

## 5.12 QUADRIVALENT INFLUENZA VACCINE

### 0.5 mL pre-filled syringe; Fluarix<sup>®</sup> Tetra; GlaxoSmithKline Australia Pty Ltd.

#### 1 Purpose of Application

- 1.1 The submission sought listing of quadrivalent influenza vaccination (Fluarix Tetra) on the National Immunisation Program (NIP) – Designated Vaccines List, for the prevention of seasonal influenza. The submission states that a further tender process would be needed for listing on the NIP.

#### 2 Requested NIP listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
Fluarix <sup>®</sup> Tetra (quadrivalent influenza vaccine) 15 µg HA/strain (4 strains) in 0.5ml suspension of phosphate buffered saline for IM injection in pre-filled syringe.				Fluarix <sup>®</sup> Tetra GlaxoSmith-Kline Australia Pty Ltd
3 to 9 years	1	1	\$ [REDACTED]	
>9 years	1		\$ [REDACTED]	
<sup>a</sup> Ex-manufacturer price				

#### Restrictions:

All persons ≥65 years and high risk individuals aged ≥3 years, consistent with the registered TGA indication and the following additional populations aged ≥3 years, which are currently recommend for consideration or under review by the PBAC for inclusion as high risk populations eligible for NIP funded seasonal influenza vaccination:

- Down syndrome, obesity (body mass index ≥30 kg/m<sup>2</sup>) and chronic liver disease
- Aboriginal and Torres Strait Islander children aged six months to 59 months

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

#### 3 Background

- 3.1 Fluarix Tetra was TGA registered on 28 August 2013 for active immunisation of adults and children from three years of age for the prevention of influenza disease caused by the influenza virus types A and B contained in the vaccine. The use of Fluarix Tetra should be based on official recommendations.

- 3.2 Fluarix Tetra has not been considered by the PBAC previously.

#### **4 Clinical place for the proposed therapy**

- 4.1 The submission stated Fluarix Tetra will be used for active immunisation against four influenza strains (two influenza A strains and two influenza B strains) in all individuals listed on the NIP, as well as the following groups:
- individuals aged three and over with Down syndrome, obesity (body mass index  $\geq 30$  kg/m<sup>2</sup>) and chronic liver disease; and
  - Aboriginal and Torres Strait Islander children aged six to 59 months.
- 4.2 The PSCR stated that the proposed obesity category of BMI  $\geq 30$  kg/m<sup>2</sup> was a typographical error in the submission and that the sponsor agreed that it should be  $\geq 40$ , in line with the ATAGI advice. The PSCR also clarified that with regards to the additional population of Aboriginal and Torres Strait Islander children aged 6 to 59 months, the submission requests use in this population for those aged at least three years, in line with the TGA registered indication. The ESC considered that this was appropriate.
- 4.3 Fluarix Tetra includes immunisation against two influenza A strains and two influenza B strains compared to the normal trivalent influenza vaccines, which include immunisation against two influenza A strains and only one influenza B strain under guidelines from the World Health Organization.
- 4.4 The ESC noted that while the source of an influenza pandemic is always an A strain, influenza B can have just as severe clinical implications for individuals.

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

#### **5 Comparator**

- 5.1 Fluarix trivalent influenza vaccine was used as the main comparator throughout the submission. This was the appropriate comparator as no other quadrivalent influenza vaccines were available on the NIP or Designated Vaccine List.

#### **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.

##### ***Clinical trials***

- 6.3 The submission was based on two head-to-head trials comparing Fluarix Tetra to Fluarix (n = 5,596). A systematic review and meta-analysis of vaccine efficacy in trivalent influenza vaccination was provided as supplementary evidence.

6.4 Details of the trials presented in the submission are provided in the following table.

**Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trials</b>		
FLU D-QIV-003 Domachowske J.B	Immunogenicity and safety study of GSK Biologicals' influenza vaccine GSK2321138A when administered in children A randomized trial of candidate inactivated quadrivalent influenza vaccine versus trivalent influenza vaccines in children aged 3-17 years	Date: 2 Dec 2011 Journal of Infectious Diseases (2013) 207:12 (1878-1887). Date: 15 Jun 2013
FLU D-QIV-008 Kieninger D	Partially-blind immunogenicity and safety study of GSK Biologicals' seasonal influenza vaccine GSK2321138A in adults Immunogenicity, reactogenicity and safety of an inactivated quadrivalent influenza vaccine candidate versus inactivated trivalent influenza vaccine: A phase III, randomized trial in adults aged (greater-than or equal to) 18 years	Date: 22 Nov 2011 BMC Infectious Diseases (2013) 13:1 Article Number: 343. Date: 24 Jul 2013
<b>Supplementary systematic review and meta-analysis</b>		
Tricco et al., 2013	Tricco AC, Chit A, Soobiah C et al. Comparing influenza vaccine efficacy against mismatched and matched strains: a systematic review and meta-analysis.	BMC Medicine 2013;11:153

Source: Technical Document 1 of the submission

6.5 The key features of the direct randomised trials are summarised in the following table.

**Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
<b>Fluarix Tetra vs. Fluarix</b>					
FLU D-QIV-003	2,645	R, DB, MC 6 mths	Low	Healthy children 3 - 17 years	GMT SCR
FLU D-QIV-008	2,951	R, DB (D-QIV & TIV-1), OL (TIV-2), MC 6 mths*	Low	Healthy adults ≥18 years	GMT SCR
<b>Supplementary comparison of matched vs mismatched influenza strains in trivalent vaccination</b>					
		<b>Included trials</b>		<b>Outcome of interest</b>	
Meta-analysis Tricco 2013	58,628	Barrett 2010, Beran 2009a, Beran 2009b, Frey 2010, Jackson 2010, Monto 2009, Ohmit 2006 and Ohmit 2008;		Vaccine efficacy of trivalent influenza vaccine against matched and mismatched B strains.	

DB = double blind; MC = multi-centre; R = randomised; GMT = haemagglutination inhibition geometric mean titre; SCR = haemagglutination inhibition seroconversion rate; NA = not applicable.

Source: compiled during the evaluation

\*Corrected in Pre-PBAC response

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

**Comparative effectiveness**

6.6 The claim in the submission was based on haemagglutination antibody geometric mean titre and seroconversion rate as a surrogate for the prevention of influenza cases. The evaluator concluded that this approach was appropriate, and these surrogate outcomes have been used previously for PBAC decision-making. The clinical claim was based on a systematic review and meta-analysis evaluating

vaccine efficacy of trivalent influenza vaccines against matched and mismatched B strains when compared to placebo. The evaluator concluded that this approach might not have been appropriate, as the data on increased vaccine efficacy was based on trivalent influenza vaccine efficacy alone. The ESC agreed that this approach was not appropriate.

6.7 The key immunogenicity results are presented in the following table. On the basis of the head to head trials:

- Fluarix Tetra appears to have had the same effect as Fluarix, in the prevention of influenza cases if the B strain is matched to the circulating influenza strains.
- Fluarix Tetra might have an improved effect compared to Fluarix, against the influenza B strain not included in the Fluarix vaccine.

Results of haemagglutination inhibition geometric mean titres

Population	Fluarix Tetra	Trivalent influenza vaccine	Adjusted GMT ratio TIV/Fluarix Tetra (95% CI)
<b>Benefits</b>			
<b>A/California/7/2009 (H1N1) vs Fluarix + TIV2</b>			
3-17 years old	398.4	423.6	1.06 (0.98, 1.15)
≥18 year	201.6	214.8	1.07 (0.96, 1.18)
Sub group ≥65 Y	██████	██████	██████
<b>A/Victoria/210/2009 (H3N2) vs Fluarix + TIV2</b>			
3-17 years old	232.9	228.7	0.98 (0.92, 1.05)
≥18 year	318.5	312.2	0.98 (0.90, 1.07)
Sub group ≥65 Y	██████	██████	██████
<b>B/Brisbane/60/2008 (Victoria) vs Fluarix</b>			
3-17 years old	245.2	245.4	1.00 (0.92, 1.09)
≥18 year	404.2	395.3	0.98 (0.90, 1.07)
Sub group ≥65 Y	██████	██████	██████*
<b>B/Brisbane/3/2007 (Yamagata) vs Fluarix</b>			
3-17 years old	572.4	224.6	0.39 (0.36, 0.42)
≥18 year	601.2	387.7	0.65 (0.59, 0.71)
Sub group ≥61 Y	██████	██████	██████
<b>B/Brisbane/60/2008 (Victoria) vs TIV-2</b>			
3-17 years old	249.2	86.9	0.35 (0.32, 0.38)
≥18 year	403.5	259.3	0.64 (0.59, 0.70)
Sub group ≥61 Y	██████	██████	██████
<b>B/Brisbane/3/2007 (Yamagata) vs TIV-2</b>			
3-17 years old	581.1	635.3	1.09 (1.01, 1.18)
≥18 year	600.8	584.7	0.97 (0.89, 1.07)
Sub group ≥65 Y	██████	██████	██████*

TIV = trivalent influenza vaccine; TIV-2 = inactivated trivalent influenza vaccine with alternate B strain to Fluarix. GMT = Geometric mean titres.

Source: Table 21-26 pp 61-70 of the submission and calculated during the evaluation

\*Corrected in Pre-PBAC response

6.8 The key influenza B strain vaccine efficacy results from the supplementary systematic review are summarised in the following table.

Summary of results of the meta-analysis and comparison of efficacy

Influenza strain	Participants N	Influenza cases TIV, n	Influenza cases Placebo, n	I <sup>2</sup>	Vaccine Efficacy (95% CI)
B strain Mismatched	39129	72	108	0	0.52 (0.19, 0.72)
B strain Matched	19499	2	12	0	0.77 (0.18, 0.94)
Difference					0.25 (NR, NR)

TIV = inactivated trivalent influenza vaccine; NR = not reported

Source: Table 59 p 110 of the submission and text page 135 of the submission.

**Comparative harms**

- 6.9 The submission presented patient-relevant harms as vaccine related symptoms. The safety profile of Fluarix Tetra was similar to Fluarix.
- 6.10 A summary of the comparative harms for Fluarix Tetra versus Fluarix is presented in the following table. No differences were observed in adverse events.

Summary of comparative harms for Fluarix Tetra and Fluarix

Population	Fluarix Tetra	Fluarix	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				Fluarix Tetra	Fluarix	
<b>Local grade 3 symptom</b>						
3-17 years old	36/915	33/912	1.09 (0.7, 1.7)	3.9	3.6	0.3% (-1.4, 2.1)
≥18 year	25/3036	12/1010	0.7 (0.4, 1.4)	0.8	1.2	-0.4% (-1.1, 0.4)
Sub group ≥65 Y	4/1517	3/504	0.44 (0.1, 2.0)	0.3	0.6	0.3% (-1.1, 0.4)
<b>General grade 3 symptom</b>						
3-17 years old	38/915	39/912	0.97 (0.6, 1.5)	4.2	4.3	-0.1% (-1.9, 1.7)*
≥18 year	62/3036	18*/1010	1.15 (0.7, 1.9)	2	1.8	0.3% (-0.7, 1.2)*
Sub group ≥65 Y	25/1517	6/504	1.38 (0.6, 3.4)	1.6	1.2	0.5% (-0.7, 1.6)

RD = Risk difference; RR = relative risk;

Trial FLU D-QIV-003 presents 3-17 years old data, Trial FLU D-QIV-008 presents ≥18 year old and Sub group ≥65 and ≥61 year's data.

Source: Tables 27, 29 & 31 pp 73-75 of the submission and calculated during the evaluation

\*Corrected in Pre-PBAC response

**Clinical claim**

- 6.11 The submission described Fluarix Tetra as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over Fluarix. The evaluator concluded that this claim was adequately supported with regards to serology data. However the submission claimed clinical superiority for its financial estimates, which was not adequately supported, due to limitations with the methodology.
- 6.12 The submission did not provide any additional clinical information with regards to the additional populations listed that are not on the NIP, e.g. individuals aged three years and over with Down syndrome, obesity (BMI ≥ 40) and chronic liver disease.
- 6.13 The PSCR argued that the clinical trials presented were not conducted specifically in identified high-risk populations due to ethical considerations and the varied subpopulations categorised as high risk. The ESC considered additional data, not provided in the submission, which suggested that the three patient groups (Down syndrome, obesity and chronic liver disease) are at higher risk of serious complications of influenza.

- 6.14 The ESC was unable to make a judgement on the effectiveness of quadrivalent influenza vaccine in the additional subgroups from the data presented in the submission. The ESC noted that immunogenicity and risk data are available to suggest that these subgroups are similarly protected; however, the submission did not provide such evidence. The ESC considered that more data are required to determine the effectiveness of the quadrivalent vaccine in additional high-risk subgroups. The ESC noted the magnitude of increased risk for serious complications of influenza in these additional groups should be comparable to the population of high-risk individuals currently receiving the vaccine through the NIP.
- 6.15 The PBAC considered that the claim of non-inferior comparative effectiveness was adequately supported by the data.
- 6.16 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

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

### **Economic analysis**

- 6.17 The submission provided a cost-minimisation analysis and considered Fluarix Tetra to be equivalent to existing trivalent influenza vaccines: Fluarix, Fluvax, and Vaxigrip.
- 6.18 Based on the presented clinical trials, the equi-effective doses were estimated as Fluarix Tetra 60 µg for once off vaccination annually and Fluarix 45 µg, Fluvax 45 µg, or Vaxigrip 45 µg for once off vaccination annually. The evaluation concluded that the cost-minimisation analysis was valid.
- 6.19 The submission proposed an ex-manufacturer price of \$■■■■ for Fluarix Tetra, which is the same as the current ex-manufacturer price for Fluarix. There was no impact of any additional costs or offsets for administration or adverse events. The evaluation concluded that this was reasonable.
- 6.20 The ESC noted that the PBAC has not previously considered the cost-effectiveness of the trivalent influenza vaccine in the current NIP high-risk populations. The ESC considered that if ATAGI has recommended expanding the high-risk population groups that receive the influenza vaccine on the NIP, it may be an appropriate opportunity for the PBAC to consider the cost-effectiveness of the program as a whole.
- 6.21 The Pre-PBAC Response noted that the sponsor would be willing to accept a recommendation for Fluarix Tetra use in the current NIP funded population.

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

### **Drug cost/patient/year**

- 6.22 The estimated drug cost per person per year was \$■■■■ (ex-manufacturer price) for all recipients aged nine years and over and previously vaccinated children from three to nine years. The estimated drug cost per person per year was \$■■■■

(ex-manufacturer price) for vaccine naive children from three to nine years. This was the same as for the main comparator.

**Estimated PBS usage & financial implications**

6.23 This submission was not considered by DUSC. The submission took a mixed epidemiological/market share approach to forecast the uptake and cost of Fluarix Tetra over a five year period.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Number treated					
Market share	%	%	%	%	%
Scripts <sup>a</sup>					
<b>Estimated net cost to NIP</b>					
Net cost to NIP	\$	\$	\$	\$	\$
Net cost to MBS	\$	\$	\$	\$	\$
<b>Estimated total net cost</b>					
Net cost to NIP/MBS	\$	\$	\$	\$	\$

<sup>a</sup> Assuming one script per year as estimated by the submission.

NIP = National Immunization Programme; MBS = Medicare Benefits Schedule

Source: Table 71, 72, 75 and 76 p 138 and 141-143 of the submission

6.24 The redacted table above shows the estimated patient numbers and estimated packs supplied to be over 200,000 per year. It is estimated that the total net NIP/MBS cost per year to be an overall cost saving.

6.25 At Year 5, the estimated number of scripts was over 200,000 per year and the net cost to the NIP would be a cost saving of less than \$10 million.

6.26 The submission estimated cost savings associated with the inclusion of Fluarix Tetra on the NIP with regard to reduced GP consultations and hospitalisations due to influenza. The evaluator concluded that the submission's estimates for MBS cost offsets were not appropriate. The increased vaccine efficacy was based on inappropriate data and would likely be an overestimate of the true effect. Accordingly, it is not certain that the inclusion of Fluarix Tetra on the NIP would lead to any cost savings to the government.

6.27 The PSCR argued that it is plausible that Fluarix Tetra will provide improved vaccine efficacy over trivalent influenza vaccine and thereby generate cost savings to Government, noting that the listing would be cost neutral if there is no difference in vaccine efficacy. The ESC considered it was not appropriate to estimate cost savings for a vaccine with claimed non-inferior efficacy. The ESC noted that, if recommended for listing, all scenarios of vaccine effectiveness for Fluarix Tetra will be cost neutral to the NIP.

6.28 The ESC noted that the submission did not present data on the financial implications of including vaccination for the additional population subgroups on the NIP. While there will be potential overlap of the proposed population and high risk populations already on the NIP (e.g. overlap in patients with obesity and type 2 diabetics), there will be additional patients to the current NIP population. In particular, the ESC

considered that including obese (BMI $\geq$ 40) Australians aged three years and over would significantly expand the population eligible for influenza vaccination through the NIP.

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the listing of quadrivalent influenza on the National Immunisation Program (NIP) – Designated Vaccines List for the prevention of seasonal influenza. The recommendation was based on a cost-minimisation basis with Fluarix trivalent influenza vaccine, with equi-effective doses of Fluarix Tetra 60  $\mu$ g for once off vaccination annually and Fluarix 45  $\mu$ g, Fluvax 45  $\mu$ g, or Vaxigrip 45  $\mu$ g for once off vaccination annually.
- 7.2 The PBAC considered that based on the clinical evidence presented, it was appropriate to conclude non-inferior efficacy and toxicity compared to Fluarix trivalent influenza vaccine.
- 7.3 The PBAC noted that the Pre-PBAC response identified errors in the Commentary and had accepted the corrections made by the sponsor. The PBAC also noted that the sponsor stated in its PSCR that the proposed obesity category of BMI  $\geq$ 30 kg/m<sup>2</sup> was a typographical error in the submission and that the sponsor agreed that it should be  $\geq$ 40, in line with the ATAGI advice.
- 7.4 The PBAC recalled their out of session recommendation, made between March and July 2014, to extend the availability of influenza vaccine under the NIP to include annual vaccination for all Aboriginal and Torres Strait Islander children aged 6 months to 5 years. The recommendation was based on the cost-effectiveness of vaccination in this population to be similar to the cost-effectiveness of vaccination in the already funded “medically at risk cohort”.
- 7.5 The PBAC noted that the ATAGI highlighted the public health need to expand the high-risk population groups that receive the influenza vaccine on the NIP. The ATAGI noted that an expanded population to include an additional subgroups (i.e. individuals aged three years and over with Down syndrome, obesity (BMI  $\geq$  40) and chronic liver disease) is of public health benefit. However, the submission did not provide any additional clinical evidence, economic analysis or financial implications about this population. Accordingly, the PBAC considered that the vaccine cost-effectiveness could not be determined in the additional high-risk populations and did not recommend expanding the population for quadrivalent influenza vaccine beyond the population that currently receives the trivalent influenza vaccine on the NIP.

### **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
Fluarix Tetra® (quadrivalent influenza vaccine) 15 µg HA/strain (4 strains) in 0.5ml suspension of phosphate buffered saline for IM injection in pre-filled syringe.			Fluarix® Tetra GSK Australia Pty Ltd
3 to 9 years	1	1	
>9 years	1		
<sup>a</sup> Ex-manufacturer price			

Restrictions:

All persons ≥65 years and high risk individuals aged ≥3 years, consistent with the registered TGA indication

## 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

GlaxoSmithKline welcomes the PBAC's recommendation to list Fluarix Tetra, a quadrivalent influenza vaccine, on the National Immunisation Program (NIP) – Designated Vaccines List for the prevention of seasonal influenza.