AUSTRALIAN PRODUCT INFORMATION

NAME OF THE MEDICINE

FluQuadri™

FluQuadri™ Junior

Inactivated Quadrivalent Influenza Vaccine (Split Virion)

DESCRIPTION

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.

FluQuadri/FluQuadri Junior suspension for injection is clear and slightly opalescent in colour. It is formulated to contain the following four influenza strains recommended for the 2013-2014 influenza season:

- A/California/07/2009 (H1N1)pdm09-like virus (A/California/07/2009 X-179A)
- A/Victoria/361/2011 (H3N2)-like virus (A/Texas/50/2012 X-223A)
- B/Massachusetts/02/2012-like virus (B/Massachusetts/02/2012 NYMC BX-51B; Yamagata lineage)
- B/Brisbane/60/2008-like virus (B/Brisbane/60/2008; Victoria lineage)

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. FluQuadri Junior containes 30 µg HA per 0.25 mL dose in the recommended ratio of 7.5 µg HA of each of the four strains.

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

The amounts of HA and other ingredients per dose of vaccine are listed in Table 1. Neither antibiotics nor preservative are used during manufacture.

FluQuadri/FluQuadri Junior is presented in prefilled syringes that are not made with natural rubber latex. FluQuadri Junior is the paediatric presentation for children aged 6 months to 35 months inclusive.

Table 1: FluQuadri Ingredients

Ingredient	Quantity (per dose)	
	FluQuadri Junior 0.25 mL Dose	**FluQuadri 0.5 mL Dose**
Active Substance: Influenza virus haemagglutinin[a]:	30 µg HA total	60 µg HA total
A (H1N1)	7.5 µg HA	15 µg HA
A (H3N2)	7.5 µg HA	15 µg HA
B (Victoria lineage)	7.5 µg HA	15 µg HA
B (Yamagata lineage)	7.5 µg HA	15 µg HA
Other:		
Sodium chloride	2.2 µg	4.4 µg
Sodium phosphate dibasic anhydrous	165.8 µg	331.5 µg
Sodium phosphate monobasic anhydrous	50 µg	100 µg
Water for injections	Up to 0.25 mL	Up to 0.5 mL
Formaldehyde	≤ 50 µg	≤ 100 µg
Octoxinol 9	≤ 125 µg	≤ 250 µg
Ovalbumin	≤ 0.5 µg	≤ 1 µg
Preservative	None	None

[a]per AIVC and WHO recommendations

PHARMACOLOGY

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 (Tables 2 and 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 2: 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 6 Months to 35 Months of Age (Per-protocol Analysis Set)[b]

Antigen Strain	FluQuadri N[c]=949	Pooled TIV[d] N[c]=470		GMT Ratio (95% CI)	Non-inferiority[e]
	GMT				
A (H1N1)	747	714		1.05 (0.89; 1.23)	Yes
A (H3N2)	526	571		0.92 (0.82; 1.04)	Yes
	Seroconversion[f](%)			Difference of Seroconversion Rate (95% CI)	Non-inferiority[g]
A (H1N1)	90.9	89.3		1.6 (-1.6; 5.1)	Yes
A (H3N2)	95.4	92.5		2.9 (0.4; 5.9)	Yes
	FluQuadri N[c]=949	TIV-1[h] N[c]=225	TIV-2[i] N[c]=245	GMT Ratio (95% CI)	Non-inferiority[e]
	GMT				
B (Victoria)	72.8	54.7	(12.0)[j]	1.33 (1.12; 1.59)	Yes
B (Yamagata)	36.2	(8.56)k[i]	32.9	1.10 (0.94; 1.28)	Yes
	Seroconversion[f](%)			Difference of Seroconversion Rate (95% CI)	Non-inferiority[g]
B (Victoria)	72.0	64.9	(14.7)[j]	7.1 (0.5; 14.1)	Yes
B (Yamagata)	57.5	(6.7)[k]	53.5	4.0 (-2.9; 11.0)	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

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

At 28 days following vaccination, 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] (%)			Difference of Seroconversion Rates (95%CI)	Superiority[f]
	FluQuadri N[c]=2339	TIV-1(B Victoria) N[c]=582	TIV-2 (B Yamagata) N[c]=599		
(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 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
(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 (NCT01240746, 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 5). 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 5). 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; 3.56)	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]
	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 ratio of GMTs (FluQuadri divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain) was > 0.66

[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
(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 two 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

INDICATIONS

FluQuadri and FluQuadri Junior are 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 3 years and older.

FluQuadri Junior is indicated for use in children aged 6 months to 35 months inclusive.

CONTRAINDICATIONS

FluQuadri/FluQuadri Junior 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 (e.g. egg or egg products) (see **DESCRIPTION**).

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.

PRECAUTIONS

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.

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/FluQuadri Junior should be based on careful consideration of the potential benefits and risks.

Immunosuppressive Treatments or Conditions

The immunogenicity of FluQuadri/FluQuadri Junior 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/FluQuadri Junior may not protect 100% of susceptible individuals.

Bleeding disorder

Because any intramuscular injection can cause an injection-site haematoma in persons with any bleeding disorder, such as haemophilia or thrombocytopenia, or in persons on anticoagulant therapy, intramuscular injections with FluQuadri/FluQuadri Junior 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.

Effects on Fertility

FluQuadri has not been evaluated for the possible effects on fertility.

Use in Pregnancy (Category B2)

Animal reproduction studies have not been conducted with FluQuadri. It is also not known whether FluQuadri can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Data from worldwide use of inactivated influenza vaccines in pregnant women and experience of use of TIV in countries where inactivated influenza vaccines are recommended in all stages of pregnancy 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. Health authorities recommend vaccination of pregnant women.

Healthcare providers are encouraged to enrol women who receive FluQuadri during pregnancy in Sanofi Pasteur's vaccination pregnancy registry by calling 1800 829 468 (in Australia) or 0800 727 838 (in New Zealand). Sanofi Pasteur is maintaining a prospective pregnancy exposure registry to collect data on pregnancy outcomes and newborn health status following vaccination with FluQuadri during pregnancy.

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. However, as FluQuadri is an inactivated vaccine, it does not share the theoretical risks associated with live vaccines.

Paediatric Use

Safety and effectiveness of FluQuadri/FluQuadri Junior in children below the age of 6 months have not been established.

Use in the elderly

Safety and immunogenicity of FluQuadri was evaluated in adults 65 years of age and older (See **CLINICAL TRIALS**). Antibody responses to FluQuadri are lower in persons ≥ 65 years of age than in younger adults.

Genotoxicity

FluQuadri/FluQuadri Junior has not been evaluated for genotoxic potential.

Carcinogenicity

FluQuadri/FluQuadri Junior has not been evaluated for carcinogenic potential.

Effect on Laboratory Tests

Interference of FluQuadri/FluQuadri Junior 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.

INTERACTIONS WITH OTHER MEDICINES

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

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

If FluQuadri/FluQuadri Junior is to be given at the same time as another injectable vaccine(s), the vaccine(s) should always be administered at different injection sites.

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.

ADVERSE 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) 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, rhinorrhea, 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 8 and Table 9.

Table 8: 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			Children 3 to 8 years of age		
	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 9: 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	-	-	-
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

Adverse Reactions from Post-Marketing Surveillance

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

The following events have been spontaneously reported during the post-approval use of Fluzone (TIV)[a]. 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

DOSAGE AND ADMINISTRATION

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

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

- Children aged 6 months to 35 months: 0.25 mL dose
- Children and adults 3 years 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

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

Immunisation Handbook for the recommended doses of influenza vaccine for young children at different ages.

Inspect FluQuadri/FluQuadri Junior 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.

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

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.

Do not administer this product intravenously.

FluQuadri/FluQuadri Junior is for single use only. Discard any remaining unused contents.

OVERDOSE

For general advce on overdose management, contact the Poisons Information Centre, telephone number 13 11 26 (Australia) or the National Poisons Centre, 0800 POISON or 0800 764 766 (New Zealand).

PRESENTATION AND STORAGE CONDITIONS

FluQuadri:

· Prefilled syringe (purple syringe plunger rod), 0.5 mL, for persons 3 years and older. Packs of 10 syringes.

FluQuadri Junior:

· Prefilled syringe (yellow syringe plunger rod), 0.25 mL, for persons 6 months to 35 months of age. Packs of 10 syringes.

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

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 Prescription Only Medicine

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

2 December 2014

DATE OF MOST RECENT AMENDMENT