

6.04 INACTIVATED QUADRIVALENT INFLUENZA VACCINE (SPLIT VIRION), Injection 0.5 mL, FluQuadri™, Sanofi-Aventis Australia Pty Ltd.

1 Purpose of Application

1.1 The submission (with clarification in the Pre-Sub-Committee Response (PSCR) requested an extension to the current listing of quadrivalent influenza vaccine (QIV) (split virion, inactivated) FluQuadri™ for the prevention of influenza on the National Immunisation Program (NIP) to include:

- At-risk children (i.e. children with certain medical conditions putting them at increased risk of severe influenza and complications, and all Aboriginal and Torres Strait Islander children) aged 6-35 months who are currently eligible for FluQuadri Junior on the NIP; and
- Healthy children aged 6 months to <5 years, in line with the PBAC's July 2019 recommendation for Vaxigrip Tetra™ (an alternative QIV manufactured by the same Sponsor) which has not yet been listed on the NIP.

1.2 The submission (with clarification in the PSCR) based the request for extending the current listing on a cost-minimisation basis compared with FluQuadri Junior, and the July 2019 PBAC recommendation for Vaxigrip Tetra (Quadrivalent influenza vaccine (QIV), Vaxigrip Tetra, Public Summary Document (PSD), July 2019 PBAC meeting).

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	All children aged ≥6 months to <5 years
Intervention	Inactivated Quadrivalent Influenza Vaccine (Split Virion), FluQuadri 0.5 mL
Comparator	Inactivated Quadrivalent Influenza Vaccine (Split Virion), FluQuadri Junior 0.25 mL and Quadrivalent Influenza Vaccine, Vaxigrip Tetra 0.5 mL
Outcomes	Rate of fever following vaccination GMTs of influenza vaccine antibodies Rate of seroconversion
Clinical claim	Non-inferior efficacy as assessed by immunogenicity outcomes of GMTs and seroconversion, and safety, in terms of fever rate following vaccination and other treatment-emergent adverse events.

GMT= geometric mean titres.

Source: Adapted from Table 1.1.1, p13 of the submission, and edited during the preparation of the ESC Advice.

2 Requested listing

Public Summary Document – November 2019 PBAC Meeting

- 2.1 The submission did not include the proposed wording for the NIP listing. The evaluation compiled the proposed listing for at-risk children aged 6-35 months. The ESC updated the proposed listing following clarification in the PSCR to include all children aged 6 months to <5 years. Changes to the currently eligible population are identified with additions in italics and deletions in strikethrough.

Public Summary Document – November 2019 PBAC Meeting

Name, Restriction, Manner of administration and form	Nationally Negotiated Price	Proprietary Name and Manufacturer
Inactivated Quadrivalent Influenza Vaccine (split virion) Injection 0.5 mL	\$ [REDACTED]	FluQuadri™ Sanofi-Aventis (Australia) Pty Ltd
Category/Program	NIP	
Groups eligible for the requested NIP listing of FluQuadri	<p>Children aged ≥6 months to <5 years of age Persons aged ≥6 months 3 years who are at increased risk of influenza complications, specifically:</p> <ul style="list-style-type: none"> • has cardiac disease including cyanotic congenital heart disease, coronary artery disease and congestive heart failure; or • has a chronic respiratory condition including suppurative lung disease, bronchiectasis, cystic fibrosis, chronic obstructive pulmonary disease, chronic emphysema and severe asthma; or • has another chronic illness requiring regular medical follow up or hospitalisation in the preceding year, including diabetes mellitus, chronic metabolic diseases, chronic renal failure, haemoglobinopathies and impaired immunity (including drug induced immune impairment); or • has a chronic neurological condition, including multiple sclerosis, spinal cord injuries, seizure disorders or other neuromuscular disorders; or • has impaired immunity, including HIV infection; or • is a person aged less than 11 years and receiving long-term aspirin therapy <p>Aboriginal and Torres Strait Islander people aged ≥6 months 3 years Persons aged ≥65 years Pregnant women</p>	
Number and timing of doses	<p>Should be administered in accordance with the national recommendation as per the current Immunisation Handbook: Children ≥6 months to <9 years of age:</p> <ul style="list-style-type: none"> • If the child has not previously been vaccinated: two 0.5 ml injections at least one month apart. • If the child has been previously vaccinated: a single 0.5 ml injection. 	

NIP = National Immunisation Program; HIV = Human Immunodeficiency Virus

Source: Compiled during the evaluation and edited during the preparation of the ESC Advice. Adapted from Tables 1.1.4 and 1.4.1, p18 and p22 of the submission; *National Health (Immunisation Program – Designated Vaccines) Determination 2014 (No.1)* (compiled 10 January 2019).

2.2 The submission stated that using the same dose of vaccine across all ages, instead of the two current doses for different age groups (FluQuadri Junior 0.25 mL and FluQuadri 0.5 mL), would simplify purchasing for healthcare providers, and reduce wastage and administration errors.

2.3 The submission proposed an ex-manufacturer price of \$ [REDACTED] for FluQuadri, equal to the current nationally negotiated prices (NNP) for FluQuadri, FluQuadri Junior and Vaxigrip Tetra.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

Registration status

- 3.1 FluQuadri was TGA registered on 2 December 2014 for the prevention of influenza caused by Influenza Virus Types A and B for use in persons aged ≥ 3 years for the prevention of influenza. On 15 August 2019, the TGA approved extending the indication to include children aged 6 to 35 months. This was effective on the ARTG from 22 August 2019.

Previous PBAC considerations

- 3.2 Currently two QIVs (FluQuadri Junior and Fluarix Tetra) are listed on the NIP for the at-risk population in the 6-35 month age group. FluQuadri Junior was recommended by the PBAC for children aged 6-35 months at increased risk of severe influenza and complications in July 2015 (QIV, FluQuadri, PSD, July 2015 PBAC meeting). Fluarix Tetra was recommended by PBAC for NIP listing in children aged ≥ 6 months at increased risk of severe influenza and complications, and all Aboriginal and Torres Strait Islander people aged ≥ 6 months in March 2019 (QIV, Fluarix Tetra, PSD, March 2019 PBAC meeting).
- 3.3 In July 2019 the PBAC recommended Vaxigrip Tetra for listing on the NIP for all children aged 6 months to < 5 years, as well as in at-risk individuals who were then eligible for vaccination through the NIP, under the same provisions (QIV, Vaxigrip Tetra, PSD, July 2019 PBAC meeting). The PBAC's recommendation for listing was based on, among other matters, its assessment, that:
- Vaxigrip Tetra provides, for some patients, a significant improvement in efficacy over placebo, and was likely to be acceptably cost-effective at the price proposed by the submission (i.e. the same NNP as FluQuadri and FluQuadri Junior of \$████) for children aged 6 months to < 5 years who are not currently eligible through the NIP; and
 - QIV (Vaxigrip Tetra) is non-inferior to currently listed QIVs for the population currently eligible through the NIP, with the equi-effective doses being one dose of 0.5 mL Vaxigrip Tetra and one dose of an alternative QIV, such as 0.5 mL FluQuadri or 0.25 mL FluQuadri Junior.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Influenza is a highly contagious viral infection that can spread rapidly from person-to-person by inhalation of virus-laden air particles or by other means of direct contact. Systemic symptoms include malaise, fever, chills, headache, anorexia, and myalgia, and may be accompanied by a cough, nasal discharge, and sneezing. Influenza symptoms typically resolve within one week after infection. Pneumonia leading to

respiratory failure and death is the most severe influenza-related complication. Other rare complications include acute myositis, neurological conditions, transverse myelitis, encephalopathy, Guillain-Barré syndrome (GBS) and myopericarditis.

- 4.2 Severe disease is more likely in at-risk people as identified in the Australian Immunisation Handbook¹. One of the target populations in the submission is children aged 6-35 months who are at-risk, which includes children with certain medical conditions who would be at increased risk of influenza complications, and all Aboriginal and Torres Strait Islander children.

5 Comparator

- 5.1 For at-risk children aged 6-35 months, the submission nominated FluQuadri Junior as the comparator. The ESC considered the nomination of FluQuadri Junior as the main comparator for this population was appropriate. Alternative QIVs that are either currently listed or recommended for this population, i.e., Fluarix Tetra and Vaxigrip Tetra, were also appropriate comparators.
- 5.2 For the broader listing in children aged 6 months to <5 years, the PSCR clarified Vaxigrip Tetra was the nominated comparator being the only vaccine which has received a positive PBAC recommendation for this population, though it has not yet been supplied through the NIP to this population since the PBAC recommendation was made after the NIP for the 2019 influenza season was finalised (i.e. July 2019). The ESC considered this was appropriate, and that Vaxigrip Tetra was the appropriate comparator for this population.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item.

¹ 2019 NIP funded seasonal influenza vaccines – vaccine guide for providers (factsheet). Department of Health.
<https://www.health.gov.au/resources/publications/2019-nip-funded-seasonal-influenza-vaccines-vaccine-guide-for-providers-factsheet>

Clinical trials

At-risk children aged 6-35 months

6.3 The submission presented one head-to-head randomised control trial (RCT) comparing FluQuadri to FluQuadri Junior in children aged 6-35 months, who were healthy and had never been vaccinated against influenza: GRC88 (N=2,190).

6.4 A claim of non-inferiority was made based on safety, in terms of fever rate; and effectiveness, in terms of immunogenicity outcomes of geometric mean titres (GMTs) and seroconversion rates (SCRs). The PBAC has previously accepted surrogate outcomes (e.g. haemagglutination antibody GMTs and SCRs) to support non-inferiority claims between QIVs (e.g. FluQuadri compared with Fluarix Tetra (paragraph 6.6, QIV, FluQuadri, PSD, July 2015 PBAC meeting) and Vaxigrip Tetra compared with FluQuadri (paragraph 7.12, QIV, Vaxigrip Tetra, PSD, July 2019 PBAC meeting)).

6.5 Details of the trial presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
GRC88 NCT02915302, referred to as GRC88	Safety and immunogenicity of Fluzone® Quadrivalent Vaccine* Administered to Healthy Children 6 to <36 Months of Age Robertson CA, Mercer M, Selmani A, Klein NP, Jeanfreau R, Greenberg DP. Safety and Immunogenicity of a Full-dose, Split-virion, Inactivated, Quadrivalent Influenza Vaccine in Healthy Children 6-35 Months of Age: A Randomized Controlled Clinical Trial.	March 2017 The Pediatric Infectious Disease Journal. 2019 Mar; 38(3):323.

*Fluzone is the brand name for FluQuadri vaccine in the United States

Source: Table 2.2.1, p28 of the submission.

6.6 The key features of the direct randomised trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
FluQuadri vs. FluQuadri Junior						
GRC 88	1950 (SAS)	Randomised, modified double-blind, multi-centre, 6 months	Low	Healthy children aged 6-35 months who have never been vaccinated against influenza	Primary: safety assessed by fever rate; Secondary: immunogenicity assessed by GMT ratios and SCR differences	Not used

GMT = geometric mean titre; SAS = Safety Analysis Set; SCR = seroconversion rate.

Source: Table 2.2.2, p28 of the submission; and compiled during the submission.

6.7 The eligibility criteria of Trial GRC88 was healthy children who were influenza vaccine naïve, which was not consistent with the proposed NIP listing for at-risk children currently eligible for influenza vaccination. However, this is a common limitation for influenza vaccine submissions to the PBAC, e.g. Fluarix Tetra compared with FluQuadri Junior (paragraph 5.3, QIV, Fluarix Tetra, PSD, March 2019) and Vaxigrip Tetra

compared with FluQuadri. In its consideration of Vaxigrip Tetra, the PBAC stated that it may be reasonable to expect that the vaccine efficacy in sub-populations is unlikely to vary significantly or to vary between the proposed listing and comparator already in use in the vaccinated cohort (paragraph 7.11, QIV, Vaxigrip Tetra, PSD, July 2019 PBAC meeting). Further, ATAGI considered it reasonable to assume that the findings of Trial GRC88 apply similarly to medically at-risk children (ATAGI October 2019 Post-Submission Advice, QIV, FluQuadri, November 2019 PBAC meeting).

- 6.8 Trial GRC88 was conducted over a 6-month period during the 2016/17 Northern Hemisphere influenza season. The virus strains included in QIVs differ year to year, as do the prevalent strains in the community, therefore vaccine efficacy during one season may not reflect vaccine efficacy in another season. However, this is a common issue for influenza vaccine submissions to the PBAC, e.g. FluQuadri compared with trivalent influenza vaccine (TIV) (paragraph 7.5, QIV, FluQuadri, PSD, July 2015 PBAC meeting) and Vaxigrip Tetra compared with FluQuadri (paragraph 7.11, QIV, Vaxigrip Tetra, PSD, July 2019 PBAC meeting).

Healthy children aged 6 months to <5 years

- 6.9 The submission did not explicitly request extending the current listing for FluQuadri to include healthy children aged 6 months to <5 years. The clinical evidence presented in the submission (Trial GRC88) was not directly relevant to this population, and no evidence was provided to show the comparative safety and effectiveness of Vaxigrip Tetra to FluQuadri.
- 6.10 The PSCR clarified that the sponsor was requesting listing for all children aged 6 months to <5 years, on the basis of an indirect comparison between Vaxigrip Tetra, FluQuadri and FluQuadri Junior, for the at-risk populations presented in the Vaxigrip Tetra submission that was considered by PBAC in July 2019. The PSCR argued that in July 2019 the PBAC accepted the claim of non-inferiority of FluQuadri/FluQuadri Junior to Vaxigrip Tetra for the at-risk populations on the basis of an indirect comparison of trials conducted in healthy individuals. The PSCR stated that the PBAC had therefore already accepted the pivotal evidence supporting extending the listing of FluQuadri to include healthy children aged 6 months to <5 years. In its consideration of Vaxigrip Tetra in July 2019, the PBAC also noted that there were uncertainties in the indirect comparison, but had considered the non-inferior comparative effectiveness to be reasonable (paragraphs 6.42-6.44, QIV, Vaxigrip Tetra, PSD, July 2019 PBAC meeting).
- 6.11 The ESC considered it would have been preferable for the submission to have explicitly requested listing in healthy children aged 6 months to <5 years and to have re-presented the indirect comparison of FluQuadri/FluQuadri Junior to Vaxigrip Tetra (with TIVs as the common comparator) in the context of the additional population.

Comparative effectiveness

At-risk children aged 6-35 months

Public Summary Document – November 2019 PBAC Meeting

6.12 Trial GRC88 presented vaccine efficacy as a secondary outcome, assessed by immunogenicity outcomes of GMT ratios and SCRs induced by FluQuadri compared with FluQuadri Junior, 28 days after two doses of each vaccine. The results are presented in Table 4 and Table 5, respectively.

Table 4: Non-inferiority comparison of FluQuadri vs FluQuadri Junior as assessed by the ratio of post-vaccination GMTs (PP analysis set and FAS)

Antigen strain	FluQuadri			FluQuadri Junior			Ratio of GMTs (95% CI)	Non-inferiority
	M	GMT	95% CI	M	GMT	95% CI		
PP analysis set	N = 543			N = 525				
A/H1N1	539	310	271; 354	520	214	185; 247	1.45 (1.19; 1.77)	Yes
A/H3N2	542	332	290; 380	525	221	191; 256	1.50 (1.23; 1.83)	Yes
B Victoria	539	348	304; 398	520	261	227; 299	1.33 (1.10; 1.62)	Yes
B Yamagata	543	349	307; 397	524	243	213; 277	1.44 (1.20; 1.73)	Yes
FAS	N = 597			N = 584				
A/H1N1	592	303	267; 345	578	211	184; 243	1.44 (1.19; 1.74)	Yes
A/H3N2	596	338	297; 384	584	219	190; 251	1.54 (1.28; 1.87)	Yes
B Victoria	592	348	305; 396	578	258	226; 295	1.35 (1.12; 1.62)	Yes
B Yamagata	596	346	306; 391	583	241	212; 272	1.44 (1.21; 1.71)	Yes

CI, confidence interval; FAS, full analysis set; GMT, geometric mean titre; M, number of subjects with available data for the considered endpoint; N, number of subjects analysed according to the Per Protocol analysis set or the FAS, as applicable.

Source: Table 2.5.2, p46 of the submission.

Table 5: Non-inferiority comparison of FluQuadri vs FluQuadri Junior as assessed by seroconversion rates (PP analysis set and FAS)

Antigen strain	FluQuadri			FluQuadri Junior			Differences in SC rates (95% CI)	Non-inferiority
	n/M	SC rate (%)	95% CI	n/M	SC rate (%)	95% CI		
PP analysis set	N = 543			N = 525				
A/H1N1	406/483	84.1	80.5; 87.2	371/470	78.9	75.0; 82.5	5.1 (0.189; 10.0)	Yes
A/H3N2	420/487	86.2	82.9; 89.2	389/475	81.9	78.1; 85.3	4.3 (-0.283; 8.99)	Yes
B Victoria	428/483	88.6	85.4; 91.3	410/470	87.2	83.9; 90.1	1.4 (-2.78; 5.56)	Yes
B Yamagata	445/488	91.2	88.3; 93.5	416/474	87.8	84.5; 90.6	3.4 (-0.465; 7.36)	Yes
FAS	N = 597			N = 584				
A/H1N1	445/527	84.4	81.1; 87.4	412/521	79.1	75.3; 82.5	5.4 (0.683; 10.0)	Yes
A/H3N2	460/532	86.5	83.3; 89.3	434/527	82.4	78.8; 85.5	4.1 (-0.263; 8.49)	Yes
B Victoria	466/527	88.4	85.4; 91.0	452/521	86.8	83.5; 89.5	1.7 (-2.34; 5.69)	Yes
B Yamagata	486/532	91.4	88.6; 93.6	461/526	87.6	84.5; 90.3	3.7 (0.006; 7.45)	Yes

CI, confidence interval; FAS, full analysis set; M, number of subjects with a valid serology result for the particular antigen; N, number of subjects analysed according to the PP analysis set or the FAS, as applicable; n, number of subjects who experienced seroconversion; PP, per protocol; SC = seroconversion.

Public Summary Document – November 2019 PBAC Meeting

Source: Adapted from Table 2.5.3, pp46-47 of the submission.

- 6.13 The lower limit of the 2-sided 95% CI of the GMT ratio between groups was greater than the pre-defined non-inferiority criteria of 0.667 nominated in the submission for all four vaccine strains, as determined by per-protocol and full analysis sets, hence non-inferiority was claimed on this outcome.
- 6.14 The lower limit of the 2-sided 95% CI of the difference in SCRs was greater than the pre-defined non-inferiority criteria of >-10%, considered separately for each vaccine strain, hence non-inferiority was claimed on this outcome.
- 6.15 The evaluation and ESC considered that the clinical claim of non-inferiority based on effectiveness for FluQuadri compared to FluQuadri Junior was reasonable.

Healthy children aged 6 months to <5 years

- 6.16 The Vaxigrip Tetra submission considered by PBAC in July 2019 presented an indirect comparison of Vaxigrip Tetra to the QIV comparators (FluQuadri and FluQuadri Junior) using TIVs as the common comparator, to support the request for listing in at-risk individuals currently eligible for vaccination under the NIP. The PBAC noted that the eligibility criteria of the trials used in the indirect comparison excluded persons for whom yearly seasonal vaccination is recommended under the NIP (i.e., the trials were conducted in healthy individuals) (paragraphs 7.10-7.11, QIV, Vaxigrip Tetra, PSD, July 2019 PBAC meeting). The PBAC noted that the submission used SCR as a surrogate measure for the assessment of comparative efficacy and recalled that immunogenicity outcomes have been used previously for PBAC decision-making. Based on the estimated SCRs there was some uncertainty regarding the non-inferiority of Vaxigrip Tetra compared to FluQuadri, especially in the elderly and young subpopulations (paragraph 7.12), with the evaluation and the ESC noting that the indirect comparison indicated that Vaxigrip Tetra may be less effective than FluQuadri (paragraphs 6.28-6.29). However, overall the PBAC considered that the claim of non-inferiority of Vaxigrip Tetra to FluQuadri to be reasonable (paragraph 7.12).
- 6.17 The ESC considered that the indirect comparison of FluQuadri/FluQuadri Junior to Vaxigrip Tetra in healthy individuals that was presented in the July 2019 Vaxigrip Tetra submission to support the request for listing in at-risk individuals (including children), indicated that FluQuadri would be at least non-inferior to Vaxigrip Tetra in healthy children aged 6 months to <5 years.
- 6.18 The ESC also noted that in January 2019, the United States (US) Food and Drug Administration (FDA) approved a change in the listing for Fluzone Quadrivalent (the brand for FluQuadri vaccine in the US) to enable use of the 0.5 mL dose in children aged 6 to 35 months, with no preference for whether the 0.25 mL or 0.5 mL dose is used.²

² FDA Approval Letter of 23 January 2019 to Sanofi Pasteur Inc.: <https://www.fda.gov/media/119855/download>

Comparative harms

- 6.19 The submission did not seek ATAGI pre-submission advice for the requested change to listing for FluQuadri. Instead, the October 2018 ATAGI advice for Vaxigrip Tetra was provided. On balance, ATAGI noted it did not have specific concerns regarding the safety of Vaxigrip Tetra for use in children aged 6 months to <5 years (ATAGI October 2018 Pre-Submission Advice, QIV, Vaxigrip Tetra).
- 6.20 The evaluation for the submission utilised this advice, considering that it may extend to FluQuadri. However, there was a lack of evidence in the submission to demonstrate the similarity between these vaccines. The PSCR argued that the use of the Vaxigrip Tetra ATAGI advice was appropriate because both Vaxigrip Tetra and FluQuadri are quadrivalent vaccines utilising the same four strains and; both are manufactured in Australia using similar technology and; the populations for both submissions considered children aged 6-35 months. The ESC noted that there are similarities between the vaccines, however no certainty was provided to confirm whether they are manufactured in the same facility.
- 6.21 Trial GRC88 presented safety results as a primary outcome, assessed by the rate of any fever associated with FluQuadri compared with FluQuadri Junior during the seven days after either vaccination (Dose 1 or Dose 2) in children 6-35 months of age. The results are presented in Table 6.

Table 6: Comparative summary of the fever rate of subjects who received FluQuadri vs subjects who received FluQuadri Junior (SAS)

FluQuadri N = 992			FluQuadri Junior N = 949		
n/M	Fever rate (%)	95% CI	n/M	Fever rate (%)	95% CI
113/930	12.15	10.12; 14.42	101/893	11.31	9.31; 13.57
Difference in fever rates (95% CI): 0.84 (-2.13; 3.80)					
Non-inferiority (upper limit of 95% CI of difference in fever rates <5%): Yes					

CI = confidence interval; M = number of subjects with valid temperature data during the 7 days after vaccination; n = number of subjects who experienced fever within the solicited period; N = number of subjects analysed according to the SAS and fulfilling column header; SAS = safety analysis set.

Fever is defined as body temperature of $\geq 100.4^{\circ}\text{F}$ (38°C).

Difference in fever rate = fever rate in FluQuadri group minus fever rate in FluQuadri Junior group.

Source: Adapted from Table 2.5.1, p45 of the submission.

- 6.22 Trial GRC88 assumed an expected fever rate of 14.3%. The upper limit of the 2-sided 95% CI of the fever rate difference was 3.80%, which is lower than the pre-defined non-inferiority criteria of 5%. Fever rates were higher in the 6 to <24 months age group (15.66% for FluQuadri and 12.05% for FluQuadri Junior) and lower in the 24 to <36 months age group (7.52% for FluQuadri and 10.38% for FluQuadri Junior). The submission did not present subgroup analysis of fever rates for younger age groups, 6 to <12 months and 12 to <24 months. The possibility of higher fever incidence in

younger age groups increased the uncertainty in the study results, as no age sub-group analyses were presented in the submission. ATAGI noted that among Vaxigrip Tetra recipients, there was a trend of decreasing rates of fever with increasing age, with 24.4% of children aged 6–11 months experiencing fever, compared with 20.4% of children aged 12–23 months, and 18.3% of children aged 24–35 months (ATAGI October 2018 Pre-Submission Advice, QIV, Vaxigrip Tetra). The PSCR stated that this ATAGI advice was not supported by a statistical test therefore, these results could have been a chance finding. The PSCR also argued none of the fever adverse events in Trial GRC88 required hospitalisation or were life-threatening events. The ESC noted the PSCR’s claim that these adverse events did not pose a significant safety risk.

- 6.23 A summary of the safety outcomes, in terms of solicited and unsolicited adverse events and reactions, for FluQuadri and FluQuadri Junior in children aged 6-35 months, are shown in Table 7.³

³ Solicited adverse events (AEs) were collected for 7 days after each vaccination; unsolicited AEs were collected from Visit 1 to Visit 2 (0-28 days) for subjects receiving 1 dose and from Visit 1 to Visit 3 (0-56 days) for subjects receiving 2 doses; and serious AEs (SAEs) and any pre-specified AEs of special interest (AESIs) were collected up-to the end of the trial (p38 of the submission).

Table 7: Safety overview after any vaccination (SAS)

Subjects experiencing at least one:	FluQuadri			FluQuadri Junior		
	n/M	%	95% CI	n/M	%	95% CI
Immediate unsolicited AE	0/992	0	0.0; 0.4	2/949	0.2	0.0; 0.8
Immediate unsolicited AR	0/992	0	0.0; 0.4	1/949	0.1	0.0; 0.6
Solicited reaction	698/941	74.2	71.3; 76.9	645/909	71	67.9; 73.9
Solicited injection site reaction	533/939	56.8	53.5; 60.0	480/909	52.8	49.5; 56.1
Solicited systemic reaction	561/941	59.6	56.4; 62.8	533/909	58.6	55.4; 61.9
Unsolicited AE	395/992	39.8	36.8; 42.9	420/949	44.3	41.1; 47.5
Unsolicited AR	30/992	3.0	2.0; 4.3	29/949	3.1	2.1; 4.4
AE leading to study discontinuation	0/992	0	0.0; 0.4	3/949	0.3	0.1; 0.9
SAEs	5/992	0.5	0.2; 1.2	5/949	0.5	0.2; 1.2
Death	0/992	0	0.0; 0.4	0/949	0	0.0; 0.4

AE = adverse event; AR = adverse reaction; CI = confidence interval; M = number of subjects with available data for the relevant endpoint; N = number of subjects analysed according to the SAS; n = number of subjects experiencing the endpoint listed; SAE = serious adverse event; SAS = safety analysis set.

Source: Table 2.5.4, p48 of the submission.

6.24 The submission reported that the overall safety of FluQuadri and FluQuadri Junior were comparable. The overall rates of solicited systemic and injection site reactions were higher in FluQuadri compared with FluQuadri Junior, whereas unsolicited adverse events and adverse reactions were lower in FluQuadri compared with FluQuadri Junior. The evaluation considered that this claim was reasonable.

Clinical claim

At-risk children aged 6-35 months

6.25 The submission described FluQuadri as non-inferior in terms of safety and effectiveness compared with FluQuadri Junior in children aged 6-35 months.

6.26 The evaluation, the ESC and ATAGI (ATAGI October 2019 Post-Submission Advice, QIV, FluQuadri, November 2019 PBAC meeting) considered the therapeutic claim regarding non-inferior effectiveness on the basis of immunogenicity outcomes was reasonable.

6.27 The evaluation considered that the therapeutic claim regarding safety was uncertain given the submission did not justify the assumption of the expected fever rate of 14.3% used in Trial GRC88. The ESC considered that the claim may be reasonable. The ATAGI (ATAGI October 2019 Post-Submission Advice, QIV, FluQuadri, November 2019 PBAC meeting) accepted the claim of non-inferior safety in terms of post-vaccination fever but noted the trend of relatively higher rates of systemic adverse reactions with FluQuadri 0.5 mL in younger children aged 6–23 months compared with in those aged 24–35 months would warrant ongoing active safety surveillance (see paragraph 6.46).

- 6.28 The PBAC considered that the claim of non-inferior comparative effectiveness of FluQuadri compared with FluQuadri Junior in at-risk children aged 6-35 months was reasonable.
- 6.29 The PBAC considered that the claim of non-inferior comparative safety of FluQuadri compared with FluQuadri Junior in at-risk children aged 6-35 months was likely to be reasonable.

Healthy children aged 6 months to <5 years

- 6.30 The submission did not make a clinical claim regarding FluQuadri compared with Vaxigrip Tetra for the immunisation of healthy children aged 6 months to <5 years. The clinical evidence presented in the submission (Trial GRC88) was not directly relevant to this population.
- 6.31 In July 2019, the PBAC accepted a claim of non-inferior comparative effectiveness for Vaxigrip Tetra compared with FluQuadri/FluQuadri Junior for the currently eligible at-risk populations, on the basis of an indirect comparison of trials conducted in healthy individuals. The ESC considered that the indirect comparison of Vaxigrip Tetra to FluQuadri/FluQuadri Junior in healthy individuals that was presented in the July 2019 Vaxigrip Tetra submission to support the request for listing in at-risk individuals (including children) indicated that FluQuadri would be at least non-inferior to Vaxigrip Tetra in healthy children aged 6 months to <5 years.
- 6.32 The July 2019 Vaxigrip Tetra submission did not present an indirect comparison of safety results; however, the PBAC considered that the safety of Vaxigrip Tetra was likely to be comparable to other QIVs (paragraph 6.45, QIV, Vaxigrip Tetra, PSD, July 2019 PBAC meeting).
- 6.33 The PBAC considered that the claim of non-inferior comparative effectiveness of FluQuadri compared with Vaxigrip Tetra in healthy children aged 6 months to <5 years was reasonable, based on the evidence considered in the July 2019 Vaxigrip Tetra submission.
- 6.34 The PBAC considered that the claim of non-inferior comparative safety of FluQuadri compared with FluQuadri Junior in healthy children aged 6 months to <5 years was likely to be reasonable.

Economic analysis

- 6.35 The submission presented a cost-minimisation analysis for children aged 6-35 months based on Trial GRC88, but did not apply the analysis to the requested listing for the broader population (i.e. all children aged 6 months to <5 years).
- 6.36 The submission stated the equi-effective doses for at-risk children aged 6-35 months to be:
- A single 0.25 mL dose of FluQuadri Junior, and

- A single 0.5 mL dose of FluQuadri.
- 6.37 The PSCR stated that the equi-effective doses for Vaxigrip Tetra and FluQuadri recommended by PBAC in its July 2019 consideration of the Vaxigrip Tetra submission, were relevant to the request in the current submission to extend listing to healthy children aged 6 months to <5 years:
- A single 0.5 mL dose of Vaxigrip Tetra, and
 - A single 0.5 mL dose of FluQuadri.
- 6.38 The submission assumed no difference in administration costs or the costs associated with management of adverse events. The evaluation considered this was reasonable.

Vaccine cost/patient/year

- 6.39 The proposed NNP for FluQuadri for the expanded population is \$ [REDACTED], in line with the current NNP for FluQuadri, FluQuadri Junior and Vaxigrip Tetra. Children aged 6-35 months who have not been previously vaccinated for influenza would receive two doses in their first year (i.e. \$ [REDACTED]/patient/year). The remaining population would receive one dose per year (i.e. \$ [REDACTED]/patient/year).

Estimated NIP usage & financial implications

- 6.40 This submission was not considered by DUSC. The submission used a market share approach to estimate the financial implications associated with listing FluQuadri for at-risk children aged 6-35 months. The submission assumed that under the proposed listing, FluQuadri was not intended to grow the market but replace market share of FluQuadri Junior only (on a one-for-one substitution basis).
- 6.41 The submission estimated the utilisation of FluQuadri for at-risk children aged 6-35 months in the first 6 years of listing. It used the utilisation of FluQuadri Junior in 2019 ([REDACTED] doses) as the base year and applied market growth rates informed by Australian Bureau of Statistics population growth rates.

Table 8: Estimated use and financial implications of expanding the existing NIP listing of FluQuadri to include at-risk children aged 6-35 months.

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of FluQuadri (based on one-for-one substitution of FluQuadri Junior)						
Number of patients treated						
Number of doses (base case)						
Estimated financial implications of FluQuadri (equal to FluQuadri Junior)						
Cost to NIP*	\$	\$	\$	\$	\$	\$
Net changes to MBS items: Administration costs for FluQuadri (equal to FluQuadri Junior)						
Doses						
Cost of GP	\$	\$	\$	\$	\$	\$
Cost of NP	\$	\$	\$	\$	\$	\$
Net financial implications of FluQuadri						
Net cost to NIP	\$0	\$0	\$0	\$0	\$0	\$0
Net cost to MBS	\$0	\$0	\$0	\$0	\$0	\$0
Net cost to NIP/MBS	\$0	\$0	\$0	\$0	\$0	\$0

ABS = Australian Bureau of Statistics; GP = General Practitioner; NP = Nurse Practitioner; MBS = Medicare Benefits Schedule; NIP = National Immunisation Program; NNP = National Negotiated Price

* Cost to the NIP was based on Nationally Negotiated Price (NNP)

Source: Tables 4.2.4-4.2.5, 4.3.1, 4.4.1 and 4.5.1-4.5.2, p69-72 of the submission.

- 6.42 The submission estimated the projected utilisation and costs of FluQuadri to be the same as that for FluQuadri Junior, resulting in a zero net cost to the NIP. This was derived by assuming one-to-one substitution of FluQuadri for FluQuadri Junior at the same price.
- 6.43 The submission assumed there would be no difference in administration costs or costs associated with management of adverse events as FluQuadri Junior and FluQuadri share the same dosing schedule. The submission stated that the proposed listing is therefore expected to have zero net cost impact on the Medicare Benefits Schedule (MBS) and the overall health budget.
- 6.44 The submission did not present utilisation or financial estimates associated with listing FluQuadri for healthy children aged 6 months to <5 years. The PSCR stated that listing FluQuadri for healthy children aged 6 months to <5 years would directly substitute for Vaxigrip Tetra and would also result in zero net cost to the NIP.

Quality Use of Medicines

- 6.45 No quality use of medicines (QUM) information was provided in the submission. The ATAGI Pre-Submission Advice for Vaxigrip Tetra considered the uniform dosage of 0.5 mL of Vaxigrip Tetra for all people aged ≥6 months “would potentially reduce the complexity of influenza program implementation and potential confusion among immunisation providers” (ATAGI October 2018 Pre-Submission Advice, QIV, Vaxigrip Tetra). The PSCR added that it is the Sponsors’ intention to delist FluQuadri Junior from the ARTG prior to the 2021 influenza season in anticipation of FluQuadri replacing FluQuadri Junior on the NIP. The ATAGI noted that with the delisting of FluQuadri Junior, all influenza vaccine dosing under the NIP in the 6-35 month age group would be standardised to 0.5 mL per dose, which is expected to provide the

benefit of reducing confusion for immunisation providers, and reducing incorrect product use or incorrect dosing (ATAGI October 2019 Post-Submission Advice, QIV, FluQuadri, November 2019 PBAC meeting).

- 6.46 The submission did not propose any post-marketing surveillance. The ATAGI Pre-Submission Advice for Vaxigrip Tetra considered that safety surveillance and program evaluation, including through AusVaxSafety, were integral activities to ensure the safety and effectiveness of the vaccination program (ATAGI October 2018 Pre-Submission Advice, QIV, Vaxigrip Tetra). The ATAGI reiterated its concerns with the relatively higher rates of fever for FluQuadri in children aged 6-23 months compared to 24-35 months, and its advice that this trend warrants ongoing safety surveillance through AusVaxSafety (ATAGI October 2019 Post-Submission Advice, QIV, FluQuadri, November 2019 PBAC meeting). The Pre-PBAC response stated that the Sponsor will work with AusVaxSafety to have all children aged 6 months to <5 years included in their active surveillance.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended extending the current listing of quadrivalent influenza vaccine (QIV) (split virion, inactivated), FluQuadri™, on the *National Health (Immunisation Program – Designated Vaccines) Determination 2014 (No.1)* (the Determination), for the prevention of influenza, to include healthy children aged 6 months to <5 years as well as at-risk children aged 6-35 months who are currently eligible for influenza vaccination through the NIP, under the same provisions (see section 8). The PBAC's recommendation for listing was based on, among other matters, its assessment, that:

- the cost-effectiveness of FluQuadri would be acceptable if it were cost-minimised against FluQuadri Junior, on the basis that FluQuadri is non-inferior to currently listed and recommended QIVs for at-risk children aged 6-35 months, with the equi-effective doses being one dose of FluQuadri 0.5 mL and one dose of an alternative QIV, such as FluQuadri Junior 0.25 mL, Fluarix Tetra 0.5 mL or Vaxigrip Tetra 0.5 mL; and
- the cost-effectiveness of FluQuadri would be acceptable if it were cost-minimised against Vaxigrip Tetra, on the basis that FluQuadri is non-inferior to Vaxigrip Tetra for healthy children aged 6 months to <5 years, with the equi-effective doses being one dose of FluQuadri 0.5 mL and one dose of Vaxigrip Tetra 0.5mL.

At-risk children aged 6-35 months

- 7.2 The PBAC accepted the proposed comparator of FluQuadri Junior for at-risk children aged 6-35 months. The PBAC also considered that alternative QIVs that are either

currently listed or recommended for this population (i.e. Fluarix Tetra and Vaxigrip Tetra) were also appropriate comparators.

- 7.3 The PBAC noted the submission presented one head-to-head RCT (Trial GRC88) comparing FluQuadri to FluQuadri Junior in healthy vaccine-naïve children aged 6-35 months. The PBAC noted the eligibility criteria was not consistent with the proposed NIP listing, however recalled that it had previously accepted that it may be reasonable to expect that VE in sub-populations are unlikely to vary significantly or to vary between the proposed listing and comparator already in use in the vaccinated cohort⁴. The PBAC noted that Trial GRC88 was conducted over a 6-month period during the 2016/17 Northern Hemisphere influenza season and that the varying dominance of virus strains year to year impacts effectiveness, however it noted that this is an uncertainty in all influenza vaccine considerations.
- 7.4 The PBAC noted that the submission used GMTs and SCRs as a surrogate measure for comparative efficacy, and recalled that it had previously accepted immunogenicity outcomes for decision-making to support non-inferiority claims between QIVs⁵. The PBAC noted that non-inferiority criteria for GMT in all strains, and for SCRs were met, demonstrating non-inferiority. Accordingly, the PBAC considered the clinical claim regarding non-inferior effectiveness compared with FluQuadri Junior was reasonable.
- 7.5 The PBAC noted that the submission presented safety data from Trial GRC88, a Safety Analysis Set and the advice of ATAGI that it had no specific concerns regarding safety of Vaxigrip Tetra in children aged 6 months to <5 years⁶. The PBAC considered the clinical claim regarding safety was likely to be reasonable, noting rates and serious adverse events, were similar between the comparator and FluQuadri, as well as similar to the rates observed in other QIVs.
- 7.6 The PBAC accepted the cost-minimisation analysis presented in the submission for the at-risk population. The PBAC advised the equi-effective doses should be one dose of FluQuadri 0.5 mL and one dose of an alternative QIV, such as FluQuadri Junior 0.25 mL, Fluarix Tetra 0.5 mL or Vaxigrip Tetra 0.5 mL.
- 7.7 The PBAC noted the submission used a market share approach to estimate the financial implications associated with listing FluQuadri for at-risk children aged 6-35 months, which it considered to be reasonable. The PBAC noted that extending the listing for FluQuadri would not result in a net cost to the NIP, since the requested NNP for FluQuadri was equal to FluQuadri Junior and there would be no difference in administration costs or management of adverse events.

⁴ p30, QIV, Vaxigrip Tetra, PSD, July 2019 PBAC meeting

⁵ p30, QIV, Vaxigrip Tetra, PSD, July 2019 PBAC meeting

⁶ p1, ATAGI October 2018 Pre-Submission Advice, QIV, Vaxigrip Tetra, July 2019 PBAC meeting

- 7.8 The PBAC considered that using the same dose (0.5 mL) of QIV across all age groups, and the planned delisting FluQuadri Junior, would simplify purchasing for healthcare providers, and reduce wastage, confusion and administration errors.

Healthy children aged 6 months to <5 years

- 7.9 The PBAC accepted Vaxigrip Tetra was the appropriate comparator for healthy children aged 6 months to <5 years, as it was the only QIV currently recommended for this population.
- 7.10 The PBAC recalled that in July 2019 it recommended Vaxigrip Tetra for at-risk individuals who were (then) currently eligible for influenza vaccination through the NIP on the basis of non-inferiority of Vaxigrip Tetra compared with FluQuadri/FluQuadri Junior on the basis of an indirect comparison of seroconversion rates⁷. The PBAC accepted that this comparison was relevant to healthy children, noting that the trials on which the indirect comparison was based excluded persons with underlying conditions for whom yearly seasonal vaccination is recommended. The PBAC noted that while recommending Vaxigrip Tetra as non-inferior to other QIVs does not necessarily equate to non-inferiority in reverse, the PBAC recalled that in July 2019 it had considered that the evidence suggested that Vaxigrip Tetra may be less effective than FluQuadri, but on balance, it had considered Vaxigrip Tetra to be non-inferior to FluQuadri⁸. Accordingly, the PBAC considered that the claim of non-inferior comparative effectiveness to Vaxigrip Tetra in healthy children aged 6 months to <5 years was likely to be reasonable.
- 7.11 The PBAC noted ATAGI's advice that the claims of non-inferiority and acceptable safety of Vaxigrip Tetra compared with FluQuadri were reasonable. The PBAC considered the safety of FluQuadri was likely to be comparable to other QIVs, noting that the rates of adverse events were similar to those seen for other QIVs.
- 7.12 The PBAC accepted the cost-minimisation analysis presented in the PSCR for the healthy children population. The PBAC advised the equi-effective doses for this population should be one dose of FluQuadri 0.5 mL and one dose of Vaxigrip Tetra 0.5 mL.
- 7.13 The PBAC recalled ATAGI's advice⁹ that ongoing safety surveillance through AusVaxSafety is warranted to ensure the safety and effectiveness of Vaxigrip Tetra. The PBAC noted that the Sponsor agreed to work with AusVaxSafety to include this population.
- 7.14 The PBAC considered that use of FluQuadri would directly substitute for use of Vaxigrip Tetra, resulting in a zero net cost to the NIP.

⁷ paragraph 5.2 & 7.10, QIV, Vaxigrip Tetra, PSD, July 2019 PBAC meeting

⁸ paragraph 7.12, QIV, Vaxigrip Tetra, PSD, July 2019 PBAC meeting

⁹ p6, ATAGI October 2019 Post-Submission Advice, QIV, FluQuadri, November 2019 PBAC meeting

- 7.15 The PBAC noted the benefit of having a second QIV formulation available for this population on the NIP.
- 7.16 The PBAC noted that the submission did not seek ATAGI pre-submission advice for this submission, providing instead the October 2018 Pre-Submission Advice for Vaxigrip Tetra that was considered by PBAC for the same population in July 2019. The PBAC considered that the Vaxigrip Tetra ATAGI advice was of relevance as the ESC had noted the similarity between the vaccines; that the submission was for a vaccine previously considered by the PBAC and for an already recommended NIP population; and that it had considered the relevant data and ATAGI advice previously. In addition, the PBAC noted the ATAGI post-submission advice provided for this submission was supportive of extending the NIP listing of FluQuadri in both proposed populations¹⁰.
- 7.17 The PBAC noted that this submission is not eligible for an Independent Review because it is only relevant to submissions relating to the PBS.

Outcome:

Recommended

8 Recommended listing

- 8.1 Amend existing listing on the NIP as follows (additions in italics, deletions in strikethrough):

¹⁰ p1, ATAGI October 2019 Post-Submission Advice, QIV, FluQuadri, November 2019 PBAC meeting

Public Summary Document – November 2019 PBAC Meeting

Name, Restriction, Manner of administration and form	Proprietary Name and Manufacturer
Inactivated Quadrivalent Influenza Vaccine (split virion) Injection 0.5 mL	FluQuadri™ Sanofi-Aventis (Australia) Pty Ltd
Category/Program	NIP
Groups eligible for the requested NIP listing of FluQuadri	<p>Children aged ≥ 6 months to < 5 years of age</p> <p>Persons aged ≥ 6 months 3 years who are at increased risk of influenza complications, specifically:</p> <ul style="list-style-type: none"> • has cardiac disease including cyanotic congenital heart disease, coronary artery disease and congestive heart failure; or • has a chronic respiratory condition including suppurative lung disease, bronchiectasis, cystic fibrosis, chronic obstructive pulmonary disease, chronic emphysema and severe asthma; or • has another chronic illness requiring regular medical follow up or hospitalisation in the preceding year, including diabetes mellitus, chronic metabolic diseases, chronic renal failure, haemoglobinopathies and impaired immunity (including drug induced immune impairment); or • has a chronic neurological condition, including multiple sclerosis, spinal cord injuries, seizure disorders or other neuromuscular disorders; or • has impaired immunity, including HIV infection; or • is a person aged less than 11 years and receiving long-term aspirin therapy <p>Aboriginal and Torres Strait Islander people aged ≥ 6 months 3 years</p> <p>Persons aged ≥ 65 years</p> <p>Pregnant women</p>
Number and timing of doses	<p>Should be administered in accordance with the national recommendation as per the current Immunisation Handbook:</p> <p>Children ≥ 6 months to < 9 years of age:</p> <ul style="list-style-type: none"> • If the child has not previously been vaccinated: two 0.5 ml injections at least one month apart. • If the child has been previously vaccinated: a single 0.5 ml injection.

NIP = National Immunisation Program; HIV = Human Immunodeficiency Virus

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Public Summary Document – November 2019 PBAC Meeting

Sanofi Pasteur welcomes the PBAC's recommendation to extend the current NIP listing of the quadrivalent influenza vaccine, FluQuadri, to include healthy children aged 6 months to under 5 years.