Afluria® Quad

WARNING: Afluria® Quad vaccine is indicated for use only in persons aged 5 years and over. It must not be used in persons under 5 years (see Section 4.3 Contraindications).

For season 2019

1. PRODUCT NAME

Afluria® Quad

Inactivated quadrivalent influenza vaccine (split virion) suspension for injection; containing Influenza virus haemagglutinin as active ingredient.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a purified, inactivated, split virion (split virus) vaccine. Each 0.5 mL dose contains antigens for the 2019 influenza season representative of the following types:

A/Michigan/45/2015 (H1N1) pdm09 – like virus (A/Singapore/GP 1908/2015 (IVR-180A):

15 micrograms HA* per dose

A/Switzerland/8060/2017 (H3N2) – like virus (A/Brisbane/01/2018 (X-311)):

15 micrograms HA* per dose

B/Colorado/06/2017 – like virus (B/Maryland/15/2016):

15 micrograms HA* per dose

B/Phuket/3073/2013 – like virus (B/Phuket/3073/2013 (BVR-1B)):

15 micrograms HA* per dose

*HA - haemagglutinin

For the full list of excipients, see Section 6.1 List of excipients.

Trace amounts of the following may also be present in each 0.5 mL dose: sodium taurodeoxycholate, ovalbumin (< 1 microgram), 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 and the New Zealand Ministry of Health for the winter of 2019. 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.

3. PHARMACEUTICAL FORM

Suspension for injection. Afluria® Quad vaccine is a clear to slightly opaque liquid with some sediment that resuspends upon shaking.

See Section 4.2 Dose and method of administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 **5** years and over.
See Section 4.2 Dose and method of administration and Section 4.4 Special warnings and precautions for use.

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

4.2 Dose and method of administration

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

Dose

Table 1: Afluria® Quad Recommended dosage, by age group

Age Group	**Dose**	**Number of Doses**
Paediatrics		
5 to < 9 years	0.5mL	1 or 2[a]
9 to < 18 years	0.5mL	1
Adults		
≥ 18 years	0.5mL	1

[a]Previously unvaccinated children 5 to < 9 years of age should be given 2 doses at least 4 weeks apart

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

Method of 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 Section 3.1 Pharmaceutical Form.

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

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

4.3 Contraindications

Afluria® Quad vaccine is contraindicated in children less than 5 years of age 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 (see Section 2 Qualitative and Quantitative Composition and Section 6.1 List of excipients).

Immunization should generally be postponed in individuals having a febrile illness or acute infection.

4.4 Special warnings and precautions for use

The safety and efficacy of Afluria® Quad vaccine in children less than 5 years of age has not been established in clinical trials.

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.

Paediatric Use

Afluria® Quad vaccine is not indicated in children less than 5 years of age.

Administration of the 2010 Southern Hemisphere trivalent influenza vaccine (Fluvax® TIV, manufactured by CSL, now Seqirus Pty Ltd) was associated with increased rates of fever and febrile convulsions, predominantly in children below the age of 5 years as compared to previous years.

Following a comprehensive investigation into the 2010 Southern Hemisphere adverse events, Seqirus has modified the manufacturing conditions. A clinical program has subsequently been conducted with Afluria® Quad in adults, and children aged 6 months to less than 18 years. Fever rates in children were lower than those observed in clinical studies conducted prior to 2010 and no related febrile convulsions were reported.

Use in the Elderly

The safety and immunogenicity of Afluria® Quad vaccine was evaluated in adults ≥ 65 years in QIV-01 (See **Section 4.8 Undesirable effects** and **Section 5.1 Pharmacodynamic properties**, **Clinical trial data**). 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.

Effect on Laboratory Tests

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

4.5 Interactions with other medicines and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Effects on Fertility

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

A reproductive study of female rats vaccinated with Seqirus' trivalent influenza vaccine (Fluvax® TIV) revealed no impairment of fertility.

Use in Pregnancy: Category A

No embryofetal development study has been conducted with Afluria® Quad vaccine. A rat reproduction study has been conducted with Seqirus' trivalent influenza vaccine (Fluvax® TIV). This study did not demonstrate any maternal or developmental toxicity.

Influenza vaccination is recommended for pregnant women during any stage of pregnancy. This recommendation is based on the known adverse consequences of influenza infection during pregnancy and the large body of data showing that large numbers of women have been vaccinated during pregnancy with inactivated influenza vaccines with no increased risk of adverse foetal or maternal outcomes attributable to the vaccine. Afluria® Quad vaccine should be given to pregnant women following an assessment of the risks and benefits.

Use in Lactation

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

4.7 Effects on ability to drive and use machines

The vaccine is unlikely to produce an effect on the ability to drive and use machinery.

4.8 Undesirable 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.

Two clinical studies with Afluria® Quad vaccine have been completed.

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.

QIV-02 (NCT02545543, see http://clinicaltrials.gov) was a randomized, observer-blind, comparator-controlled trial that evaluated the immunogenicity and safety of Afluria® Quad vaccine

in subjects aged 5 to < 18 years with a 2015-2016 comparator quadrivalent influenza vaccine. Study subjects were scheduled to receive either a single vaccination or two-vaccination regime as clinically indicated. Local (injection site) adverse reactions and systemic adverse events were solicited for 7 days post vaccination (Table 3). Unsolicited adverse events and cellulitis-like reactions at the injection site were collected for 28 days after the last vaccination; and serious adverse events for six months following last vaccination.

Adult data

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.

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

Abbreviations: Gr3, Grade 3

[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%).

Paediatric data

Afluria® Quad vaccine was administered to children 5 to < 18 years of age in Study QIV-02.

In children 5 to < 18 years, the most common (≥ 10%) injection site reactions were pain (51.4%), redness (17.1%), and induration/swelling (13.8%); the most common solicited systemic adverse events were headache (15.5%) and myalgia (13.1%).

Table 3: QIV-02: 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 Comparator QIV

	Percentage (%) [a] of Subjects in each Age Cohort Reporting an Event							
	Subjects 5 to < 9 years				Subjects 9 to < 18 years			
	Afluria® Quad vaccine N=829 [b]		Comparator QIV N=274 [b]		Afluria® Quad vaccine N=792 [b]		Comparator QIV N=261 [b]	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
Local Adverse Reactions [c]								
Pain	51.3	0.8	49.6	0.7	51.5	0.3	45.2	0.4
Redness	19.4	3.5	18.6	1.8	14.8	1.9	16.1	1.9
Swelling/Lump	15.3	3.4	12.4	2.2	12.2	2.0	10.7	1.9
Systemic Adverse Events [d]								
Headache	12.3	0.1	10.6	0.4	18.8	0.4	14.6	0.4
Myalgia	9.8	0.1	11.3	0.4	16.7	0.3	11.1	0.4
Malaise and Fatigue	8.8	0.4	5.8	0	10.0	0.4	7.7	0
Nausea	7.1	0.1	8.4	0	7.7	0	8.0	0
Diarrhoea	5.2	0	3.6	0	5.4	0	4.2	0
Fever	4.5	1.2	3.6	0.7	2.1	0.5	0.8	0
Vomiting	2.4	0.2	4.4	0	1.8	0	2.3	0

Abbreviations: Gr 3, Grade 3; Comparator QIV, Fluarix® Quadrivalent [GlaxoSmithKline Biologicals])

[a] Percent (%) is derived from the number of subjects that reported the event divided by the Solicited Safety Population in each vaccine group and age cohort.

[b] N = number of subjects in the Solicited Safety Population (subjects who were vaccinated and provided any solicited safety data) for each study vaccine group. Solicited Safety Population was the same for each event.

[c] Local adverse reactions: Grade 3 pain is that which prevents daily activity; Swelling/Lump and redness: any = > 0mm diameter, Grade 3 = > 30mm 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.

There were no vaccine-related deaths reported in this paediatric study QIV-02. There was one

vaccine-related serious adverse event (influenza) reported in this study.

One subject experienced a cellulitis-like reaction (defined as concurrent severe pain, redness and swelling) at the injection site after vaccination with Afluria® Quad vaccine.

In children 5 to < 18 years administered Afluria Quad™ vaccine, cough (2.1%) was the most commonly reported unsolicited adverse event in subjects 5 to < 18 years of age. Other commonly reported unsolicited adverse events (reported by ≥ 1% of subjects) were oropharyngeal pain (1.3%), pyrexia (1.3%) and upper respiratory tract infection (1.1%).
The most commonly reported unsolicited adverse events among subjects who received Afluria® Quad vaccine in ages 5 to < 9 years following the first or second dose included cough (2.8%), pyrexia (2.1%), headache (1.2%), rhinorrhoea (1.2%), upper respiratory tract infection (1.2%), influenza-like illness (1.0%), and oropharyngeal pain (1.0%).

For subjects aged 9 to < 18 years who received Afluria® Quad vaccine, the most common unsolicited adverse events included oropharyngeal pain (1.6%), cough (1.3%), and upper respiratory tract infection (1.0%).

Post-marketing surveillance:
There are limited post-marketing data available for Afluria® Quad vaccine.

As the Afluria® Quad vaccine formulation is consistent with Seqirus' 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 (including febrile 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.

Reporting suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions using the following website https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose
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.
In New Zealand, call the New Zealand Poisons Centre on 0800 POISON or 0800 764 766.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Influenza Vaccines
ATC Code: J07B B02

Pharmacodynamic effects
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 trial data

Adult Studies
One clinical study has been completed with Afluria® Quad vaccine on adults 18 years and older.

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 Titre (GMT) ratios (adjusted for baseline HI titres) 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 4), 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 4: 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	
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)**	**Met both pre-defined non-inferiority criteria? [c]**
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 titre.

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

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

Paediatric studies

One clinical study has been completed with Afluria® Quad vaccine in children aged 5 to < 18 years of age.

QIV-02 (NCT02545543, see http://clinicaltrials.gov) was a randomised, observer-blinded, comparator-controlled trial conducted in the US in children 5 to < 18 years of age. Subjects received either one or two doses of either Afluria® Quad vaccine (N=1605) or a comparator quadrivalent influenza vaccine (N=528) in a 3:1 randomisation treatment schedule. Subjects 5 to < 9 years of age were eligible to receive a second dose at least 28 days after the first dose depending on their influenza vaccination history. Approximately 25% of subjects in each treatment group in the 5 to < 9 years of age sub-group received two vaccine doses. Baseline serology prior to vaccination and sera obtained 28 days after the last vaccination dose was collected and immunogenicity was evaluated by HI assay.

The co-primary endpoints were HI Geometric Mean Titres (GMT) (adjusted for baseline HI titres and other covariates) and seroconversion rates for each vaccine strain, 28 days after the last vaccination. Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the GMT ratio (Comparator QIV/Afluria Quad™ vaccine) did not exceed 1.5 and the upper bound of the 2-sided 95% CI of the seroconversion rate difference (Comparator QIV minus Afluria Quad™ vaccine) did not exceed 10% for each strain.

Serum HI antibody responses to Afluria Quad™ vaccine were non-inferior for both GMT and seroconversion rates relative to the Comparator QIV for all influenza strains (Table 5). Analyses of immunogenicity endpoints by gender did not demonstrate meaningful differences between males and females. The study population was not sufficiently diverse to assess differences between races or ethnicities.

Table 5: QIV-02: Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of Non-Inferiority of Afluria Quad™ Vaccine Relative to Comparator QIV for each Strain 28 Days after Last Vaccination Among a Paediatric Population 5 to < 18 Years of Age (Per Protocol Population)[f]

	Post-vaccination GMT		GMT Ratio [a]	Seroconversion % [b]		Difference [c]	Met both pre-defined non-inferiority criteria? [d]
Strain	Afluria Quad™ vaccine N=1605	Comparator QIV N=528	Comparator QIV over Afluria Quad™ vaccine (95% CI)	Afluria Quad™ vaccine N=1605 (95% CI)	Comparator QIV N=528 (95% CI)	Comparator QIV minus Afluria Quad™ vaccine (95% CI)	
A/H1N1	952.6 (n=1604 [e])	958.8	1.01 (0.93, 1.09)	66.4 (64.0, 68.7)	63.3 (59.0, 67.4)	-3.1 (-8.0, 1.8)	Yes
A/H3N2	886.4 (n=1604 [e])	930.6	1.05 (0.96, 1.15)	82.9 (81.0, 84.7)	83.3 (79.9, 86.4)	0.4 (-4.5, 5.3)	Yes
B/YAM	60.9 (n=1604 [e])	54.3	0.89 (0.81, 0.98)	58.5 (56.0, 60.9)	55.1 (50.8, 59.4)	-3.4 (-8.3, 1.5)	Yes
B/VIC	145.0 (n=1604 [e])	133.4	0.92 (0.83, 1.02)	72.1 (69.8, 74.3)	70.1 (66.0, 74.0)	-2.0 (-6.9, 2.9)	Yes

Abbreviations: B/VIC, B Victoria lineage; B/YAM, B Yamagata lineage; CI, confidence interval; Comparator QIV, Fluarix® Quadrivalent [GlaxoSmithKline Biologicals]; GMT (adjusted), geometric mean titre.

[a] GMT Ratio = Comparator QIV / Afluria Quad™ vaccine. Adjusted analysis model: Log-transformed Post-Vaccination HI Titre = Vaccine + Age Strata [5-8, 9-17] + Gender + Vaccination History [y/n] + Log-transformed Pre-Vaccination HI Titre + Site + Number of Doses (1 vs 2) + Age Strata*Vaccine. The Age Strata*Vaccine interaction term was excluded from the model fit for the strains B/Yamagata and B/Victoria as the interaction result was non-significant (p>0.05). Least square means were back transformed.

[b] Seroconversion rate (SCR) was defined as the percentage of subjects with either a pre-vaccination HI titre < 1:10 and a post-vaccination HI titre ≥ 1:40 or a pre-vaccination HI titre ≥ 1:10 and a 4-fold increase in post-vaccination HI titre.

[c] Seroconversion rate difference = Comparator QIV SCR percentage minus Afluria Quad™ vaccine SCR percentage.

[d] Non-inferiority (NI) criterion for the GMT ratio: upper bound of two-sided 95% CI on the GMT ratio of Comparator QIV/QIV should not exceed 1.5. NI criterion for the SCR difference: upper bound of two-sided 95% CI on the difference between SCR Comparator QIV – Afluria Quad™ vaccine should not exceed 10%.

[e] Subject 8400394-0046 was excluded from the Per-Protocol Population for the adjusted GMT analysis for the GMT ratio since the subject did not have information on all covariates (unknown pre-vaccination history).

[f] The Per-Protocol Population comprised all subjects in the Evaluable Population who did not have any protocol deviations that were medically assessed as potentially impacting on immunogenicity results.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

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.

Genotoxicity

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

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each 0.5 mL dose also contains, nominally: sodium chloride 4.1 mg, dibasic sodium phosphate 0.3 mg, monobasic sodium phosphate 0.08 mg, potassium chloride 0.02 mg, monobasic potassium phosphate 0.02 mg, calcium chloride dihydrate 0.5 microgram and water for injections to 0.5mL. See also Section 2 – QUALITATIVE AND QUANTITATIVE COMPOSITION.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

15 months from the date of manufacture.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Afluria® Quad inactivated quadrivalent influenza vaccine (split virion), 60 microgram HA, suspension for injection, is supplied in a single-dose 0.5 mL pre-filled needle-free syringe (type 1 glass). Pack sizes: 1’s 10’s.

Afluria® Quad inactivated quadrivalent influenza vaccine (split virion), 60 microgram HA, suspension for injection, is also supplied in a single-dose 0.5 mL pre-filled syringe (type 1 glass) with attached needle for injection. Pack sizes: 1’s 10’s.

The syringe and all assocaiated syringe components for Afluria® Quad do not contain natural rubber latex.

Not all presentations or pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Seqirus (NZ) Ltd

PO Box 62590

Greenlane

Auckland 1546

NEW ZEALAND

Telephone: 0800 502 757

9. DATE OF FIRST APPROVAL

12 October 2017

10. DATE OF REVISION OF THE TEXT

27 November 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
N/A	Initial Afluria® Quad Data Sheet
6.5 Nature and contents of container	Revision of text regarding packaging
Header	Revision of text regarding YEAR
2. Qualitative and Quantitative composition	Composition revised as per AIVC & NZ strain composition
6.3 Shelf life	Revision of shelf life from 12 months to 15 months
6.5 Nature and contents of container	Revision of text regarding packaging
WARNING and 4.1 Therapeutic Indications	New indication for use in children 5 years and older added
4.2 Dose and method of administration	Dosing information added for use in children 5 years and older
4.3 Contraindications	Contraindications updated to children less than 5 years of age
4.4 Special warnings and precautions for use	Precautions updated to reference use in children 5 years and older
4.6 Fertility, pregnancy and lactation	Wording updated to reference Seqirus' trivalent influenza vaccine, recommendation added for use in pregnant women
4.8 Undesirable effects	Clinical trial section updated with paediatric trial data and outcomes, Post-marketing surveillance section updated to reference Seqirus' trivalent influenza vaccine and to clarify wording for adverse events – convulsions
5.4 Pharmacodynamic properties	Clinical trial data section updated with paediatric trial data and outcomes
1, 5.3, 6.1 and 6.5	Revision of text and updated for clarification.
2 Qualitative and Quantitative Composition	Influenza strain composition and season year updated for Southern Hemisphere 2019 season.
4.6 Fertility, pregnancy and lactation	Change to Pregnancy Category from B2 to A