AUSTRALIAN PRODUCT INFORMATION - FLUQUADRI INFLUENZA VIRUS HAEMAGGLUTININ

1 NAME OF THE MEDICINE

Inactivated Quadrivalent Influenza Vaccine, Split Virion (Influenza virus haemagglutinin)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

FluQuadri for intramuscular injection is an inactivated influenza virus vaccine, prepared from influenza viruses propagated in embryonated chicken eggs. The virus-containing allantoic fluid is harvested and inactivated with formaldehyde. Influenza virus is concentrated and purified in a linear sucrose density gradient solution using a continuous flow centrifuge. The virus is then chemically disrupted using a non-ionic surfactant, octoxinol-9 (Triton® X-100), producing a "split virus". The split virus is further purified and then suspended in sodium phosphate-buffered isotonic sodium chloride solution. Antigens from the four strains included in the vaccine are produced separately and then combined to make the quadrivalent formulation.

It is formulated to contain the following four influenza strains* recommended for the 2022 influenza season:

Active Substance	Quantity (per 0.5 mL dose)
A/Victoria/2570/2019 (H1N1)pdm09 - like strain (A/Victoria/2570/2019, IVR-215)	15 micrograms HA**
A/Darwin/9/2021 (H3N2)-like strain (A/Darwin/9/2021, SAN-010)	15 micrograms HA**
B/Austria/1359417/2021-like strain (B/Michigan/01/2021, wild type)	15 micrograms HA**
B/Phuket/3073/2013 - like strain (B/Phuket/3073/2013, wild type)	15 micrograms HA**

* propagated in fertilised hens' eggs from healthy chicken flocks

****** haemagglutinin

FluQuadri contains 60 micrograms (µg) haemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 µg HA of each of the four strains.

The type and amount of viral antigens contained in FluQuadri conform to the annual requirements of the Australian Influenza Vaccine Committee (AIVC) and the World Health Organization (WHO) recommendations for the season.

Neither antibiotics nor preservative are used during manufacture.

FluQuadri is presented in prefilled syringes that are not made with natural rubber latex.

3 PHARMACEUTICAL FORM

Sterile aqueous suspension for injection.

FluQuadri suspension for injection is clear and slightly opalescent in colour.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

FluQuadri is indicated for active immunisation of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

FluQuadri is indicated for use in adults and children 6 months and older.

4.2 DOSE AND METHOD OF ADMINISTRATION

FluQuadri should be given in accordance with the national recommendation as per the current Immunisation Handbook.

Inspect FluQuadri visually for particulate matter and/or discolouration prior to administration. If any of these defects or conditions exist, the vaccine should not be administered.

Before administering a dose of vaccine, shake the prefilled syringe.

The syringe is for single use only and must not be reused. Discard any remaining unused contents.

For needle size and length, refer to the national recommendations as per the current Immunisation Handbook.

FluQuadri should not be mixed with any other vaccine in the same syringe or vial.

Administration should be carried out by the intramuscular route. The dose and schedule are as follows:

- Adults and children 6 months of age and older: 0.5 mL dose

For children who have not been adequately primed based on influenza vaccination history, a second dose should be administered approximately 4 weeks apart. Refer to the current Immunisation Handbook for the recommended doses of influenza vaccine for young children at different ages.

The preferred site of administration is into the deltoid muscle in adults and children ≥ 12 months of age. The preferred site for infants and young children (6 months to < 12 months of age) is the anterolateral aspect of the thigh. The vaccine should be administered into healthy well developed muscle and should not be injected into the gluteal region where there may be a risk of local neural, vascular and tissue injury.

4.3 CONTRAINDICATIONS

FluQuadri should not be administered to anyone with a known systemic hypersensitivity reaction, such as anaphylaxis, after previous administration of any influenza vaccine or to any component of the vaccine (see Section 2 Qualitative and quantitative composition and Section 6.1 List of excipients).

Vaccination should be postponed in case of moderate or severe acute or febrile disease with or without fever but a mild disease with low-grade fever is usually not a reason to postpone vaccination.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Do not administer intravenously.

Hypersensitivity

Prior to any vaccine injection, all known precautions should be taken to prevent hypersensitivity reactions. This includes a review of the individual's prior vaccination history with respect to possible hypersensitivity to the vaccine or similar vaccines.

As each dose may contain traces of formaldehyde and octoxinol-9 which are used during vaccine production, caution should be exercised when the vaccine is administered to individuals with hypersensitivity to either one of these products.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following administration of the vaccine especially for individuals who have a known allergy to egg protein.

Neurological disorders

Patients with a history of Guillain-Barré Syndrome (GBS) with an onset related in time to influenza vaccination may be at increased risk of again developing GBS, but whether vaccination specifically might increase the risk for recurrence is unknown. Because patients with a history of GBS have an increased likelihood of again developing the syndrome, the chance of them coincidentally developing the syndrome following influenza vaccination may be higher than in individuals with no history of GBS. If GBS has occurred within 6 weeks following previous influenza vaccination, the decision to give FluQuadri should be based on careful consideration of the potential benefits and risks. Refer to the current Immunisation Handbook for further details.

Immunosuppressive treatments or conditions

The immunogenicity of FluQuadri may be reduced by immunosuppressive treatment or in individuals with immune deficiency syndromes. Vaccination of individuals with chronic immunodeficiencies is recommended even though the antibody response may be limited.

Protection

Influenza virus is remarkably unpredictable in that significant antigenic changes may occur from time to time. It is known that influenza vaccines, as now constituted, are not effective against all possible strains of influenza virus. Protection is limited to those strains of virus from which the vaccine is prepared or to closely related strains.

As with any vaccine, vaccination with FluQuadri may not protect 100% of susceptible individuals.

Bleeding disorder

Because any intramuscular injection can cause an injection-site haematoma in individuals with any bleeding disorder, such as haemophilia or thrombocytopenia, or in individuals on anticoagulant therapy, intramuscular injections with FluQuadri should not be administered to such individuals unless the potential benefits outweigh the risk of administration. If the decision is made to administer any product by intramuscular injection to such individuals, it should be given with caution, with steps taken to avoid the risk of haematoma formation following injection.

Syncope

Syncope (fainting) has been reported following vaccination with FluQuadri. Procedures should be in place to prevent falling injury and manage syncopal reactions.

Use in the elderly

Safety and immunogenicity of FluQuadri were evaluated in adults 65 years of age and older (See Section 5.1 Pharmacodynamic Properties, Clinical Trials). Antibody responses to FluQuadri are lower in individuals ≥ 65 years of age than in younger adults.

Adults aged ≥ 65 years are strongly recommended to receive either high-dose or adjuvanted influenza vaccine every year. Refer to the current Immunisation Handbook.

Paediatric use

Safety and effectiveness of FluQuadri in children below the age of 6 months have not been established. Children in Study GRC88 aged between 6 and < 12 months were required to be born at full term of pregnancy (≥ 37 weeks) and/or with a birth weight ≥ 2.5 kg.

Preterm infants (< 37 weeks gestation) are strongly recommended to receive influenza vaccine each year, starting at ≥ 6 months of age. Refer to the current Immunisation Handbook.

Effects on laboratory tests

Interference of FluQuadri with laboratory and/or diagnostic tests has not been studied.

Following influenza vaccination, false positive results in serology tests using the ELISA method to detect antibodies against HIV1, hepatitis C, and especially HTLV1 have been

observed. An appropriate Western Blot test should be used to confirm or disprove the results of the ELISA test. The transient false-positive reactions could be due to a non-specific IgM response induced by the vaccine.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

FluQuadri should not be mixed with any other vaccine in the same syringe or vial.

Data evaluating the concomitant administration of FluQuadri with other vaccines are not available.

If FluQuadri is to be given at the same time as another injectable vaccine(s), the vaccine(s) should always be administered at different injection sites. Refer to the current Immunisation Handbook for further details.

Although inhibition of hepatic clearance of phenytoin, theophylline and warfarin has been reported after influenza vaccination, subsequent studies have not shown any evidence of undesirable effects related to this phenomenon.

If the vaccine is used in individuals deficient in producing antibodies due to immunosuppressive therapy, the expected immune response may not be obtained.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

FluQuadri has not been evaluated for the possible effects on human fertility. A reproductive toxicity study in which female rabbits were administered FluQuadri 24 and 10 days before insemination showed no effects on female fertility (see Use in Pregnancy).

Use in pregnancy (Category A)

A developmental and reproductive toxicity study has been performed in female rabbits at a dose approximately 20 times the human dose (on a mg/kg basis) and has revealed no evidence of impaired female fertility or harm to the foetus due to FluQuadri. There are, however, no adequate and well-controlled studies in pregnant women.

In the developmental and reproductive toxicity study, female rabbits were administered FluQuadri or control saline (each 0.5 mL/dose) by intramuscular injection 24 and 10 days before insemination, and on Days 6, 12, and 27 of gestation. The administration of FluQuadri did not result in systemic maternal toxicity (no adverse clinical signs and no change in body weight or food consumption). In addition, no adverse effects on pregnancy, parturition, lactation, or embryo-foetal or pre-weaning development were observed. There were no vaccine-related foetal malformations or other evidence of teratogenesis noted in this study.

Data from studies involving large numbers of women (> 80,000) vaccinated during pregnancy with inactivated influenza vaccines do not indicate any adverse fetal and maternal outcomes attributable to the vaccine. FluQuadri should be given to a pregnant woman following an assessment of the risks and benefits. Because of the known adverse

consequences of influenza infection in pregnant women, health authorities recommend vaccination of pregnant women.

Use in lactation

It is not known whether FluQuadri is excreted in human milk hence, caution should be used when administering vaccine to breastfeeding women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive or use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials experience

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

The safety of FluQuadri was evaluated in 3,307 trial participants in 3 clinical trials in the United States (1,223 children 6 to 35 months of age, 1,669 children 3 to 8 years of age, 190 adults ≥18 years of age, and 225 adults ≥65 years of age). For children requiring a second dose, the doses were administered approximately 4 weeks apart. The most common injection-site reaction in children and adults was pain. The most frequent systemic reaction in infants and toddlers (6 to 35 months receiving 0.25 mL) was irritability, while myalgia was the most frequent systemic reaction reported in children (3 to 8 years) and adults.

In children, the most commonly reported unsolicited non-serious adverse events were cough, vomiting, and pyrexia. In adults, oropharyngeal pain, rhinorrhoea, injection-site induration, and headache were the most commonly reported unsolicited adverse events.

Across the 3 trials, one serious adverse event was thought to be caused by vaccination with FluQuadri: a 13-month-old who experienced croup 3 days post-first vaccination; the participant recovered within 18 days without sequelae and continued in the trial. In clinical trial QIV04 other serious adverse events considered to be possibly related to vaccination were; in the US-licensed comparator 2010-2011 TIV group a 4-year-old who experienced a febrile convulsion one day post-first vaccination, and in the unlicensed investigational TIV group an 11-month-old who experienced a febrile convulsion on the day of second vaccination.

The frequency of the solicited injection-site and systemic reactions reported in the trials are shown in Table 1 and Table 2.

Table 1 - Percentage of Solicited Injection-Site Reactions and Systemic Adverse Events in Children After Vaccination with FluQuadri (Safety Analysis Set)[a]

	Children 6 to 35 months of age (0.25 mL)			Children 3 to 8 years of age (0.5 mL)		
	FluQuadri N[b]=1223	TIV-1[c] B (Victoria) N[b]=310	TIV-2[d] B (Yamagata) N[b]=308	FluQuadri N[b]=1669	TIV-1[c] B (Victoria) N[b]=424	TIV-2[d] B (Yamagata) N[b]=413
Injection site reactions						
Pain	57.0[c]	52.3[c]	50.3[c]	66.6	64.6	63.8
Tenderness	54.1[d]	48.4[d]	49.7[d]	-	-	-
Erythema	37.3	32.9	33.3	34.1	36.8	35.2
Swelling	21.6	19.7	17.3	24.8	25.4	25.9
Systemic reactions						
Myalgia	26.7[e]	26.6[e]	25.0[e]	38.6	34.1	38.4
Headache	8.9[e]	9.4[e]	12.2[e]	23.1	21.2	24.4
Malaise	38.1[e]	35.2[e]	32.4[e]	31.9	32.8	33.4
Irritability	54.0[f]	52.8[f]	53.5[f]	-	-	-
Crying-abnormal	41.2[f]	36.5[f]	29.9[f]	-	-	-
Drowsiness	37.7[f]	32.1[f]	31.9[f]	-	-	-
Appetite loss	32.3[f]	33.3[f]	25.0[f]	-	-	-
Vomiting	14.8[f]	11.3[f]	13.9[f]	-	-	-
Fever	14.3	16.0	13.0	7.0	7.1	7.6

[a]The safety analysis set includes all persons who received study vaccine

[b] N is the number of subjects in the safety analysis set

[c]2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed in the United States

[d]Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed

[e]Assessed in children 24 months to 35 months of age

[f]Assessed in children 6 months to 23 months of age

Table 2 - Percentage of Solicited Injection-Site Reactions and Systemic Adverse Events in Adults After Vaccination with FluQuadri (Safety Analysis Set)[a]

	Adults 18 years of age and older			Adults 65 years of age and older		
	FluQuadri N[b]=190	TIV-1[c] B (Victoria) N[b]=190	TIV-2[d] B (Yamagata) N[b]=190	FluQuadri N[b]=225	TIV-1[e] B (Victoria) N[b]=225	TIV-2[f] B (Yamagata) N[b]=225
Injection site reactions						
Pain	47.4	52.1	43.2	32.6	28.6	23.1
Erythema	1.1	1.6	1.6	2.7	1.3	1.3
Swelling	0.5	3.2	1.1	1.8	1.3	0.0
Induration	0.5	1.6	0.5	-	-	-

	Adults 18 years of age and older			Adults 65 years of age and older		
Ecchymosis	0.5	0.5	0.5	-	-	-
Systemic reactions						
Myalgia	23.7	25.3	16.8	18.3	18.3	14.2
Headache	15.8	18.4	18.0	13.4	11.6	11.6
Malaise	10.5	14.7	12.1	10.7	6.3	11.6
Shivering	2.6	5.3	3.2	-	-	-
Fever	0.0	0.5	0.5	1.3	0.0	0.9

[a]The safety analysis set includes all persons who received study vaccine

[b] N is the number of subjects in the safety analysis set

[c]2009-2010 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed in the United States

[d]2008-2009 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Florida/04/2006 (Yamagata lineage), licensed in the United States

[e]2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed in the United States

[f]Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed

A 0.5-mL Dose of FluQuadri in Children 6 Months through 35 Months of Age

GRC88 was an observer-blind multi-centre study conducted in the US, including healthy children age between 6 and 35 months. Infants less than 12 months of age were of gestational age ≥ 37 weeks and/or birth weight ≥ 2.5 kg. Participants were randomly assigned to receive a FluQuadri dose of 0.25 mL (Group 1) or 0.5 mL (Group 2). For children requiring a second dose, the same dose was administered 4 weeks after the first. Participants who received at least one dose of study vaccine were included in the safety analysis set: Group 1 n = 949; Group 2 n = 992.

The primary objective was to assess difference in fever rate ≥ 38°C (Group 2 minus Group 1). The difference, 0.84% (95% CI: -2.13%; 3.80%), met the prespecified non-inferiority criterion (upper limit of the 2-sided 95% CI of the difference in fever rates < 5%).

The frequencies of solicited injection-site reactions occurring within 7 days after vaccination (Group 1 vs. Group 2) were: tenderness (47% vs. 50%), erythema (23% vs. 24%), and swelling (13% vs. 15%).

The frequency of systemic adverse reactions occurring within 7 days after vaccination (Group 1 vs. Group 2) were: irritability (47% vs. 49%), abnormal crying (33% vs. 34%), drowsiness (32% vs. 31%), appetite loss (27% vs. 28%), fever of ≥ 38°C (11% vs. 12%), and vomiting (10% vs. 10%).

The frequency of solicited systemic reactions tended to be higher in the subgroup aged 6 to < 24 months than the subgroup aged 24 to > 36 months. , Group 1 (n = 533) vs. Group 2 (n = 561): fever 12% vs. 16%, vomiting 12% vs. 14%, abnormal crying 38% vs. 39%, drowsiness 34% vs. 35%, loss of appetite 27% vs. 31% and irritability 49% vs. 54%.

Participants were monitored for unsolicited adverse events for the 28 days following vaccination. Non-serious adverse events were reported in 44% of Group 1 and 40% of Group 2, the most commonly reported in both groups being cough and rhinorrhoea. Five serious

adverse events were reported in each group, one event of chronic urticaria occurring in Group 1 was considered vaccine related and an event of special interest. There were no deaths reported during the trial period.

Adverse reactions from post-marketing surveillance

Currently, there are limited post-marketing data available for FluQuadri.

The following events have been spontaneously reported during the post-approval use of Fluzone (TIV)[1]. Because these events 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. Adverse events were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to Fluzone.

- Blood and Lymphatic System Disorders: Thrombocytopenia, lymphadenopathy
- Immune System Disorders: Anaphylaxis, other allergic/hypersensitivity reactions (including urticaria, angioedema)
- *Eye disorders*: Ocular hyperemia
- *Nervous System Disorders*: Guillain-Barré syndrome (GBS), convulsions, febrile convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), dizziness, paresthesia
- *Vascular Disorders*: Vasculitis, vasodilation/flushing
- *Respiratory, Thoracic and Mediastinal Disorder*s: Dyspnea, pharyngitis, rhinitis, cough, wheezing, throat tightness
- *Skin and Subcutaneous Tissue Disorders*: Stevens-Johnson syndrome
- *General Disorders and Administration Site Conditions*: Pruritus, asthenia/fatigue, pain in extremities, chest pain
- *Gastrointestinal Disorders:* Vomiting

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

For general advice on overdose management, contact the Poisons Information Centre, telephone number 13 11 26 or the National Poisons Centre, 0800 POISON.

[1] Fluzone is the US-licensed TIV upon which manufacture of FluQuadri is based.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Influenza vaccine, ATC code: J07BB

Mechanism of action

FluQuadri provides active immunisation against the four influenza virus strains (two A subtypes and two B strains) contained in the vaccine. FluQuadri induces humoral antibodies against the haemagglutinins. Specific levels of haemagglutination-inhibition (HI) antibody titre post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza illness, but HI antibody titres have been used as a measure of vaccine activity. In some human challenge studies, HI antibody titres of ≥ 1:40 have been associated with protection from influenza illness in up to 50% of participants. HI antibody titres ≥ 1:40 are generally obtained within 3 to 4 weeks. Annual influenza vaccination is recommended as immunity declines during the year after vaccination and because circulating strains of influenza virus may change from year to year.

Clinical trials

Immunogenicity of FluQuadri in Children 6 Months to 8 Years of Age

QIV04 (NCT01240746, see http://clinicaltrials.gov) was a phase III, randomised, observer-blinded, active-controlled, 3-arm, multi-centre trial of children aged 6 months to 8 years stratified into 2 age groups: 6 to 35 months of age and 3 to 8 years of age. The trial was conducted in the United States during November 2010 – January 2012.

The aim was to compare the immunogenicity and safety of FluQuadri containing A/California A/Victoria, B/Brisbane (Victoria lineage), and B/Florida (Yamagata lineage) with the 2010-2011 seasonal trivalent inactivated influenza vaccine (TIV) containing B/Brisbane, and an investigational TIV containing B/Florida. Each TIV contained the same A strains as FluQuadri. The manufacturing process was the same for each vaccine and was based on the production process for the US-licensed TIV (Fluzone®).

Participants were randomised to receive one of three vaccines (FluQuadri, 2010-2011 TIV, or investigational TIV). Children 6 to 35 months of age were administered 0.25 mL of assigned vaccine containing 7.5 µg of HA per strain. Children 3 to 8 years were administered 0.5 mL of assigned vaccine containing 15 µg of HA per strain. As per recommendations of the United States Advisory Committee on Immunization Practices, children who were considered adequately primed based on influenza vaccination history received one dose; all other children received two doses with a four-week interval between vaccinations.

The primary objective was to demonstrate non-inferiority of antibody responses to each of the four virus strains in FluQuadri compared with each TIV within each age group and overall.

- Non-inferiority was demonstrated if the lower limit of the two-sided 95% confidence interval (CI) of the post-vaccination geometric mean titre (GMT) ratio (FluQuadri/TIV) was > 0.66 for each of the four virus strains separately.

- Non-inferiority in terms of seroconversion rates was demonstrated if the lower limit of the two-sided 95% CI of the difference in rates (FluQuadri – TIV) was > -10% for each of the four virus strains separately.

The secondary objective was to demonstrate superiority of antibody responses to each B strain in FluQuadri compared with responses to the TIV not containing the corresponding B strain, as assessed by GMT ratios and seroconversion rates.

- Superiority by GMT ratios was demonstrated if the lower limit of the two-sided 95% CI of post-vaccination GMT ratios (FluQuadri/TIV) was > 1.5 for each B strain in FluQuadri compared with the corresponding B strain not contained in each TIV.
- Superiority by seroconversion rates was demonstrated if the lower limit of the two-sided 95% CI of the difference in post-vaccination seroconversion rates (FluQuadri – TIV) was > 10% for each B strain in FluQuadri compared with the corresponding B strain not contained in each TIV.

Description of seroprotection rates, defined as the percentages of participants with serum HI antibody titre ≥ 1:40, was an observational objective.

A total of 4348 participants were vaccinated: 2893 in the FluQuadri group, 734 in the 2010-2011 TIV group, and 721 in the investigational TIV group. Demographic characteristics for vaccine recipients were similar among vaccine groups; mean ages were 49.6 – 49.9 months, females accounted for approximately half of each vaccine group, and the majority of participants were Caucasian (range: 57.8% – 58.9%). The per-protocol analysis set, which was used for the immunogenicity analyses, included the following numbers (% of randomised): 2339 (80.6%) children in the FluQuadri group, 582 (79.1%) in the 2010-2011 TIV group, and 599 (82.6%) in the investigational TIV group.

All non-inferiority criteria were met. GMT ratios and seroconversion rates 28 days following vaccination with FluQuadri were non-inferior to those following TIV for all four strains overall and for each age group (Table 3). In addition, HI antibody GMTs and seroconversion rates following FluQuadri were superior to those following TIV for the B strain not contained in each respective TIV based on pre-specified criteria (Table 4).

Table 3 - QIV04[a]: Non-inferiority of FluQuadri Relative to TIV for Each Strain by HI Antibody GMTs and Seroconversion Rates at 28 Days Post-Vaccination, Persons 3 Years to 8 Years of Age (Per-protocol Analysis Set)[b]

Antigen Strain	FluQuadri N[c]=1390	Pooled TIV[d] N[c]=711	GMT Ratio (95% CI)	Non-inferiority[e]
	GMT			
A (H1N1)	1484	1453	1.02 (0.90; 1.16)	Yes
A (H3N2)	1112	1058	1.05 (0.95; 1.17)	Yes
	Seroconversion[f](%)		Difference of Seroconversion Rate (95% CI)	Non-inferiority[g]
A (H1N1)	93.4	92.8	0.6 (-1.6; 3.0)	Yes
A (H3N2)	83.0	78.8	4.2 (0.7; 7.9)	Yes

	FluQuadri N[c]=1390	TIV-1[h] N[c]=357	TIV-2[i] N[c]=354	GMT Ratio (95% CI)	Non-inferiority[e]
	GMT				
B (Victoria)	96.6	71.2	(27.3)[j]	1.36 (1.17; 1.57)	Yes
B (Yamagata)	88.5	(24.4)[k]	86.9	1.02 (0.89; 1.17)	Yes
	Seroconversion[f](%)			Difference of Seroconversion Rate (95% CI)	Non-inferiority[g]
B (Victoria)	71.7	58.7	(23.7)[j]	12.9 (7.4; 18.6)	Yes
B (Yamagata)	71.9	(25.0)[k]	71.4	0.6 (-4.5; 6.0)	Yes

[a]NCT01240746

[b]Per-protocol analysis set included all persons who had no study protocol deviations

[c]N is the number of participants in the per-protocol analysis set

[d]Pooled TIV group includes participants vaccinated with either 2010-2011 TIV or Investigational TIV

[e]Non-inferiority was demonstrated if the lower limit of the 2-sided 95% confidence interval (CI) of the ratio of geometric mean titres (GMTs) (FluQuadri divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain) was > 0.66

[f]Seroconversion: Paired samples with pre-vaccination HI titre < 1:10 and post-vaccination titre ≥ 1:40 or a minimum 4-fold increase for participants with pre-vaccination titre ≥1:10

[g]Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference in seroconversion rates (FluQuadri minus pooled TIV for the A strains, or the TIV containing the corresponding B strain) was > -10%

[h]2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed in the United States

[i]Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed

[j]TIV-2 did not contain B/Brisbane/60/2008

[k]TIV-1 did not contain B/Florida/04/2006

Twenty-eight days following vaccination with a dose of 0.25mL, the percentages of FluQuadri recipients with serum HI antibody titre ≥ 1:40 were:

Age 6 to 35 months: 97.7% (95% CI: 96.5; 98.5) for H1N1, 99.9% (95% CI: 99.4; 100.0) for H3N2, 75.5% (95% CI: 72.7; 78.2) for B/Brisbane, and 58.0% (95% CI: 54.8; 61.2) for B/Florida.

Age 3 to 8 years: 99.3% (95% CI: 98.7; 99.7) for H1N1, 99.5% (95% CI: 99.0; 99.8) for H3N2, 80.7% (95% CI: 78.5; 82.8) for B/Brisbane, and 80.9% (95% CI: 78.7; 82.9) for B/Florida.

Table 4 - QIV04[a]: Superiority of FluQuadri Relative to Each TIV Not Containing the Respective B Strain by GMTs and Seroconversion Rates, at 28 Days Post-Vaccination, Persons 6 Months Through 8 Years of Age (Per-protocol Analysis Set)[b]

Antigen Strain	GMT			GMT Ratio (95%CI)	Superiority[d]
	FluQuadri N[c]=2339	TIV-1 B (Victoria) N[c]=582	TIV-2 B (Yamagata) N[c]=599		
B (Victoria)	86.1	-	19.5	4.42 (3.94; 4.97)	Yes
B (Yamagata)	61.5	16.3	-	3.79 (3.39; 4.23)	Yes
	Seroconversion[e] (%)				Superiority[f]

	FluQuadri N[c]=2339	TIV-1 B (Victoria) N[c]=582	TIV-2 B (Yamagata) N[c]=599	Difference of Seroconversion Rates (95%CI)	
B (Victoria)	71.8	-	20.0	51.8 (47.9; 55.3)	Yes
B (Yamagata)	66.1	17.9	-	48.2 (44.3; 51.6)	Yes

[a]NCT01240746

[b]Per-protocol analysis set included all persons who had no study protocol deviations

[c]N is the number of subjects in the per-protocol analysis set

[d]Superiority was demonstrated if the lower limit of the 2-sided 95% confidence interval (CI) of the ratio of the geometric mean titres (GMTs) (FluQuadri divided by TIV) was > 1.5 for each B strain in FluQuadri compared with the corresponding B strain not contained in eachTIV

[e]Seroconversion: Paired samples with pre-vaccination HI titre < 1:10 and post-vaccination titre ≥ 1:40 or a minimum 4-fold increase for participants with pre-vaccination titre ≥ 1:10

[f]Superiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference of the seroconversion rates (FluQuadri minus TIV) was > 10% for each B strain in FluQuadri compared with the corresponding B strain not contained in each TIV

Immunogenicity of a 0.5 mL Dose of FluQuadri in Children 6 months to 35 months

GRC88 (NCT02915302 see http://clinicaltrials.gov) was a randomised, observer-blind, multi-centre study including healthy children age between 6 and 35 months, randomly assigned to receive a FluQuadri dose of 0.25 mL (Group 1) or 0.5 mL (Group 2). For children requiring a second dose, the same dose was administered 4 weeks after the first. The per-protocol immunogenicity set included 715 participants in Group 1 and 745 in Group 2. Immunogenicity was assessed 28 – 35 days after the final vaccination. (See also Section 4.8 Adverse effects).

HI antibody GMTs following the 0.5 mL dose of FluQuadri were non-inferior to those following a 0.25 mL dose for all four strains, based on pre-specified criteria of lower limit of the 2-sided 95% CI of the ratio of GMTs (GMT0.5mL/GMT0.25mL) > 0.667

- A/H1N1 strain: GMT ratio = 1.42(95% CI: 1.16; 1.74).
- A/H3N2 GMT ratio: = 1.48 (95% CI: 1.21; 1.82).
- B Victoria lineage strain GMT ratio: = 1.33 (95% CI: 1.09; 1.62).
- B Yamagata lineage strain GMT ratio: = 1.41 (95% CI: 1.17; 1.70).

Seroconversion rates 28 days following final vaccination with a 0.5 mL dose of FluQuadri were non-inferior to those following a 0.25 mL dose for all four strains, based on pre-specified criteria of lower limit of the 2-sided 95% CI of the difference in seroconversion rates> -10% (GMT0.5mL minus GMT0.25mL) > -10%).

- A/H1N1 strain: difference in SC rates = 4.6% (95% CI: 0.4%; 9.6%).
- A/H3N2 strain: difference in SC rates = 5.1 % (95% CI: 0.4%; 9.8%).
- B Victoria lineage strain: difference in SC rates = 1.3% (95% CI: -2.9%; 5.6%).
- For the B Yamagata lineage strain: difference in SC rates = 2.6% (95% CI: -1.4%; 6.5%).

Immunogenicity of FluQuadri in Adults ≥ 18 Years of Age

GRC43 (NCT00988143, see http://clinicaltrials.gov) was a phase II, open-label, active-controlled, 3-arm, multi-centre trial of adults ≥ 18 years of age conducted in the United States during October 2009 – December 2009.

The aim was to compare the immunogenicity and safety of FluQuadri containing A/Brisbane, A/Uruguay, B/Brisbane (Victoria lineage), and B/Florida (Yamagata lineage) with the 2009-2010 seasonal TIV (containing B/Brisbane) and the 2008-2009 seasonal TIV (containing B/Florida). Each TIV contained the same A strains as FluQuadri. The manufacturing process was the same for each vaccine and was based on the production process for the US-licensed TIV (Fluzone).

Participants were randomised to receive one of three vaccines (FluQuadri, 2009-2010 TIV, or 2008-2009 TIV) and were administered one 0.5 mL dose of assigned vaccine, which contained 15 µg of HA per strain.

The primary objective was to demonstrate non-inferiority of B-strain antibody responses induced by FluQuadri compared with the 2009-2010 TIV and the 2008-2009 TIV in terms of GMT ratios. Non-inferiority was shown if the lower limit of the two-sided 95% CI for the ratio of GMT FluQuadri/GMT TIV was > 2/3 for each A and B strain separately.

Description of seroprotection rates, defined as the percentages of participants with serum HI antibody titre ≥ 1:40, was an observational objective.

A total of 570 participants were vaccinated: 190 in each vaccine group. Demographic characteristics for vaccine recipients were similar among vaccine groups; mean ages were 54.9 – 56.7 years, females accounted for approximately two-thirds of each vaccine group, and the majority of participants were Caucasian (range: 86.8% – 91.1%). The per-protocol analysis set included the following numbers (% of randomised): 190 (100%) adults in the FluQuadri group, 187 (98.4%) in the 2009-2010 TIV group, and 188 (98.9%) in the 2008-2009 TIV group.

HI antibody GMTs 21 days following vaccination with FluQuadri were non-inferior to those following TIV for all four strains (Table 5).

Table 5 - GRC43[a]: Non-inferiority of FluQuadri Relative to TIV for Each Strain by HI Antibody GMTs at 21 Days Post-Vaccination, Adults 18 Years of Age and Older (Per-protocol Analysis Set)[b]

Antigen Strain	FluQuadri N[c]=190	Pooled TIV[d] N[c]=375		GMT Ratio (95% CI)	Non-inferiority[e]
	GMT	GMT			
A (H1N1)	161	151		1.06 (0.87; 1.31)	Yes
A (H3N2)	304	339		0.90 (0.70; 1.15)	Yes
	FluQuadri N[c]=190	TIV-1[f] B (Victoria) N[c]=187	TIV-2[g] B (Yamagata) N[c]=188	GMT Ratio (95% CI)	Non-inferiority[e]
	GMT	GMT	GMT		
B (Victoria)	101	114	(44.0)[h]	0.89 (0.70; 1.12)	Yes

Antigen Strain	FluQuadri N[c]=190	Pooled TIV[d] N[c]=375		GMT Ratio (95% CI)	Non-inferiority[e]
	GMT	GMT			
B (Yamagata)	155	(78.1)[i]	135	1.15 (0.93; 1.42)	Yes

[a]NCT00988143

[b]Per-protocol analysis set included all persons who had no study protocol deviations

[c]N is the number of participants in the per-protocol analysis set

[d]Pooled TIV group includes participants vaccinated with either 2009-2010 TIV or 2008-2009 TIV

[e]Non-inferiority was demonstrated if the lower limit of the 2-sided 95% confidence interval (CI) of the ratio of geometric mean titres (GMTs) (FluQuadri divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain) was > 2/3

[f]2009-2010 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed in the United States

[g]2008-2009 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Florida/04/2006 (Yamagata lineage), licensed in the United States

[h]TIV-2 did not contain B/Brisbane/60/2008

[i]TIV-1 did not contain B/Florida/04/2006

At 21 days following vaccination, the percentages of FluQuadri recipients with serum HI antibody titre ≥ 1:40 were 92.6% (95% CI: 87.9; 95.9) for H1N1, 94.7% (95% CI: 90.5; 97.4) for H3N2, 85.3% (95% CI ; 79.4; 90.0) for B/Brisbane, and 92.1% (95% CI: 87.3; 95.5) for B/Florida.

Immunogenicity of FluQuadri in Adults ≥ 65 Years of Age

QIV03 (NCT01218646, see http://clinicaltrials.gov) was a phase III, randomised, double-blind, active-controlled, 4-arm, multi-centre trial of adults ≥ 65 years of age. The trial was conducted in the United States during October 2010 – December 2010.

The aim was to compare the immunogenicity and safety ofFluQuadri containing A/California, A/Victoria, B/Brisbane (Victoria lineage) and B/Florida (Yamagata lineage) with the 2010-2011 seasonal TIV containing B/Brisbane, and an investigational TIV containing B/Florida. Each TIV contained the same A strains as FluQuadri. The manufacturing process was the same for each vaccine and was based on the production process for the US-licensed TIV (Fluzone).

Participants were randomised to one of three vaccine groups (FluQuadri, 2010-2011 TIV, or investigational TIV) and were administered one 0.5 mL dose of assigned vaccine, which contained 15 µg of HA per strain.

The primary objective was to demonstrate non-inferiority of GMT antibody responses to each of the four virus strains in FluQuadri compared with each TIV.

- Non-inferiority was demonstrated if the lower limit of the two-sided 95% CI of the post-vaccination GMT ratio (FluQuadri/TIV) was > 0.66 for each of the four virus strains separately.

Observational objectives were to:

- Demonstrate non-inferiority of antibody responses induced by FluQuadri compared with each TIV as assessed by seroconversion rates. Non-inferiority was demonstrated if the lower limit of the two-sided 95% CI of the difference in rates (FluQuadri – TIV) was > -10%.

- Demonstrate superiority of antibody responses to each B strain in FluQuadri compared with responses to the TIV not containing the corresponding B strain, as assessed by GMT ratios and seroconversion rates.
    - Superiority by GMT ratios was demonstrated if the lower limit of the two-sided 95% CI of post-vaccination GMT ratios (FluQuadri/TIV) was > 1.5 for each B strain in QIV compared with the corresponding B strain not contained in each TIV.
    - Superiority by seroconversion rates was demonstrated if the lower limit of the two-sided 95% CI of the difference in post-vaccination seroconversion rates (FluQuadri – TIV) was > 10% for each B strain in QIV compared with the corresponding B strain not contained in each TIV.
- Describe seroprotection rates, defined as the percentages of participants with serum HI antibody titre ≥ 1:40.

A total of 675 participants were vaccinated: 225 in each vaccine group. Demographic characteristics for vaccine recipients were similar among vaccine groups; mean ages were 72.4 – 72.8 years, females accounted for slightly more than half of each vaccine group, and the majority of participants were Caucasian (range: 87.6% – 91.1%). The per-protocol analysis set included the following numbers (% of randomised): 220 (97.8%) participants in the FluQuadri group, 219 (97.3%) in the 2010-2011 TIV group, and 221 (98.2%) in the investigational TIV group.

HI antibody GMTs 21 days following vaccination with FluQuadri were non-inferior to those following TIV for all four strains, based on pre-specified criteria (Table 6). Seroconversion rates 21 days following FluQuadri were non-inferior to those following TIV for H3N2, B/Brisbane, and B/Florida, but not for H1N1 (Table 6). The HI antibody GMT following FluQuadri was superior to that following 2010-2011 TIV for B/Florida but not superior to that following investigational TIV for B/Brisbane; based on pre-specified criteria. Seroconversion rates following FluQuadri were superior to those following TIV for the B strain not contained in each respective TIV, based on pre-specified criteria.

Table 6 - QIV03[a]: Non-inferiority of FluQuadri Relative to TIV for Each Strain by HI Antibody GMTs and Seroconversion Rates at 21 Days Post-Vaccination, Adults 65 Years of Age and Older (Per-protocol Analysis Set)[b]

Antigen Strain	FluQuadri N[c]=220	Pooled TIV[d] N[c]=440		GMT Ratio (95% CI)	Non-inferiority[e]
	GMT				
A (H1N1)	231	270		0.85 (0.67; 1.09)	Yes
A (H3N2)	501	324		1.55 (1.25; 1.92)	Yes
	Seroconversion[f](%)			Difference of Seroconversion Rate (95% CI)	Non-inferiority[g]
A (H1N1)	65.91	69.77		-3.86 (-11.50; 5.56)	No
A (H3N2)	69.09	59.32		9.77 (1.96; 17.20)	Yes
	FluQuadri N[c]=220	TIV-1[h] N[c]=219	TIV-2[i] N[c]=221	GMT Ratio (95% CI)	Non-inferiority[e]

Antigen Strain	FluQuadri N[c]=220	Pooled TIV[d] N[c]=440		GMT Ratio (95% CI)	Non-inferiority[e]
	GMT				
	GMT				
B (Victoria)	73.8	57.9	(42.2)[j]	1.27 (1.05; 1.55)	Yes
B (Yamagata)	61.1	(28.5)[k]	54.8	1.11 (0.90; 1.37)	Yes
	Seroconversion[f](%)			Difference of Seroconversion Rate (95% CI)	Non-inferiority[g]
B (Victoria)	28.64	18.72	(8.60)[j]	9.91 (1.96; 17.70)	Yes
B (Yamagata)	33.18	(9.13)[k]	31.22	1.96 (-6.73; 10.60)	Yes

[a]NCT01218646

[b]Per-protocol analysis set included all persons who had no study protocol deviations

[c]N is the number of participants in the per-protocol analysis set

[d]Pooled TIV group includes participants vaccinated with either 2010-2011 TIV or investigational TIV

[e]Non-inferiority was demonstrated if the lower limit of the 2-sided 95% confidence interval (CI) of the ratio of geometric mean titres (GMTs) (FluQuadri divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain) was > 0.66

[f]Seroconversion: Paired samples with pre-vaccination HI titre < 1:10 and post-vaccination titre ≥ 1:40 or a minimum

4-fold increase for participants with pre-vaccination titre ≥ 1:10

[g]Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference in seroconversion rates (FluQuadri minus pooled TIV for the A strains, or the TIV containing the corresponding B strain) was > -10%

[h]2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed in the United States

[i]Investigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed

[j]TIV-2 did not contain B/Brisbane/60/2008

[k]TIV-1 did not contain B/Florida/04/2006

Results for the observational objective, the percentages of FluQuadri recipients with serum HI antibody titre ≥ 1:40 at 21 days post-vaccination were: 91.4% (95% CI: 86.8; 94.7) for H1N1, 100% (95% CI: 98.3; 100) for H3N2, 77.7% (95% CI:71.6; 83.0) for B/Brisbane, and 73.2% (95% CI: 66.8; 78.9) for B/Florida.

Table 7 - QIV03[a]: Superiority of FluQuadri Relative to Each TIV Not Containing the Respective B Strain by GMTs and Seroconversion Rates at 21 Days Post-Vaccination, Adults 65 Years of Age and Older (Per-protocol Analysis Set)[b]

Antigen Strain	GMT			GMT Ratio (95%CI)	Superiority[d]
	FluQuadri N[c]=220	TIV-1 B (Victoria) N[c]=219	TIV-2 B (Yamagata) N[c]=221		
B (Victoria)	73.8	-	42.2	1.75 (1.43; 2.14)	No
B (Yamagata)	61.1	28.5	-	2.14 (1.74; 2.65)	Yes
	Seroconversion[f] (%)			Difference of Seroconversion Rates (95%CI)	Superiority[e]
	FluQuadri N[c]=220	TIV-1 B (Victoria) N[c]=219	TIV-2 B (Yamagata) N[c]=221		
B (Victoria)	28.64	-	8.60	20.04 (12.90; 27.00)	Yes

Antigen Strain	GMT			GMT Ratio (95%CI)	Superiority[d]
	FluQuadri N[c]=220	TIV-1 B (Victoria) N[c]=219	TIV-2 B (Yamagata) N[c]=221		
B (Yamagata)	33.18	9.13	-	24.05 (16.60; 31.20)	Yes

[a]NCT01218646

[b]Per-protocol analysis set included all persons who had no study protocol deviations

[c]N is the number of subjects in the per-protocol analysis set

[d]Superiority was demonstrated if the lower limit of the 2-sided 95% confidence interval (CI) of the ratio of the geometric mean titres (GMTs) (FluQuadri divided by TIV) was > 1.5 for each B strain in FluQuadri compared with the corresponding B strain not contained in eachTIV

[e]Superiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference of the seroconversion rates (FluQuadri minus TIV) was > 10% for each B strain in FluQuadri compared with the corresponding B strain not contained in each TIV

[f]Seroconversion: Paired samples with pre-vaccination HI titre <1:10 and post-vaccination titre ≥1:40 or a minimum 4-fold increase for participants with pre-vaccination titre ≥1:10

5.2 PHARMACOKINETIC PROPERTIES

No pharmacokinetic studies have been performed.

5.3 PRECLINICAL SAFETY DATA

FluQuadri has not been evaluated in non-clinical studies.

Genotoxicity

FluQuadri has not been evaluated for genotoxic potential.

Carcinogenicity

FluQuadri has not been evaluated for carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Buffer Solution:

- Sodium chloride
- Dibasic sodium phosphate
- Monobasic sodium phosphate
- Water for injections

FluQuadri may also contain traces of octoxinol-9 (≤ 250µg), formaldehyde (≤ 100 µg) and ovalbumin (≤ 1 µg).

6.2 INCOMPATIBILITIES

FluQuadri should not be mixed with any other vaccine in the same syringe or vial.

6.3 SHELF LIFE

12 months when stored at 2°C to 8°C.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate, Do not freeze). Discard if vaccine has been frozen.

6.5 NATURE AND CONTENTS OF CONTAINER

Prefilled syringe (clear syringe plunger rod), 0.5 mL with or without separate needle. Packs of 5 or 10 syringes.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

After use, any remaining vaccine and container must be disposed of safely, according to locally acceptable procedures.

6.7 PHYSIOCHEMICAL PROPERTIES

Not applicable for vaccines.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 Prescription Only Medicine

8 SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113
Australia

Tel: 1800 818 806

9 DATE OF FIRST APPROVAL

2 December 2014

10 DATE OF REVISION

3 December 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2	Annual strain update