influenza.

Dosage:

See Indications and Precautions.

Adults from 18 years: 0.5 mL

To provide continuing protection, annual vaccination with vaccine containing the most recent strains is necessary.

Administration:

Afluria Quad™ vaccine should be administered by a health care practitioner in an appropriate setting with an appropriate post-vaccination observation period.

Shake before use. After shaking, the vaccine should appear as a homogenous suspension. The vaccine must be inspected visually prior to administration and should not be used if there is any variation of physical appearance.

See Description.

The vaccine should be administered by intramuscular or deep subcutaneous injection.

Afluria Quad™ vaccine is presented as a single-use syringe and any remaining contents should be discarded.

Afluria Quad™ vaccine can be administered concurrently with other vaccines, however separate syringes and a separate arm should be used.

OVERDOSAGE

There is no specific information on overdose of Influenza Vaccines.
For general advice on overdose management:
In Australia, contact the Poisons Information Centre on 131 126.

PRESENTATION AND STORAGE CONDITIONS

Presentation:

Each disposable syringe contains a single 0.5 mL dose of vaccine.

The Afluria Quad™ vaccine (AUST R 262428) syringe (with fixed-needle) is supplied encased within a clear film wrapper. The presence of the film wrapper provides assurance that the product has not been opened. Do not use if the clear film wrapper is damaged or missing.

Storage Conditions:

Afluria Quad™ vaccine should be stored, protected from light, at 2ºC to 8ºC. IT MUST NOT BE FROZEN.

NAME AND ADDRESS OF THE SPONSOR

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POISONS SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

Date of first inclusion in the ARTG: 22 July 2016 (AUST R 262428)

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