

5.01 QUADRIVALENT INFLUENZA VACCINE, Pre-filled syringe, 0.5mL, Afluria® Quad, Seqirus.

1 Purpose of Application

- 1.1 The submission sought listing of quadrivalent influenza vaccination (QIV, Afluria® Quad) on the National Immunisation Program (NIP) – Designated Vaccines list for the prevention of seasonal influenza.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	NIP price for Max. Qty	Proprietary Name and Manufacturer
INACTIVATED QUADRIVALENT INFLUENZA VACCINE (SPLIT VIRION), 15 µg HA/strain (4 strains) for IM injection (pre-filled syringe), 0.5 mL A single dose for adults aged 18 years or older <i>^aIndicative price</i>	1	0	\$ [REDACTED] ^a	Afluria® Quad Seqirus

- 2.1 The listing was requested on a cost minimisation basis compared to Fluarix® Tetra influenza vaccine.

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

3 Background

- 3.1 **TGA status at time of PBAC consideration:** Afluria® Quad was TGA registered on 15 July 2016 for the prevention of influenza caused by influenza virus Types A and B contained in the vaccine in persons aged 18 years and over.

- 3.2 The ARTG registration letter from the TGA to the sponsor notes that supply of Afluria® Quad will not be permitted until the sponsor provides evidence to satisfy the TGA on a number of [REDACTED] issues. [REDACTED]

- 3.3 Afluria® Quad has not been considered by the PBAC previously.

- 3.4 The PBAC has previously recommended three QIVs to be listed on the NIP. Fluarix® Tetra was recommended at the March 2015 PBAC meeting for use in people aged ≥3 years. FluQuadri® and FluQuadri® Junior were recommended at the July 2015 PBAC meeting for people aged ≥3 years and children aged 6 months to <3 years, respectively.

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

4 Clinical place for the proposed therapy

- 4.1 Afluria® Quad will be used for active immunisation against four influenza strains (two influenza A strains and two influenza B strains) in all eligible individuals listed on the NIP aged 18 years and older.
- 4.2 ATAGI indicated that QIV formulations will replace trivalent influenza vaccine (TIV) on the NIP, “[t]he inactivated quadrivalent influenza vaccine (QIV) will be used exclusively in the NIP from 2016.” [ATAGI Advice to PBAC, inactivated QIV, February 2016]

5 Comparator

- 5.1 Fluarix® Tetra influenza vaccine was used as the main comparator. The evaluation considered that this was the appropriate comparator given it is listed on the NIP for people age ≥3 years. In July 2015, the PBAC considered that Fluarix® Tetra was the appropriate comparator in its consideration of FluQuadri®.

6 Consideration of the evidence

Clinical trials

- 6.1 The submission was based on an indirect comparison between Afluria® Quad and Fluarix® Tetra using TIV as the common comparator. The submission was based on four head-to-head randomised trials; one comparing Afluria® Quad to TIV [CSLCT, N=3,484] and three comparing Fluarix® Tetra to TIV [Kieninger et al. (2013), N=4,659; Tinoco et al. (2014); N = 1,707; Beran et al. (2013), N=420].
- 6.2 The clinical trial populations are not the same as the requested NIP population. Differences include:
- no representation of the Aboriginal and Torres Strait Islander population in the trial, no sites were in Australia;
 - pregnant women not included in the trial; and
 - none of the studies enrolled patients with specific medical conditions associated with an increased risk of influenza complications, and some of which were excluded.

6.3 Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
NCT02214225 CSLCT	Phase III, randomised, multi-centre, double-blinded, immunogenicity and safety study	Date: 10 August 2014
NCT01204671 Kieninger et al (2013)	Phase III, randomised, partially-blind, multi-national study, immunogenicity, reactogenicity and safety Kieninger, D, E Sheldon, W Lin, C Yu, and J Bayas. Immunogenicity, reactogenicity and safety of an inactivated quadrivalent influenza vaccine candidate versus inactivated trivalent influenza vaccine: a phase III, randomized trial in adults aged ≥18 years.	Date: 16 September 2010 BMC Infectious Diseases 2013, 13(343):1-13
NCT01196975 Tinoco et al (2014)	Phase III, randomised, lot-to-lot consistency of QIV vs TIV, immunogenicity, reactogenicity, safety trial Tinoco, J, N Pavia-Ruz, A Cruz-Valdez, C Aranza Doniz, and V Chandrasekaran. Immunogenicity, reactogenicity, and safety of inactivated quadrivalent influenza vaccine candidate versus inactivated trivalent influenza vaccine in healthy adults aged >18 years: A phase III, randomized trial.	Date: 7 September 2010 Vaccine 2014; 32 (13): 1480-7
NCT00714285 Beran et al (2013)	Phase I/II, single-centre, single-blind, controlled study, immunogenicity Beran, J, M Peeters, W Dewé, J Raupachová, L Hobzová, and J Devaster. Immunogenicity and safety of quadrivalent versus trivalent inactivated influenza vaccine: a randomized, controlled trial in adults.	Date: 11 July 2008 BMC Infectious Diseases 2013; 13(224):1-10

Source: Table B.2.1, p.22 of the submission

6.4 The key features of the direct randomised trials are summarised in the table below.

Table 2: Key features of the included evidence

Trial ID	N	Design/duration	Risk of bias	Population	Main outcomes
Afluria® Quad vs. TIV					
CSLCT	3,484	Ph III, R, DB, 21 days	Low	Adults ≥18 years	Primary: NI GMTs, NI SCR Secondary: S GMTs; S SCRs Other: immunogenicity, safety
Fluarix® Tetra vs. TIV					
Kieninger et al. 2013	4,659	Ph III, R, PB, 21 days	Low	Adults ≥18 years	Primary: NI GMTs and SCRs; S GMTs and SCRs; Other: immunogenicity, safety
Tinoco et al. 2014	1,707	Ph III R, DB, 21 days	Low	Adults ≥18 years	Primary: NI GMTs Secondary: S; GMT Other: immunogenicity, safety
Beran et al. 2013	420	Ph I/II, R, SB, 21 days	Low	Adults 18-60 years	Primary: NI GMTs S GMTs Secondary: Other: immunogenicity, safety
Meta-analysis	Included Kieninger et al. (2013) and Tinoco et al. (2014); GMTR				NI GMTR

Abbreviations: D, double-blind; GMT, Geometric Mean Titres; GMTR, Geometric Mean Titre Ratio; MD, mean difference; NI, Non inferiority; PB, partially blind; R, randomised; S, superiority; SB, single blind; SCR, Seroconversion rate
Source: compiled during the evaluation

Comparative effectiveness

- 6.5 The non-inferiority claim in the submission was based on an indirect comparison of haemagglutination antibody geometric titres (GMTs) and seroconversion rates (SCRs). These surrogate outcomes have previously been used for PBAC decision making (5.12, July 2015, QIV, PSD). The results of indirect meta-analysis for GMTRs and indirect comparison for GMTRs and mean difference SCRs are indicated in Table 3, Table 4 and Table 5 respectively.

Table 3: Results of meta-analysis of GMTR across the direct randomised trials

Study ID	Strain	TIV vs. QIV			Heterogeneity Chi ² ; I ²	NNT
		GMTR	95% CI	p-value		
Fluarix® Tetra trials						
Kieninger et al. (2013)	A/H1N1	0.92	0.67; 1.25	0.59	12.76; 92%	1
Tinoco et al. (2014)	A/H3N2	1.07	0.89; 1.30	0.46		
	B/Yamagata	0.88	0.72; 1.08	0.21	6.19; 84%	1
	B/Victoria	0.86	0.66; 1.12	0.27		

Source: Figure B.6.1, p. 59; Figure B.6.2; p.59; Figure B.6.3; p.60 and Figure B.6.4, p.60 of the submission

Table 4: Summary of results of the indirect comparison – GMTR

Strain	Afluria® Quad TIV/QIV		Fluarix® Tetra TIV/QIV		Afluria® Quad vs Fluarix® Tetra	
	GMTR	95% CI	GMTR	95% CI	GMTR	95% CI
A/H1N1	0.92	0.87, 0.98	0.92	0.67, 1.25	1.00	0.73, 1.37
A/H3N2	0.93	0.88, 0.98	1.07	0.89, 1.30	1.15	0.95, 1.40
B/YAM	0.87	0.81, 0.93	0.88	0.72, 1.08	1.01	0.82, 1.25
B/VIC	0.94	0.86, 1.01	0.86	0.66, 1.12	0.92	0.69, 1.21

Note: analysis includes CSLCT, Kieninger et al. (2013) and Tinoco et al. (2014)

Source: Table B.6.23, p. 61 of the submission

Table 5: Summary of results of the indirect comparison – mean difference in SCR

Strain	Afluria® Quad (TIV – QIV)		Fluarix® Tetra (TIV – QIV)		Afluria® Quad vs Fluarix® Tetra	
	SCR MD	95% CI	SCR MD	95% CI	SCR MD	95% CI
A/H1N1	-1.1	-4.4, 2.2	1.08	-2.03, 4.11	2.18	-2.33, 6.69
A/H3N2	-1.7	-5.0, 1.6	-3.71	-7.15, -0.30	-2.01	-6.77, 2.75
B/YAM	-3.2	-7.0, 0.5	-2.69	-7.47, 2.01	0.51	-5.53, 6.55
B/VIC	-1.6	-5.6, 2.4	-2.71	-7.29, 1.83	-1.11	-7.18, 4.96

Note: analysis includes CSLCT and Kieninger et al. (2013)

Source: Table B.6.24, p. 61 of the submission

Comparative harms

- 6.6 The submission presented patient-relevant harms in the form of vaccine related symptoms. The evaluation considered that the safety profile of Afluria® Quad appeared to be similar to Fluarix® Tetra.

Clinical claim

- 6.7 The submission described Afluria® Quad as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over Fluarix® Tetra in adults. The PBAC considered that these claims were reasonable.

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

Economic analysis

- 6.8 The submission provided a cost-minimisation analysis and considered Afluria® Quad to be equivalent to Fluarix® Tetra.
- 6.9 The equi-effective doses are estimated as Afluria® Quad 0.5 mL 15 µg HA/4 strains for once off vaccination annually and Fluarix® Tetra 0.5 mL 15 µg HA/4 strains for one off vaccination annually.
- 6.10 The submission provides an indicative price of Fluarix® Tetra which at that time was assumed to be \$█.
- 6.11 There was no impact of any additional costs/offsets for administration or adverse events.

Drug cost/patient/year: \$█

- 6.12 The estimated cost per person per year was \$█ (ex-manufacturer price) for all recipients aged 18 years and over who are eligible to receive NIP-funded influenza vaccine.

Estimated PBS usage & financial implications

- 6.13 This submission was not considered by DUSC. The submission presented a mixed epidemiological/market share approach to forecast the uptake and cost of Afluria® Quad over a five year period.

Table 6: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	█	█	█	█	█
Market share	%	%	%	%	%
Scripts ^a	█	█	█	█	█
Estimated total net cost					
Net cost to NIP	\$0	\$0	\$0	\$0	\$0

^a Assuming one script per year as estimated by the submission.

Source: Table E.2.3, p. 79; Table E.3.1, p.81 and Table E.4.1, p. 82 of the submission

- 6.14 At year 5, the estimated number of patients was over 200,000, with no net cost to the NIP.
- 6.15 The evaluation considered that the estimates appeared reasonable. The analysis considered only the costs associated with the vaccine. The submission does not claim any additional health benefits (in terms of morbidity or mortality) in listing Afluria® Quad. As such, the analysis predicts that including Afluria® Quad on the NIP as proposed will be cost neutral to both the program and Australian government health budgets.

- 6.16 The evaluation considered there may be a risk of use in younger age groups (less than 18 years). The comparator is listed on the NIP for children aged 3 years and older, whereas, Afluria® Quad has requested a listing for adults aged 18 years and older who are eligible to receive NIP-funded vaccine. ATAGI acknowledged the risk of use in younger age group and is "... aware of cases of young children receiving Fluvax® [trivalent]...despite current recommendations and risk management activities" [ATAGI Supplementary Advice to PBAC, Seqirus QIV vaccine for adults', June 2016]. Additionally, the TGA has requested a "boxed warning ...to highlight that the vaccine should be given to adults" [Advisory Committee on Prescription Medicines (ACPM), Ratified minute of meeting 310 – 2-3 June 2016].
- 6.17 The pre-PBAC response stated that Seqirus has been working closely with TGA to minimise the potential risk of use in age groups less than 18 years. Measures to minimise the potential risk include (in addition to the boxed warning in the PI referred to in paragraph 6.16):
- Change of the brand name from Fluvax Quad to Afluria® Quad to mitigate confusion with generic influenza vaccines and Fluvax® (TIV) which is indicated for persons aged 5 years and older.
 - Inclusion of the age indication for Afluria® Quad vaccine on the package labelling
 - A different colour label for Afluria® Quad (yellow) compared to Fluvax (blue)
 - A letter advising that Afluria® Quad is indicated ONLY for adults 18 years and older will be mailed to all pharmacists, general practitioners and medical practices, during the month of March.
 - An electrostatic vaccine refrigerator sticker that clearly states the age indication of Afluria® Quad will be mailed to all medical practices and pharmacies during the month of March.
 - An A5 card that summarises the current ATAGI recommendations for the use of influenza vaccine by brand, age group and availability on the NIP, will be mailed to all general practitioners and pharmacists during the month of March.

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

7 PBAC Outcome

- 7.1 The PBAC deferred making a recommendation on whether Afluria® Quad should be included on the Designated Vaccines list for the NIP for the prevention of seasonal influenza until such time as the TGA is in a position to advise its concerns [REDACTED] have been addressed. [REDACTED]
- 7.2 The PBAC recalled that it previously recommended that Fluarix® Tetra (in March 2015) and FluQuadri® (in July 2015) be included on the Designated Vaccines list for the NIP for the prevention of seasonal influenza for eligible persons aged 3 years and older. The PBAC noted that listing was requested for adults aged 18 years and older who are eligible for NIP-funded vaccine, and that Seqirus intends to

implement a number of measures to prevent the administration of Afluria® Quad to people under 18 years of age (see paragraph 6.17).

- 7.3 The PBAC noted that if Afluria® Quad were included on the Designated Vaccine list, it would be the third quadrivalent seasonal influenza vaccine able to be supplied under the NIP to eligible persons aged 18 years and older.
- 7.4 The PBAC accepted that Fluarix® Tetra was the appropriate comparator. The PBAC recalled that in July 2015 it considered that FluQuadri® was non-inferior in efficacy and safety compared with Fluarix® Tetra and therefore recommended FluQuadri® on a cost minimisation basis to Fluarix® Tetra.
- 7.5 The PBAC noted that the submission was based on an indirect comparison between Afluria® Quad and Fluarix® Tetra using TIV as the common comparator. The non-inferiority claim was based on an indirect comparison of surrogate outcomes (haemagglutination antibody geometric titres and seroconversion rates). The PBAC noted that ATAGI accepted that the immunogenicity and safety of Afluria® Quad is likely to be similar to that of other QIVs.
- 7.6 The PBAC noted that listing of Afluria® Quad was requested on a cost-minimisation basis compared with Fluarix® Tetra and accepted that one dose of 0.5 mL Afluria® Quad is likely to be equi-effective to one dose of 0.5 mL Fluarix® Tetra.
- 7.7 The PBAC considered that the utilisation and financial estimates presented in the submission appeared reasonable, noting that if Afluria® Quad were included on the NIP it would be likely to replace other influenza vaccines and cost to Government would therefore be expected to be neutral.

Outcome:

Deferred

ADDENDUM

Subsequent to the August 2016 meeting, the sponsor provided the PBAC with a copy of a letter from the TGA, which stated that [REDACTED] Seqirus had provided evidence sufficient to satisfy the TGA that the product can be supplied.

The PBAC recommended the listing of Afluria® Quad on the NIP – Designated Vaccines List for the prevention of seasonal influenza for adults aged 18 years and older who are eligible to receive NIP-funded influenza vaccine. The recommendation was made on a cost-minimisation basis with Fluarix® Tetra influenza vaccine, with the equi-effective doses being one dose of 0.5 mL Afluria® Quad and one dose of 0.5 mL Fluarix® Tetra.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item to the NIP:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
INACTIVATED QUADRIVALENT INFLUENZA VACCINE (SPLIT VIRION), 15 µg HA/strain (4 strains) for IM injection (pre-filled syringe), 0.5 mL	1	0	Afluria® Quad	Seqirus

A single dose for adults aged 18 years or older who are eligible to receive NIP-funded influenza vaccine.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor had no comment.