

## 6.16 QUADRIVALENT INFLUENZA VACCINE (SPLIT VIRION, INACTIVATED)

Prefilled syringe, 0.5 mL,

Fluarix Tetra<sup>®</sup>,

GlaxoSmithKline Australia Pty Ltd

### 1 Purpose of Application

- 1.1 The minor submission requested an extension to the listing of quadrivalent influenza vaccine (split virion, inactivated) – Fluarix Tetra (Fluarix Tetra) on Schedule 1 (Designated vaccines and circumstances in which vaccines may be provided) of the *National Health (Immunisation Program – Designated Vaccines) Determination 2014 (No.1)* (the Determination).

### 2 Requested listing

- 2.1 The submission requested extension of the existing Determination listing for Fluarix Tetra to include vaccination of infants and young children aged 6 - 35 months of age eligible for free vaccination under the National Immunisation Program (NIP) for the prevention of seasonal influenza.
- 2.2 The submission did not propose the revised Determination listing. The current Determination listing for Fluarix Tetra with changes is below.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Nationally Negotiated Price	Proprietary Name and Manufacturer
QUADRIVALENT INFLUENZA VACCINE (SPLIT VIRION, INACTIVATED) PREFILLED SYRINGE, 0.5 ML	1	0*	\$ [REDACTED]	Fluarix Tetra GlaxoSmithKline Australia Pty Ltd

\* For children ~~36 months~~ ~~years~~ and older but less than 9 years, 2 doses at least 1 month apart are required for the first vaccination, as per the Determination listing and the recommendations in the Australian Immunisation Handbook.

Table 1: Current listing for Fluarix Tetra on the Determination

Vaccine and the circumstances in which vaccine may be provided	Brand	Formulation	Number and timing of doses
<b>Vaccine</b> Influenza  <b>Circumstances</b> Vaccine may be provided in the circumstances set out in subsection 7(8)	Fluarix Tetra	Injection (0.5 mL)	For children <del>6 months</del> <del>3 years</del> and older but less than 9 years, 2 doses at least 1 month apart for the first vaccination and 1 dose per calendar year after that. For persons 9 years and above, 1 dose per calendar year.

- 2.3 The submission referred to immunisation of all infants and children aged 6 - 35 months (p10) however the proposed listing would only cover the infant and child groups

already able to receive influenza vaccination under the NIP; those at increased risk of severe influenza as per Table 2 and Aboriginal and Torres Strait Islander Children.

**Table 2: Medical conditions that are associated with an increased risk of influenza disease complications and for which individuals are eligible for free vaccination under the NIP**

Category	Vaccination strongly recommended but not limited to individuals with the following clinical conditions
Cardiac disease	Cyanotic congenital heart disease, congestive heart failure, coronary artery disease
Chronic respiratory conditions	Severe asthma, cystic fibrosis, bronchiectasis, suppurative lung disease, chronic obstructive pulmonary disease, chronic emphysema
Chronic neurological conditions	Hereditary and degenerative CNS diseases, seizure disorders, spinal cord injuries, neuromuscular disorders
Immunocompromising conditions	Immunocompromised due to disease or treatment, asplenia or splenic dysfunction, HIV infection
Diabetes and other metabolic disorders	Type 1 or 2 diabetes, chronic metabolic disorders
Renal disease	Chronic renal failure
Haematological disorders	Haemoglobinopathies
Long-term aspirin therapy in children aged 6 months to 10 years	These children are at increased risk of Reye syndrome following influenza infection

Source: ATAGI Pre-PBAC Submission Advice, Fluarix Tetra, December 2018, p8.

- 2.4 The requested change falls within the indication for Fluarix Tetra approved by the TGA and is a cohort already NIP funded for the prevention of seasonal influenza. The Australian Technical Advisory Group on Immunisation (ATAGI) considered Fluarix Tetra as suitable for listing on the National Immunisation Program (NIP) for this cohort (Pre-PBAC Submission Advice).
- 2.5 If the PBAC were to recommend expanding the Fluarix Tetra listing, changes would be required to the Determination listing including the relevant circumstances.

*For more detail on PBAC’s view, see section 6 PBAC outcome.*

### 3 Background

- 3.1 Fluarix Tetra is TGA registered for the active immunisation of adults and children from 6 months of age for the prevention of influenza disease caused by the influenza virus types A and B contained in the vaccine.
- 3.2 Fluarix Tetra is an inactivated and purified split influenza vaccine containing 15ug of each of the four influenza strains: type A/H1N1-like virus, type A/H3N2-like virus, type B/Victoria lineage and type B/Yamagata lineage. Fluarix Tetra has a uniform presentation (0.5 mL) per dose for all people aged ≥6 months.
- 3.3 The PBAC recommended the listing of Fluarix Tetra for people aged 3 years and older on the Determination in March 2015 prior to the reporting of trial data for the 6 - 35 month age cohort (Fluarix Tetra, Public Summary Document – March 2015 PBAC Meeting). The PBAC has not previously considered Fluarix Tetra for this age group.
- 3.4 Fluarix Tetra received TGA registration for use in infants and young children 6 - 35 months of age in May 2018. However, as the vaccine had already been manufactured and packed for the 2018 Australian influenza season at the time of TGA registration,

the labelling on the packs stated that it was for use in children aged  $\geq 3$  years, which aligned with the NIP listing for use in high- risk groups  $\geq 3$  years.

- 3.5 Given that at the time of the submission, the TGA registration for use of Fluarix Tetra in infants and children was  $\geq 6$  months, PBAC consideration was requested to extend NIP-funded access to children  $\geq 6$  months. NIP listing as proposed would align the TGA-approved indication, updated pack labelling and NIP listing and also enable an additional supply option for this cohort. Alignment of these factors would also avoid confusion about the appropriate age range for the use of Fluarix Tetra, or the inadvertent administration of NIP vaccines to a non-covered age cohort.

*For more detail on PBAC's view, see section 6 PBAC outcome.*

## **4 Comparator**

- 4.1 The minor submission nominated FluQuadri Junior (Sanofi-Pasteur) as the comparator in the 6 - 35 month age group. FluQuadri Junior is the only NIP listed vaccine for this age group (ATAGI Pre-Submission Advice, p1), considered this to be appropriate.
- 4.2 A key difference between FluQuadri Junior and Fluarix Tetra is the latter can be used in both paediatric and adult patients using the same dose, whereas the former is restricted to the 6 - 35 month patient age group.

*For more detail on PBAC's view, see section 6 PBAC outcome.*

## **5 Consideration of the evidence**

### ***Sponsor hearing***

- 5.1 There was no hearing for this item.

### ***Consumer comments***

- 5.2 The PBAC noted and welcomed the input from individuals (1) via the Consumer Comments facility on the PBS website. The comment referred to the benefit of making influenza vaccines affordable to immunocompromised individuals.

### ***Clinical trials***

The minor submission presented the following clinical trials:

**Table 3: Trials and associated reports presented in the submission**

Trial ID/First Author	Protocol title/ Publication title	Publication citation
<b>Indirect randomised trial(s)</b>		
FLU D-QIV-004 / Claeys	An efficacy study of GSK Biologicals' quadrivalent influenza vaccine GSK2321138A (FLU D-QIV) when administered in children. / "Prevention of vaccine-matched and mismatched influenza in children aged 6-35 months: a multinational randomised trial across five influenza seasons	Lancet Child Adolescent Health; 2: 338-49.
FLU D-QIV-009	Immunogenicity, safety and reactogenicity study of GSK Biologicals' quadrivalent seasonal influenza candidate vaccine GSK2321138A, administered to children who previously participated in study 115345.	<i>Unpublished</i>
FLU D-QIV-015/ Claeys	Safety and immunogenicity study of GSK Biologicals' Quadrivalent Influenza Vaccine (GSK2321138A) manufactured with a new process in adults and children. / "Assessment of an optimized manufacturing process for inactivated quadrivalent influenza vaccine: A phase III, randomized, double-blind, safety and immunogenicity study in children and adults."	BMC Infectious Diseases, vol:18 iss:1, 1471-2334
FLU-Q-QIV-022 CSR / Jain	Immunogenicity and safety study of GSK Biologicals' quadrivalent influenza vaccine (GSK2282512A) compared to Fluzone® Quadrivalent in children 6 - 35 months of age. / "Time to Change Dosing of Inactivated Quadrivalent Influenza Vaccine in Young Children: Evidence From a Phase III, Randomized, Controlled Trial."	Journal of the Pediatric Infectious Diseases Society, 6 (March): 9 -19

Source: Clinical result summaries of D-QIV-004, D-QIV-009, D-QIV-015, Q-QIV-022

- 5.3 An inclusion criterion in the literature search was healthy infants/children, which did not cover the entire proposed cohort for the proposed listing. While this was a limitation, it may be reasonable to expect that the clinical outcomes in sub-populations are unlikely to vary significantly, or to vary between the proposed listing and the comparator that is already used in this cohort.
- 5.4 The key clinical trial (FLU-Q-QIV-022) used 'FluLaval Tetra' (GlaxoSmithKline) as a surrogate for Fluarix Tetra, and Fluzone Quadrivalent (Sanofi-Aventis) as a surrogate for FluQuadri Junior, justifying these surrogates as they have equivalent antigen contents as their respective surrogates.

### **Comparative effectiveness**

- 5.5 The submission claimed that Fluarix Tetra was non-inferior with respect to efficacy and safety to FluQuadri Junior for the prevention of seasonal influenza disease caused by the influenza virus types A and B contained in the vaccine in the proposed cohort.
- 5.6 Among a subset of subjects from study D-QIV-004 (753 vaccinated with Fluarix Tetra, 579 in the control group), the immunogenicity of Fluarix Tetra was demonstrated with post vaccination seroconversion rates (SCR) between 68.8% for A/H3N2 and 81.2% for B/Yamagata strains, and significant increases in post vaccination geometric mean titres (GMT) for all strains. There were no immunogenicity data directly comparing Fluarix Tetra with the comparator. ATAGI noted (Pre-Submission PBAC Advice, p3-4) that there were limitations in using immunogenicity data to predict protective immunity, particularly in young children, where conventional titres are associated

with limited levels of clinical protection. Accordingly, ATAGI considered vaccine efficacy (VE) against influenza a more appropriate endpoint for determining protection provided by influenza vaccine than immunogenicity data, particularly in children aged 6 - 35 months.

- 5.7 There were no indirect comparisons of vaccine efficacy between Fluarix Tetra and FluQuadri Junior given the lack of vaccine efficacy studies for FluQuadri Junior. ATAGI (Pre-PBAC Submission Advice) considered “the Fluarix Tetra vaccine efficacy (VE) of 63.2% (95%CI: 51.8–72.3%) against moderate-severe influenza to be comparable to vaccine efficacy and effectiveness estimates of other TIVs and QIVs. Recognising that influenza vaccine efficacy/effectiveness can vary year to year, and in the absence of a direct comparison of the vaccine efficacy/effectiveness of FluQuadri Junior to Fluarix Tetra in 6 – 35 month olds, ATAGI consider the efficacy of Fluarix Tetra likely to be equivalent to FluQuadri Junior in children aged 6–35 months.”
- 5.8 ATAGI (Pre-PBAC Submission Advice) also noted evidence of priming of antibody response in young children who received Fluarix Tetra and that a study investigating co-administration with 23-valent pneumococcal polysaccharide vaccine (PPV23) in adults aged  $\geq 50$  years found the immune responses were similar for all Fluarix Tetra strains and the six pneumococcal serotypes evaluated in PPV23.

### ***Comparative harms***

- 5.9 In its December 2018 Pre-PBAC Submission Advice, ATAGI stated:
- ‘ATAGI does not have specific concerns regarding the safety of Fluarix Tetra for use in children aged 6–35 months under the NIP; however, ATAGI considers ongoing surveillance of adverse events following immunisation to be essential.’ (p4). ATAGI specified this to include spontaneous reporting to the Therapeutic Goods Administration (TGA) and active surveillance via AusVaxSafety. ATAGI provided additional advice regarding surveillance activities more broadly (p6).
  - ‘ATAGI also “recognises that if listed under the NIP for children aged 6–35 months, clear communication with and education of general practitioners and other immunisation providers will be required to minimise the possibility of i) half doses being given to young children and ii) other influenza vaccines recommended for older age groups being inadvertently administered to children aged <5 years.’ (ATAGI Pre-PBAC Submission advice).
- 5.10 ATAGI (Pre-PBAC Submission Advice) noted a lack of available data on concomitant use of Fluarix Tetra with other vaccines in this age cohort, however noted that a study in adults aged 50 years and over found similar safety and reactogenicity among groups receiving concomitant and non-concomitant doses of Fluarix Tetra. The Pre-PBAC Response acknowledged the lack of available data and noted ATAGI’s advice that it did not have substantial concerns re co-administration.

- 5.11 ATAGI (Pre-PBAC submission advice) also noted and agreed with the safety profile of the TGA Clinical Evaluation Report (provided by GSK to ATAGI in confidence), that supported TGA approval of the change in age indication for Fluarix Tetra.
- 5.12 ATAGI (Pre-PBAC Submission Advice) noted that as the studies assessing safety did not specifically include children with risk factors for severe or complicated influenza, “it is uncertain whether the risk of AE following immunisation, such as fever and febrile seizures, would be higher among children with underlying medical conditions, such as epilepsy, than observed in the study populations. However, the comparability of the safety profile with other vaccines does not indicate greater risk associated with Fluarix Tetra than currently available influenza vaccines.”

### ***Clinical claim***

- 5.13 The submission claimed that Fluarix Tetra was non-inferior with respect to efficacy and safety to FluQuadri Junior in the prevention of seasonal influenza disease caused by the influenza virus types A and B contained in the vaccine for infants and young children aged 6 - 35 months.
- 5.14 In its December 2018 Pre-PBAC Submission Advice , ATAGI considered Fluarix Tetra suitable to be listed on the National Health (Immunisation Program – Designated Vaccines) Determination for the prevention of seasonal influenza in infants and children aged 6 - 35 months who have medical conditions associated with an increased risk of influenza disease complications and who are eligible for influenza vaccines under the National Immunisation Program (NIP). This was on the basis of:
- clinical trial evidence of efficacy of Fluarix Tetra in children aged 6–35 months; and
  - the acceptable safety profile of Fluarix Tetra in children aged 6–35 months based on clinical trials.
- 5.15 ATAGI summarised its advice (Pre-PBAC Submission Advice), that ‘While there is no data directly comparing Fluarix Tetra and FluQuadri Junior™, the QIV currently used under the NIP for children aged 6–35 months, based upon the evidence of Fluarix Tetra efficacy and safety, ATAGI consider Fluarix Tetra to be equivalent in efficacy and safety to FluQuadri Junior.’
- 5.16 In providing its advice, ATAGI (Pre-PBAC Submission advice) identified the key uncertainties relating to the proposal as being around the evidence of the non-inferiority of Fluarix Tetra to FluQuadri Junior in children aged 6–35 months including the lack of a direct comparison of VE and immunogenicity between Fluarix Tetra and the comparator (or an equivalent QIV), issues around interpretation of immunogenicity data in children aged 6–35 months and uncertainty around the safety and effectiveness of Fluarix Tetra in children with underlying medical risk factors. Whilst acknowledging these uncertainties, based upon the evidence of clinical efficacy and safety, ATAGI still considered the benefits of Fluarix Tetra in children aged 6 – 35 months to be equivalent to that of FluQuadri Junior.

- 5.17 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 5.18 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

### **Economic analysis**

- 5.19 As a minor submission, there was no economic comparison presented/ an economic comparison was not relevant.
- 5.20 The submission claimed cost-minimisation based on the equi-effective dose of one 0.5 mL dose of Fluarix Tetra (containing 60 mcg hemagglutinin) to one 0.25 mL dose of FluQuadri Junior (containing 30 mcg hemagglutinin). The submission noted there were no differences in costs of Fluarix Tetra and FluQuadri Junior with respect to administration, monitoring or safety.

### **Drug cost/patient/dose: \$█ per dose**

- 5.21 The submission claimed cost-minimisation based on price parity with FluQuadri Junior at a nationally negotiated vaccine cost of \$█ based on a single dose per child per year. This was equivalent to the nationally negotiated price for FluQuadri Junior.
- 5.22 For influenza vaccine naïve children aged 6 months to <9 years, the cost would be \$█ in the first year based on the child receiving two vaccinations four weeks apart in the first year, followed by \$█ per child per year thereafter. The dosage frequency was equivalent to the comparator.

### **Estimated NIP usage & financial implications**

- 5.23 The minor submission estimated there to be no financial implications to the NIP as the submission expected Fluarix Tetra to substitute for FluQuadri Junior and both vaccines have the same nationally negotiated price.

## **6 PBAC Outcome**

- 6.1 The PBAC recommended an extension to the listing of Fluarix Tetra® (quadrivalent influenza vaccine (split virion, inactivated)), on the *National Health (Immunisation Program – Designated Vaccines) Determination 2014 (No.1)* (the Determination), for the prevention of seasonal influenza to include high risk and Aboriginal and/or Torres Strait Islander infants and children aged 6 to 35 months of age. The PBAC considered that Fluarix Tetra was cost-effective on a cost-minimisation basis to the comparator FluQuadri® Junior on the basis of an equi-effective dose of one 0.5 mL dose of Fluarix Tetra to one 0.25 mL dose of the currently NIP listed comparator FluQuadri Junior. The PBAC noted that the inclusion of Fluarix Tetra on the NIP would be a useful addition to the supply of influenza vaccinations in infants and young children.
- 6.2 The PBAC noted that the NIP currently provides free seasonal influenza vaccines each year to infants, children, and adults who meet the criteria outlined in Table 2, and that this cohort is covered by a single vaccine, FluQuadri Junior, in a dose specific to the 6-

35 month age cohort. The recommended change would provide access to a seasonal influenza vaccine in a uniform dose.

- 6.3 The PBAC considered that FluQuadri Junior was the appropriate comparator to Fluarix Tetra as FluQuadri Junior is currently NIP listed for this age cohort. The PBAC also considered that the clinical place for FluQuadri Junior and Fluarix Tetra was appropriate.
- 6.4 The PBAC noted the submission claimed non-inferior comparative effectiveness and safety to the comparator. The PBAC noted the results of D-QIV-004, demonstrating vaccine efficacy (VE) against PCR confirmed influenza of 49.8% in any influenza and 63.2% in moderate to severe influenza, results which the PBAC considered to be similar to that observed in other influenza vaccines. The submission also included a direct head-to-head trial, FLU-Q-QIV-022, to compare Fluarix Tetra and FluQuadri Junior using two surrogate vaccines, using vaccine efficacy endpoints. The PBAC considered the surrogacy was reasonable due to the antigen content being equivalent between the target vaccines and the surrogate vaccines. The PBAC noted that the literature search in the submission specifically mentioned healthy infants and children, which may not cover the entire proposed cohort for the proposed listing. The PBAC considered that while this is a limitation, it may be reasonable to expect that the clinical outcomes in sub-populations are unlikely to vary significantly, or to vary between the proposed listing and the comparator which is already used in this cohort.
- 6.5 The PBAC noted the ATAGI advice that based on the VE results of FLU-Q-QIV-022, the VE of FluQuadri Junior to Fluarix Tetra was likely to be equivalent in the proposed cohort; and that vaccine efficacy against influenza is a more appropriate endpoint for determining protection provided by influenza vaccine than immunogenicity data, particularly in children aged 6 - 35 months (Pre-PBAC Advice). The PBAC also noted ATAGI's advice (Pre-Submission Advice, p6-7) that the key uncertainties relating to the submission were around the lack of a direct comparison between Fluarix Tetra and FluQuadri Junior and uncertainty around the safety and effectiveness of Fluarix Tetra in children with underlying medical risk factors. Overall, the PBAC considered the clinical evidence demonstrated that 0.5 mL (containing 60 mcg haemagglutinin) of Fluarix Tetra was non-inferior in terms of efficacy and safety to 0.25mL (containing 30 mcg haemagglutinin) of FluQuadri Junior for the 6 to 35 month age group.
- 6.6 The PBAC considered that the incidence of solicited fever was comparable to other influenza vaccines and noted there was a lack of available data on concomitant use of Fluarix Tetra with other vaccines in patients aged 6 to 35 months. The PBAC also noted that the ATAGI Pre-Submission Advice (p4) concluded there were no substantial concerns regarding co-administration of Fluarix Tetra with other routine childhood vaccinations in children aged 6–35 months, and the PBAC further noted evidence demonstrating co-administration of Fluarix Tetra with other vaccines in adults did not raise any concerns. Overall, the PBAC did not consider co-administration of Fluarix Tetra with routine childhood vaccines to be a significant risk and considered Fluarix Tetra to be non-inferior to FluQuadri Junior with regards to safety.

- 6.7 The PBAC noted the dose of Fluarix Tetra is twice that of the comparator, which increases the risk of incorrect dosing in children. It also noted the Pre-PBAC Response which acknowledged this risk and outlined a risk management strategy including communication with, and education of, general practitioners and vaccine providers; and provided a sample flyer to be distributed with vaccines outlining correct administration. The PBAC considered the risk management strategy to be appropriate.
- 6.8 The PBAC noted that the submission was expected to be cost neutral to the NIP, based on cost-minimisation to the nationally negotiated price, and noted that the tender price on the NIP may be lower than the nationally negotiated price. The PBAC noted that should both the Fluarix Tetra and FluQuadri Junior vaccines remain on the NIP, Fluarix Tetra would likely be preferred by immunisation providers over FluQuadri Junior because the vaccine covers both adults and children, and would likely simplify administration and storage arrangements in practice.
- 6.9 The PBAC noted that this submission is not eligible for an Independent Review because Independent Review is only relevant to submissions seeking PBS listing.

**Outcome:**

Recommended

## 7 Recommended listing

Amend existing/recommended Determination listing as follows:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
QUADRIVALENT INFLUENZA VACCINE (SPLIT VIRION, INACTIVATED) PREFILLED SYRINGE, 0.5 ML	1	0*	Fluarix Tetra GlaxoSmithKline Australia Pty Ltd

\* For children 6 months and older but less than 9 years, 2 doses at least 1 month apart are required for the first vaccination, as per the Determination listing and the recommendations in the Australian Immunisation Handbook.

**Committee-in-Confidence information**

The NIP tender price for Fluarix Tetra is \$ [REDACTED]

[REDACTED]

**End Committee-in-Confidence information**

## 8 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.

## **9 Sponsor's Comment**

GSK welcomes the PBAC positive recommendation for inclusion of Fluarix Tetra on the NIP for eligible infants and children aged 6 – 35 months of age.