5.05 QUADRIVALENT INFLUENZA VACCINE, Injection 0.5 mL, Vaxigrip Tetra™, Sanofi-Aventis Australia Pty Ltd.

1 Purpose of Application

1.1 There were two purposes of the submission:

- National Immunisation Program (NIP) listing for quadrivalent influenza vaccine QIV (Vaxigrip Tetra) for the prevention of seasonal influenza in the patient population aged 6 months to <5 years, who are not currently eligible through the NIP. The submission based the request for listing on a cost-utility analysis compared with placebo.
- NIP listing for QIV (Vaxigrip Tetra) for the prevention of seasonal influenza in at-risk individuals who are currently eligible for vaccination through the NIP, under the same provisions as the other QIVs currently listed on the NIP for seasonal influenza. The eligible population currently includes: adults aged ≥65 years; persons aged ≥6 months at increased risk of complications from influenza; Aboriginal and Torres Strait Islanders aged ≥6 months; and pregnant women. The submission based the request for listing on a cost-minimisation basis compared with two brands of QIVs currently listed on the NIP (FluQuadri and FluQuadri Junior).

1.2 The PBAC had not previously considered this vaccine.

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

Component	Requested NIP listing for children aged 6 months to <5 years	Requested NIP listing for at-risk individuals currently eligible for NIP-funded influenza vaccination
Population	Children aged 6 months to <5 years who are not currently eligible through the NIP.	Adults aged 65 and older; Aboriginal and Torres Strait Islander (ATSI) people aged ≥6 months; Persons aged ≥6* months at increased risk of influenza complications; and, Pregnant women.
Intervention	QIV (Vaxigrip Tetra)	QIV (Vaxigrip Tetra)
Comparator	No vaccination	QIVs (FluQuadri and FluQuadri Junior)
Outcomes	Clinically diagnosed & laboratory confirmed influenza and immunogenicity	Immunogenicity
Clinical claim	Reduction in cases of clinically diagnosed & laboratory confirmed influenza Superiority in terms of key immunogenicity outcomes Acceptable safety profile	Non-inferiority in terms of key immunogenicity outcomes Comparable safety profile

NIP: National Immunisation Program
Source: Table1.1.1 and Table 1.1.2, p11-12 of the submission
*The submission stated this population was "Persons aged ≥5 months at increased risk of influenza complications"; this was corrected during the evaluation.

2 Requested listing

Name, Restriction, Manner of administration and form	Nationally negotiated price	Proprietary Name and Manufacturer	
Quadrivalent Influenza Vaccine, 0.5mL injection	$[redacted]	Vaxigrip Tetra	Sanofi-Aventis (Australia)Pty Ltd

Category/Program:	NIP
Population	Children aged ≥6 months to <5 years. Adults aged ≥65 years; Aboriginal and Torres Strait Islander (ATSI) people aged ≥6 months Persons aged ≥6 months who are at increased risk of influenza complications, specifically: • 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 • a person aged less than 11 years and receiving long-term aspirin therapy. Pregnant women.
Number and timing of doses:	Should be administered in accordance with the national recommendation as per the current Immunisation Handbook: Individuals from 9 years of age: a single 0.5 mL injection. Children from 6 months to <9 years of age: • 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; QIV: quadrivalent influenza vaccine
Source: Table 1.1.3 and Table 1.4.1, p10-11 and p17 of the submission; National Health (Immunisation Program – Designated Vaccines) Determination 2014 (No.1) (compiled 10 January 2019)

2.1 The submission proposed an ex-manufacturer price of $[redacted], the same as the nationally negotiated price for QIVs for the populations currently eligible for NIP funded influenza vaccine.

3 Background

Registration status

3.1 **TGA status at time of PBAC advice:** QIV (Vaxigrip Tetra) was listed on the ARTG on 20 May 2019. The approved indication was "for active immunisation of adults and children from 6 months of age and older for the prevention of influenza disease caused

by the two influenza A virus subtypes and the two influenza B virus types contained in the vaccine." (TGA approval letter, 15 May 2019, Vaxigrip Tetra)

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

4 Population and disease

4.1 Influenza virus infection causes a wide spectrum of disease, from no or minimal symptoms, to respiratory illness with systemic features, to multisystem complications and death from primary viral or secondary bacterial pneumonia. Systemic symptoms include malaise, fever, chills, headache, anorexia, and myalgia, and may be accompanied by a cough, nasal discharge, and sneezing. Severe disease is more likely in at-risk groups such as those identified in the current NIP restrictions (see Requested Listing).

4.2 The incidence of laboratory confirmed influenza-related hospitalisation (without adjustment for under-ascertainment) in children aged 6 months to <5 years and those aged 6-23 months (based on notifications in 2006-2013 from Li-Kim-Moy 2016) is 64 (range: 44–87) per 100,000 and 128 (range: 74–186) per 100,000, respectively (ATAGI October 2018 pre-submission advice).

4.3 Influenza symptoms resolve after approximately two weeks of illness. However, many children experience complications requiring hospitalisation. The most common severe complication in children infected with influenza is bacterial pneumonia, which can lead to respiratory failure and death. Other rare complications include otitis media, asthma exacerbation, sinusitis, febrile convulsions, myelitis, encephalopathy and Guillain-Barre syndrome.

4.4 Currently four QIVs (Fluarix Tetra, FluQuadri Junior, FluQuadri, and Afluria Quad) are listed on the NIP for the nominated populations. FluQuadri Junior is available for children ≥6 months to <3 years and FluQuadri is available for persons aged ≥3 years; Fluarix Tetra is available for persons aged persons aged ≥6 months; and Afluria Quad is available for persons aged ≥5 years.

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

5 Comparator

5.1 For children aged 6 months to <5 years, the submission nominated 'no vaccination' (placebo) as the comparator.

5.2 For at-risk individuals currently eligible for NIP-funded influenza vaccination the submission nominated QIVs (FluQuadri Junior and FluQuadri) as the comparators. FluQuadri Junior and FluQuadri are registered for children 6 months to <3 years and ≥3 years, respectively.

5.3 QIVs that are currently registered and listed on the Determination for the requested populations are FluQuadri, FluQuadri Junior, Fluarix Tetra and Afluria Quad. The nominated comparators for the requested population (FluQuadri/FluQuadri Junior) were appropriate.

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 and welcomed the input from individuals (1), and organisations (5) via the Consumer Comments facility on the PBS website:

- Diabetes NSW & ACT and Diabetes Queensland both noted the higher risk of hospitalisation due to influenza for people living with diabetes and expressed support for all Australians with diabetes and their families, all children under 5 years of age, and older Australians to be vaccinated against influenza.
- Health Protection NSW (NSW Health) was supportive of the requested listing and noted that infants and children younger than 5 years of age, and especially those under 3 years of age, have an increased risk of hospitalisation due to influenza that decreases with increasing age. NSW Health found that in the first year of the state funded paediatric influenza program, around one quarter of NSW children under 5 were recorded on the Australian Immunisation Register as having received at least one dose of influenza vaccine with true uptake estimated to be around twice that recorded.
- The Immunisation Coalition and Health Protection NSW (NSW Health) both claimed that reducing transmission of influenza from children can provide indirect protection for the wider community, including individuals who are unable to be vaccinated or who do not reliably mount protective immune responses to influenza vaccines, such those with compromised immune systems and frail older people.
- The Immunisation Foundation of Australia was supportive of listing an influenza vaccine for young children on the NIP. This organisation claimed that NIP funding of an influenza vaccine for young children would improve awareness and uptake of the vaccine in childhood, compared with under the current state funded programs.

Clinical trials

Children aged 6 months to <5 years

6.3 The submission presented one head-to-head RCT comparing QIV (Vaxigrip Tetra) to placebo (no vaccine) in children aged 6-35 months, who were healthy and had never been vaccinated against influenza: GQM05 (N=5,806).

6.4 A claim of superiority in terms of vaccine efficacy and acceptable safety profile was made based on laboratory-confirmed influenza cases.

At-risk individuals currently eligible for NIP-funded influenza vaccination

6.5 The submission did not identify any head-to-head RCTs comparing QIV (Vaxigrip Tetra) and QIV (FluQuadri).

6.6 The submission presented four head-to-head RCTs comparing QIV (Vaxigrip Tetra) with licensed and/or investigational trivalent influenza vaccines (TIVs):

- QIV (Vaxigrip Tetra) compared to placebo (no vaccination) and TIVs in children aged 6-35 months: GQM05 (N=5,806);
- QIV (Vaxigrip Tetra) compared to TIVs in adults aged 18 years and over: GQM01 (N=1,568);
- QIV (Vaxigrip Tetra) compared to TIVs in children aged 3-8 years: GQM02 (N=1,242); and
- QIV (Vaxigrip Tetra) compared to TIVs in adults aged 18 years and over: GQM11 (N=2,225).

6.7 The submission also presented three head-to-head RCTs comparing QIVs (FluQuadri/ FluQuadri Junior) to licensed and/or investigational TIV products:

- QIV (Investigational) compared to TIVs (either Fluzone or an investigational TIV) in adults aged 65 years and over: QIV03 (N=675);
- QIV (Investigational) compared to TIVs (Fluzone 2008-09 or Fluzone 2009-10 formulation) in adults aged 18 years and over: GRC43 (N=570); and
- QIV (Investigational) compared to TIVs (either Fluzone or an investigational TIV) in infants aged 6-35 months and children aged 3-9 years: QIV04 (N=4,363).

6.8 The submission presented an indirect comparison of QIV (Vaxigrip Tetra) to QIV (FluQuadri/FluQuadri Junior) with TIVs as the common comparator.

6.9 A claim of non-inferiority in terms of vaccine immunogenicity and safety outcomes of QIV (Vaxigrip Tetra) compared to QIV (FluQuadri/FluQuadri Junior) was made based on the indirect comparison of seroconversion rates (SCRs).

6.10 The PBAC has previously accepted surrogate outcomes (e.g. haemagglutination antibody geometric mean titres (GMT) and SCRs) for the assessment of influenza vaccines, e.g. Afluria Quad, compared with Fluarix Tetra (PSD, November 2018) and FluQuadri, compared with Fluarix Tetra (PSD, July 2015).

6.11 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
QIV (Vaxigrip Tetra) – Children aged 6-35 months		
GQM05 QIV (Vaxigrip Tetra) EudraCT 2013-001231-51	CSR 'Efficacy and Immunogenicity Study of Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Healthy Children Aged 6-35 Months'	Unpublished Sanofi Pasteur. Final report version 1.0 dated 25 April 2017.
Pepin, et al. 2019	Efficacy, immunogenicity, and safety of a quadrivalent inactivated influenza vaccine in children aged 6–35 months: A multi-season randomised placebo-controlled trial in the Northern and Southern Hemispheres	Vaccine, 37 (2019): 1876-1884
Pepin, et al. 2019	Impact of a quadrivalent inactivated influenza vaccine on influenza associated complications and health care use in children aged 6-35 months: Analysis of data from a phase III trial in the Northern and Southern Hemispheres	Vaccine, 37 (2019): 1885-1888
Meta-analyses of direct randomised trials – At risk populations		
GQM01 QIV (Vaxigrip Tetra) EudraCT 2011-001976-21	CSR 'Safety and Immunogenicity of a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Adult and Elderly Subjects'	Unpublished Sanofi Pasteur. Final report version 1.0 dated 16 November 2012
Pepin, et al. 2013	Safety and immunogenicity of a quadrivalent inactivated influenza vaccine in adults	Vaccine, 31 (2013): 5572-5578
GQM02 QIV (Vaxigrip Tetra) EudraCT 2011-005374-33	CSR 'Safety and Immunogenicity of a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Children Aged 3 to 8 Years'	Unpublished Sanofi Pasteur. Final report version 1.0 dated 24 October 2014
Pepin, et al. 2016	Safety and immunogenicity of an intramuscular quadrivalent influenza vaccine in children 3 to 8 y of age: A phase III randomized controlled study	Human Vaccines & Immunotherapeutics (2016) 12: 3072–3078
GQM11 QIV (Vaxigrip Tetra) EudraCT 2014-000785-21	CSR 'Immunogenicity and Lot-to-Lot Consistency Study of a Quadrivalent Influenza Vaccine in Adult and Elderly Subjects'	Unpublished Sanofi Pasteur. Final report version 3.0 dated 25 February 2016.
Sesay, et al. 2018	Safety, immunogenicity, and lot-to-lot consistency of a split-virion quadrivalent influenza vaccine in younger and older adults: A phase III randomized, double-blind clinical trial	Human Vaccines & Immunotherapeutics (2018) 14 (3): 596-608
QIV03 QIV (FluQuadri) NCT01218646	CSR 'Safety and Immunogenicity Among Adults Administered Quadrivalent Influenza Vaccine'	Unpublished Sanofi Pasteur. Final report version 2.0 dated 20 February 2012.
Greenberg, et al. 2017	Safety and immunogenicity of a quadrivalent influenza vaccine in adults 65 y of age and older	Human Vaccines & Immunotherapeutics (2017) 13 (9): 2058-2064
QIV04 QIV (FluQuadri) NCT01240746	CSR 'Safety and Immunogenicity Among Children Administered Quadrivalent Influenza Vaccine'	Unpublished

Trial ID/First Author	Protocol title/ Publication title	Publication citation
		Sanofi Pasteur. Final report version 1.0 dated 23 April 2012.
Greenberg, et al. 2014	Safety and Immunogenicity of an Inactivated Quadrivalent Influenza Vaccine in Children 6 Months through 8 Years of Age	The Pediatric Infectious Disease Journal (2014) 33 (6): 630-636
GRC43 QIV (FluQuadri) NCT00988143	CSR 'Immunogenicity and Safety Among Children and Adults of the 2009-2010 Trivalent Influenza Vaccine, 2008-2009 Trivalent Influenza Vaccine, and Quadrivalent Influenza Vaccine (Intramuscular Route).'	Unpublished Sanofi Pasteur. Final report version 2.0 dated 01 June 2012.
Greenberg, et al. 2013	Safety and immunogenicity of a quadrivalent inactivated influenza vaccine compared to licensed trivalent inactivated influenza vaccines in adults	Vaccine, 31 (2013): 770-776

Source: Table 2.2.1, p20-21 of the submission, Attachment B

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

Table 3: Key features of the included evidence: Children aged 6 months to <5 years

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Used in modelled evaluation
QIV (Vaxigrip Tetra) vs. placebo						
GQM05	QIV (Vaxigrip Tetra): N=2,584 Placebo: N=2,591 (FASE)	Phase III, R, OB, MC. 6 months	Low	Healthy children aged 6-35 months who have never been vaccinated against influenza	Primary: occurrence of influenza like illness starting ≥ 14 days after last vaccination and laboratory-confirmed as positive for: (1) influenza type A or B, or (2) viral strains similar to those contained in the vaccine. Secondary: Safety	Used

FASE: Full Analysis Set for Efficacy; OB: observer blind; R: randomised; MC: multi centre
Source: Compiled during the evaluation.

6.13 The key features of the trials for the requested listing for populations of at-risk individuals currently eligible for NIP funded influenza vaccines vaccination are summarised in Table 4.

Table 4: Key features of the included evidence: At-risk individuals currently eligible for NIP-funded influenza vaccination

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Used in modelled evaluation
QIV (Vaxigrip Tetra) vs. TIV						
GQM05	Cohort 2 (FASI): QIV (Vaxigrip Tetra): N=341; Placebo: N=344; TIV-1: N=172; TIV-2: N=179	Phase III, R, OB, MC, 6 months	Low	Children aged 6-35 months who have never been vaccinated against influenza	Secondary: Efficacy, immunogenicity and safety. Seroconversion was defined as a HAI titre <10 on day 0 and a HAI titre ≥40 measured 28 days after the last vaccination. A significant increase was defined as a HAI titre ≥10 on day 0 and a ≥4-fold increase from baseline in HAI titre 28 days after the last vaccination.	Not used
GQM01	QIV (Vaxigrip Tetra): N=1112;	Phase III, R, DB (except	Low	Adults ≥ 18 years	Primary: GMT for each strain, 21 days post vaccination.	Not used

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Used in modelled evaluation
	Licensed TIV: N=226; Investigational TIV: N=223	TIV2 group), MC, 6 months			Secondary: Immunogenicity and safety. The seroconversion rate for each group was the percent of subjects with either a pre-vaccination titre <10 and a post-vaccination titre ≥40 or a pre-vaccination titre ≥10 and a ≥4-fold increase in titre at day 21.	
GQM02	QIV (Vaxigrip Tetra): N=887; TIV-1: N=181; TIV-2: N=174	Phase III, R, DB, active controlled, MC, 6 months	Low	Children aged 3-8 years	Primary: GMT for each strain, 28 days post vaccination. Secondary: Immunogenicity and safety. Seroconversion was defined as a HAI titre <10 on day 0 and a HAI titre ≥40 measured 28 days after the last vaccination. A significant increase was defined as a HAI titre ≥10 on day 0 and a ≥4-fold increase from baseline in HAI titre 28 days after the last vaccination.	Not used
GQM11	QIV Lot 1 (Vaxigrip Tetra): N=554; QIV Lot 2 (Vaxigrip Tetra): N=555; QIV Lot 3 (Vaxigrip Tetra): N=561; TIV-1: N=279; TIV-2: N=276	Phase III, R, DB (TIV2 and QIV groups), SB up to day 21 in (TIV-1 group), MC,13 months	Low-medium	Adults ≥ 18 years	Primary: different GMT for each strain, 21 days post vaccination. Secondary: Immunogenicity and safety. The seroconversion rate for each group was the percent of subjects with either a pre-vaccination titre <10 and a post-vaccination titre ≥40 or a pre-vaccination titre ≥10 and a ≥4-fold increase in titre at day 21. Safety follow-up was up to 6 months for serious adverse events and 12 months for fatal SAEs.	Not used
QIV (FluQuadri) vs TIV						
QIV03	QIV (FluQuadri): N=225; Licensed TIV-1: N=225; Investigational TIV-2: N=225	Phase III, R, four-arm, trivalent controlled, MC , 76 days	Low	Adults ≥ 18 years	Primary: GMTRs for B strains Secondary: Immunogenicity and safety. The seroconversion rate for each group was the percent of subjects with either a pre-vaccination titre <10 and a post-vaccination titre ≥40 or a pre-vaccination titre ≥10 and a ≥4-fold increase in titre at day 21 (window ranging from 21 – 28 days). Safety follow-up for solicited AEs was up to 7 days post-vaccination, and up to 28 days for unsolicited AEs or SAEs.	Not used
QIV04	QIV (FluQuadri Junior): N=2902; Licensed TIV: N=736;	Phase III, R, three-arm, active controlled, OB, 6 months	Low	Children aged 6 months to < 9 years	Primary: GMTRs and SCRs for all four strains Secondary: Immunogenicity and safety. The seroconversion rate for each group was the percent of	Not used

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Used in modelled evaluation
	Investigational TIV: N=725				subjects with either a pre-vaccination titre <10 and a post-vaccination titre ≥40 or a pre-vaccination titre ≥10 and a ≥4-fold increase in titre at day 28 (window ranging from 28-35 days). Safety follow-up consisted of a telephonic safety call 6 months after the final vaccination.	
GRC43	QIV (FluQuadri): N=190 (adults); 2008/9 TIV: N=190 (adults); 2009/10 TIV: N=190 (adults) and N=30 (children)	Phase II, OL, three-arm (QIV compared to two TIVs), 83 days	High (for safety outcomes)	Children aged ≥ 6 months to < 5 years or Adults ≥ 18 years	Primary: GMTRs for B strains. Secondary: Immunogenicity and safety. The seroconversion rate for each group was the percent of subjects with either a pre-vaccination titre <10 and a post-vaccination titre ≥40 or a pre-vaccination titre ≥10 and a ≥4-fold increase in titre at day 21 (window ranging from 21 – 28 days). Safety follow-up: nominally, 21 days for subjects receiving one vaccination and nominally, 49 days for subjects receiving two vaccinations.	Not used

AE: adverse event; DB: double blind; FASE: full analysis set for efficacy; FASI: full analysis set immunogenicity; HAI: haemagglutination inhibition titre; OB: observer blind; OL: open label; R: randomised; MC: multi centre; GMT: geometric mean titre; GMTR: GMT ratio; QIV: quadrivalent influenza vaccine; SAE: serious adverse event; SB: single blind; SCR: seroconversion rate; TIV: trivalent influenza vaccine
Source: Compiled during the evaluation based on Tables 2.3.1 and 2.3.2, p23-27 of the submission, and Tables 2.4.17 – 2.4.20 & Tables 2.4.22- 2.4.24 p40-49 of the submission

Children aged 6 months to <5 years

6.14 The eligibility criteria of trial GQM05 were not consistent with the proposed NIP listing for all children aged 6 to <5 years.

- Trial GQM05 was conducted in children aged 6-35 months; however, the requested NIP listing is for vaccination of children aged 6 to <5 years (i.e. 59 months). The ESC noted that ATAGI considered it reasonable to assume the efficacy of QIV (Vaxigrip Tetra) is similar in 3 to 4 year-old children as in 6-35 month-old children (the ATAGI October 2018 Pre-submission advice).

- Trial GQM05 only included healthy children who had not previously received influenza vaccination and so received two doses. By comparison, the proposed NIP listing is for all children, including those who may have received influenza vaccination in previous seasons and so would receive only one dose. The ATAGI advised that it was reasonable to expect a similar level of vaccine efficacy among vaccine-naïve children who receive two doses of QIV (Vaxigrip Tetra) and previously primed children who receive one dose after having been vaccinated with a QIV in a prior influenza season (ATAGI June 2019 post-submission advice).

6.15 Trial GQM05 was conducted over four influenza seasons (Southern Hemisphere 2014 and 2015 and Northern Hemisphere 2014/2015 and 2015/2016). As the strains included in QIVs differ year to year, as do the prevalent strains in the community, 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. Afluria Quad, compared with Fluarix Tetra (PSD, November 2018) and FluQuadri, compared with Fluarix Tetra (PSD, July 2015).

<u>At-risk individuals currently eligible for NIP-funded influenza vaccination</u>

6.16 The eligibility criteria of trials (GQM05, GQM01, GQM02, GQM11, QIV03, GRC43 and QIV04) were not consistent with the proposed NIP listing for at-risk individuals currently eligible for influenza vaccination. The trials excluded persons with underlying conditions for whom yearly seasonal vaccination is recommended, ATSI people and pregnant women.

6.17 The trials were conducted over different seasons. As noted for trial GQM05 above, the strains included in QIVs differ year to year, as do strains in the community, and thus the vaccine efficacy may differ year to year. This may affect the exchangeability of the trials.

6.18 The demographic and clinical baseline characteristics differed between trials, and only GQM01 and GQM11 reported participant history of influenza vaccination and influenza illness. This may affect vaccine efficacy and thus the exchangeability of the trials.

6.19 Individuals in trial GQM05 received two doses, while individuals in most other trials received one dose. This may affect vaccine efficacy and thus the exchangeability of the trials.

6.20 The PSCR argued that exchangeability of the clinical trials of QIV (Vaxigrip Tetra) and QIV (FluQuadri) was supported as trials reported results using similar age groups and SCRs that considered the increase of antibody level after vaccination, compared with baseline. However, the ESC noted that there were differences between the baseline and clinical characteristics of participants, trial design, trial duration and trial follow-up in the trials included in the indirect comparison. Only trials GQM01 and GQM11 reported participant history of influenza vaccination and influenza illness. Furthermore, the common comparator trivalent influenza vaccine (TIV) had different SCRs for the same influenza strains in each trial. Accordingly, the ESC considered these issues may have affected the exchangeability of the trials. Comparative effectiveness

<u>Children aged 6 months to <5 years not currently eligible under the NIP</u>

6.21 Trial GQM05 presented vaccine efficacy of QIV (Vaxigrip Tetra) compared with placebo (no vaccination) in terms of laboratory-confirmed influenza illness caused by any influenza A or B type in the FASE (Full Analysis Set Efficacy). The results of GQM05 are presented in Table 5.

Table 5: Vaccine efficacy against laboratory-confirmed influenza illness and hospitalisations – Trial GQM05 (Full Analysis Set Efficacy)

	QIV (Vaxigrip Tetra) N=2,584 n (%)	Placebo N=2,591 n (%)	Efficacy % (2-sided 97% CI)
Laboratory-confirmed influenza illness caused by: Any influenza A or B type	**122 (4.72)**	**255 (9.84)**	**52.03 (38.88; 62.56)**
Viral strains similar to those contained in the vaccine	26 (1.01)	85 (3.28)	69.33 (49.79; 81.99)
PCR-confirmed influenza illness caused by: Any influenza A or B type	120 (4.64)	253 (9.76)	52.44 (40.67; 62.05)
Viral strains similar to those contained in the vaccine	26 (1.01)	85 (3.28)	69.33 (51.93; 81.03)
Culture-confirmed influenza illness caused by: Any influenza A or B type	93 (3.60)	222 (8.57)	57.99 (46.25; 67.39)
Viral strains similar to those contained in the vaccine	24 (0.93)	81 (3.13)	70.29 (52.65; 81.99)
Laboratory-confirmed influenza illness associated to hospitalisation caused by: Any influenza A or B type	**3 (0.12)**	**3 (0.12)**	**-0.27 (-648.6; 86.57)**
Viral strains similar to those contained in the vaccine	0 (0.0)	0 (0.0)	NA
Death (within 180 days after last injection)*	**5/1614 (0.2)**	**1/1612 (<0.1)**	**NA**

*Safety dataset. CI: confidence interval; NA: not assessed; QIV: quadrivalent influenza vaccine. Bolded values considered the most relevant for the submission. Italicised text adding during evaluation.
Source: Table 2.5.1 and Table 2.5.2, p50 of the submission and Table 5.1 and Table 5.2, pages 143-144 GQM05 CSR, p207 of GQM05 CSR.

6.22 The lower bound of the 97% CI for laboratory-confirmed influenza illness caused by any influenza A or B type exceeded 20%, the pre-defined superiority threshold for QIV (Vaxigrip Tetra) compared with placebo.

6.23 There were only 6 events of laboratory-confirmed influenza illness associated with hospitalisation and caused by any influenza A or B types: 3 in the QIV (Vaxigrip Tetra) arm and 3 in the placebo arm (vaccine efficacy observed around 0%). The ESC noted that the GQM05 clinical study report (CSR) stated that the efficacy against laboratory-confirmed influenza illness associated with hospitalisation could not be assessed and the 95% CI was wide (p145 GQM05 CSR). ATAGI (June 2019 Post-submission advice) stated that it was reasonable to assume that VE against hospitalisations was equal to the VE for influenza (52.03%) for the purposes of the economic evaluation.

6.24 QIV (Vaxigrip Tetra) reduced the risk of healthcare medical visits (including outpatient visits, outpatient hospitalization, and inpatient hospitalisation within 15 days after the onset of influenza like illness) by 40.80% (95% CI: 29.62-55.59%), compared with placebo (p101 of GQM05 CSR). The ESC noted that the reduction in healthcare medical visits was less than the reduction in laboratory-confirmed influenza illness.

<u>At-risk individuals currently eligible for NIP-funded influenza vaccination</u>

6.25 The clinical claim of non-inferiority in the submission was based on an indirect comparison of SCRs (Table 6). GMTs were not presented in the meta-analysis used as the basis for the indirect comparison of the submission. The submission stated that SCRs were used as they were assessed similarly, reported reasonably consistently and defined identically across the two trial sets. The use of comparative GMT ratios for the

clinical claim of non-inferiority would have been more appropriate, as all the RCTs reported GMT or GMT ratios as their primary study objective and used similar non-inferiority and superiority margins.

Table 6: Indirect comparison of SCRs against A and B strains for QIV (Vaxigrip Tetra) and QIV (FluQuadri) to demonstrate non-inferiority

Age group	OR	95% CI	OR	95% CI	OR	95% CI
Adults	**QIV (Vaxigrip Tetra) vs TIV**		**QIV (FluQuadri) vs TIV**		**QIV (Vaxigrip Tetra) vs QIV (FluQuadri)**	
A/H1N1	1.01	0.81; 1.26	0.77	0.46; 1.28	1.312	0.751; 2.29
A/H3N2	0.77	0.61; 0.97	0.63	0.36; 1.08	1.222	0.673; 2.219
B1	1.21	0.89; 1.66	0.60	0.33; 1.11	2.017	1.02; 3.988
B2	1.05	0.78; 1.40	1.19	0.67; 2.12	**0.882**	0.462; 1.683
Elderly	**QIV (Vaxigrip Tetra)**		**QIV (FluQuadri)**		**QIV (Vaxigrip Tetra) vs QIV (FluQuadri)**	
A/H1N1	0.86	0.70; 1.06	1.26	0.54; 2.94	**0.683**	0.285; 1.633
A/H3N2	0.88	0.72; 1.09	1.31	0.90; 1.92	**0.672**	0.436; 1.035
B1	1.11	0.85; 1.46	1.55	1.09; 2.21	**0.716**	0.459; 1.118
B2	1.19	0.90; 1.57	1.63	0.71; 3.76	**0.73**	0.303; 1.758
Children	**QIV (Vaxigrip Tetra)**		**QIV (FluQuadri)**		**QIV (Vaxigrip Tetra) vs QIV (FluQuadri)**	
A/H1N1	1.00	0.77;1.30	1.09	0.76; 1.55	**0.917**	0.59; 1.428
A/H3N2	0.88	0.67;1.14	1.31	1.05; 1.65	**0.672**	0.474; 0.952
B1	0.60	0.35;1.02	1.78	1.40; 2.26	**0.337**	0.188; 0.606
B2	0.87	0.50;1.49	1.03	0.79; 1.33	**0.845**	0.461; 1.547
Infants	**QIV (Vaxigrip Tetra)**		**QIV (FluQuadri)**		**QIV (Vaxigrip Tetra) vs QIV (FluQuadri)**	
A/H1N1	1.17	0.72; 1.91	1.19	0.83; 1.73	**0.983**	0.534; 1.811
A/H3N2	1.27	0.79; 2.06	1.69	1.07; 2.69	**0.751**	0.386; 1.461
B1	0.49	0.05; 4.44	1.39	1.02; 1.89	**0.353**	0.037; 3.393
B2	0.17	0.02; 1.32	1.18	0.89; 1.56	**0.144**	0.017; 1.193

CI: confidence interval; QIV: quadrivalent influenza vaccine; n: number of subjects experiencing the endpoint; SCR: seroconversion rate; TIV: trivalent influenza vaccine. Bolded values indicate the point estimates of the odds ratio that are less than 1.
Source: Table 2.6.4; p76 of the submission.

6.26 SCRs were defined across the trials as the number and proportion of patients achieving either:

- a pre-vaccination HAI titre < 1:10 and a post-vaccination titre ≥ 1:40, or
- a pre-vaccination titre ≥ 1:10 and a 4-fold increase in post-vaccination.

6.27 Non-inferiority of QIV (Vaxigrip Tetra) compared with TIV could not be concluded for strain A/H3N2 in adults based on the meta-analysis of SCR results as the OR was 0.77 with the p-value of 0.03. The submission claimed that QIV (Vaxigrip Tetra) is broadly non-inferior to QIVs in terms of SCRs for all virus strains in both adults and children (p76 of the submission).

6.28 The evaluation noted that the majority of point estimates for the odds ratio were often less than 1 when QIV (Vaxigrip Tetra) is compared to QIV (FluQuadri), indicating that QIV (Vaxigrip Tetra) may be less effective than QIV (FluQuadri).

6.29 The PSCR argued that "individual variations in immune response inevitably result in wider confidence intervals and occasionally aberrant findings. However, the results of the indirect comparison are further supported by the outcomes of the robust, within-trial comparisons". The PSCR concluded that, "on balance, taking into consideration the totality of the evidence, it is reasonable to conclude that Vaxigrip Tetra and FluQuadri are non-inferior". The ESC agreed with the evaluation that the results of the indirect comparison indicated that QIV (Vaxigrip Tetra) may be less effective than QIV (FluQuadri).

Comparative harms

Children aged 6 months to <5 years not currently eligible under the NIP

6.30 Among QIV (Vaxigrip Tetra) recipients, the frequency of fever (≥38°C) was higher in younger children, with 24.4% of children aged 6 to 11 months experiencing fever compared to 20.4% in children aged 12 to 23 months and 18.3% in children aged 24 to 35 months (ATAGI October 2018 pre-submission advice).

6.31 A summary of the solicited and unsolicited adverse events for QIV (Vaxigrip Tetra) trials are presented in Table 7[1]. ATAGI advised that it did not have specific concerns regarding the safety of QIV (Vaxigrip Tetra) for use in children aged 6 months to <5 years under the NIP, subject to approval by the TGA (ATAGI October 2018 pre-submission advice).

At-risk individuals currently eligible for NIP-funded influenza vaccination

6.32 The submission did not present an indirect comparison of safety endpoints, as it stated presented trials had found QIV (Vaxigrip Tetra) to have a similar safety profile to QIV (FluQuadri) and TIVs (p76 of the submission). It is uncertain whether the safety profiles are similar as the results were not presented and cannot be verified.

[1] Solicited adverse events were a series of pre-specified local and systemic symptoms occurring between day 1 and day 7. Unsolicited adverse events were an observed AE that does not fulfil the conditions prelisted in the CRF in terms of diagnosis and/or onset post-vaccination, i.e., excluding solicited reactions, that occurred between day 1 and the study exit (p91 of the GQM05 clinical study report).

Table 7: Summary of key solicited and unsolicited adverse events in QIV (Vaxigrip Tetra) trials

Subjects experiencing at least 1, n/N (%)	GQM05			GQM01				GQM02		GQM11			
	6 months to <5 years			18 to 60 years		≥60 years		3 to 8 years		18 to 60 years		≥60 years	
	QIV (N=1614)	Placebo (N=1612)	Pooled TIV (N=367)	QIV (N=558)	Pooled TIV (N=223)	QIV (N=558)	Pooled TIV (N=226)	QIV (N=884)	Pooled TIV (N=354)	Pooled QIV (N=834)	Pooled TIV (N=278)	Pooled QIV (N=834)	Pooled TIV (N=276)
Within 21 or 28 days after vaccine injection													
Immediate unsolicited AE	1/1614 (<0.1)	2/1612 (0.1)	1/367 (0.3)	1/558 (0.2)	0/223 (0.0)	0/558 (0.0)	0/226 (0.0)	1/884 (0.1)	0/354 (0.0)	1/834 (0.1)	1/278 (0.4)	0/834 (0.0)	1/276 (0.4)
Immediate unsolicited AR	1/1614 (<0.1)	1/1612 (<0.1)	0/367 (0.0)	1/558 (0.2)	0/223 (0.0)	0/558 (0.0)	0/226 (0.0)	1/884 (0.1)	0/354 (0.0)	0/834 (0.0)	1/278 (0.4)	0/834 (0.0)	0/276 (0.0)
Solicited reaction	1017/1592 (63.9)	921/1595 (57.7)	216/362 (59.7)	407/557 (73.1)	158/223 (70.9)	258/558 (46.2)	93/226 (41.2)	622/882 (70.5)	254/354 (71.8)	578/833 (69.4)	190/278 (68.3)	327/833 (39.3)	109/276 (39.5)
Solicited injection site reaction	635/1591 (39.9)	508/1593 (31.9)	124/361 (34.3)	348/557 (62.5)	125/223 (56.1)	191/558 (34.2)	67/226 (29.6)	550/882 (62.4)	221/354 (62.4)	484/833 (58.1)	160/278 (57.6)	231/833 (27.7)	69/276 (25.0)
Solicited systemic reaction	772/1592 (48.5)	741/1595 (46.5)	180/362 (49.7)	271/557 (48.7)	101/223 (45.3)	154/558 (27.6)	53/226 (23.5)	431/882 (48.9)	161/354 (45.5)	354/833 (42.5)	113/278 (40.6)	203/833 (24.4)	66/276 (23.9)
Unsolicited AE	1044/1614 (64.7)	1079/1612 (66.9)	261/367 (71.1)	149/558 (26.7)	52/223 (23.3)	88/558 (15.8)	39/226 (17.3)	370/884 (41.9)	127/354 (35.9)	189/834 (22.7)	54/278 (19.4)	114/834 (13.7)	45/276 (16.3)
Unsolicited AR	91/1614 (5.6)	96/1612 (6.0)	7/367 (1.9)	45/558 (8.1)	12/223 (5.4)	30/558 (5.4)	8/226 (3.5)	30/884 (3.4)	7/354 (2)	55/834 (6.6)	11/278 (4.0)	23/834 (2.8)	9/276 (3.3)
Within 180 days after last injection†													
SAE	68/1614 (4.2)	78/1612 (4.8)	14/367 (3.8)	7/558 (1.3)	3/223 (1.3)	19/558 (3.4)	5/226 (2.2)	10/884 (1.1)	3/354 (0.8)	15/834 (1.8)	8/278 (2.9)	30/834 (3.6)	7/276 (2.5)
Death	4/1614 (0.2) Should be 5/1614 (0.2)	1/1612 (<0.1)	0/367 (0.0)	0/558 (0.0)	0/223 (0.0)	2/558 (0.4)	0/226 (0.0)	0/884 (0.0)	0/354 (0.0)	1/834 (0.1)	0/278 (0.0)	2/834 (0.2)	0/276 (0.0)

AE: adverse event; AR: adverse reaction; n: number of participants experiencing the endpoint; N: number of participants with available data for the endpoint; QIV: quadrivalent influenza vaccine; SAE: serious adverse event; TIV: trivalent influenza vaccine. *Submission incorrectly stated deaths as 4/1614 however page 45 of the GQM05 CSR states 5/1614 deaths occurred.

Source: Table 2.5.26; Table 2.5.27; Table 2.5.28; Table 2.5.29; p63-66 of the submission

Benefits/harms

6.33 Table 8 presents the benefits and harms table for QIV (Vaxigrip Tetra) compared with placebo in healthy children aged 6-35 months in GQM05.

Table 8: Summary of comparative benefits and harms for the QIV (Vaxigrip Tetra) and no vaccine in children aged 6-35 months in trial GQM05

Trial	QIV, n/N	PBO, n/N	VE (95% CI)	Event rate/1,000 patients*		RD/1,000 patients
				QIV	PBO	
Benefits: GQM05						
Laboratory confirmed influenza cases	122/2489	255/2491	52.03% (38.88; 62.56)	4.72	9.84	-5.12
Harms						
	QIV, n/N	**PBO, n/N**	**RR (95% CI)**	**Event rate/1,000 patients**		**RD/1,000 patients**
				QIV	**PBO**	
Solicited injection site reaction	635/1591	508/1593	NR	399	319	81
Fever following first vaccination^						
Grade 1-3 (≥38°C)	203/1577	183/1578	NR	12.9	11.6	1.3
Fever following second vaccination^						
Grade 1-3 (≥38°C)	157/1547	134/1558	NR	10.1	8.6	1.5
Serious adverse events within 180 days after last injection						
SAE	68/1614	78/1612	NR	42	48	-6

CI: confidence interval; n: number of participants reporting data; N: total participants in group; NR: not reported; PBO: placebo; QIV: quadrivalent influenza vaccine; RD: risk difference; RR: relative risk; SAE: serious adverse event; VE: vaccine efficacy.
^Solicited systemic reaction within 7 days for Cohorts 1 and 2 (Safety Analysis Set).
* Duration of follow-up: 28-day safety assessment and/or 6-month follow-up period (using within 180 days cut-off period).
Calculated during the evaluation
Source: Table 2.5.1, p50 of the submission; Table 16, p20 of the ATAGI October 2018 pre-submission advice; p133-134of GQM05 CSR, Appendix 15.

6.34 On the basis of direct evidence presented by the submission, for every 1,000 patients treated with QIV (Vaxigrip Tetra) in comparison to placebo (no vaccination) and starting ≥ 14 days after the last vaccination and up to 6 months:

- Approximately 5 fewer patients would have laboratory-confirmed influenza

6.35 On the basis of direct evidence presented by the submission, for every 1,000 patients treated with QIV (Vaxigrip Tetra) in comparison to placebo (no vaccination):

- Approximately 81 additional solicited injection site reactions;
- Approximately 1.3 and 1.5 additional cases of Grade 1-3 fever within 7 days of the first and second vaccinations, respectively; and
- Approximately 6 fewer serious adverse events within 6 months after the last vaccination.

Clinical claim

Children aged 6 months to <5 years not currently eligible under the NIP

6.36 The submission described QIV (Vaxigrip Tetra) as superior in terms of vaccine efficacy compared with placebo (no vaccination) and had an acceptable safety profile.

6.37 The ESC considered that the therapeutic conclusion regarding efficacy was reasonable, however the magnitude of benefit was uncertain given that:

- Trial GQM05 included only vaccine naïve children and all received two doses of QIV (Vaxigrip Tetra), while a varying proportion of the proposed NIP population over time will have received a previous influenza vaccine and so would receive only one dose. The Pre-PBAC Response referred to the guidance in the Australian Immunisation Handbook regarding the need for a single dose of influenza vaccine in previously vaccinated children.
- Efficacy against laboratory-confirmed influenza illness associated with hospitalisation and mortality due to influenza could not be assessed in trial GQM05. In the Pre-PBAC Response it was considered that influenza cases avoided were no more or less likely to result in hospitalisation or death and this was more clinically plausible than assuming no impact against either factor.

6.38 The evaluation considered that the claim regarding safety was uncertain given the incidence of fever in younger children in trial GQM05. The ATAGI October 2018 pre-submission advice noted that among QIV (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% for children aged 12–23 months and 18.3% for children aged 24-35 months (Table 16, ATAGI October 2018 pre-submission advice; the CSR). However at this time, ATAGI advised (p19) that it did not have concerns regarding the safety of Vaxigrip Tetra in children aged 6 months to <5 years subject to TGA approval.

6.39 The ATAGI considered (the ATAGI June 2019 post-submission advice) that it was reasonable to assume that Vaxigrip Tetra (QIV) VE against both influenza related hospitalisation and mortality is similar to that against all laboratory-confirmed influenza, based on evidence suggesting that all inactivated influenza vaccines provide similar protection against influenza of varying severity. ATAGI also considered it reasonable to assume the efficacy of a single dose of Vaxigrip Tetra (QIV) vaccine in previously influenza vaccine-primed children is the same as the efficacy of a 2-dose Vaxigrip Tetra vaccine priming in influenza vaccine-naïve children.

6.40 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

6.41 The PBAC considered that the claim of acceptable comparative safety was reasonable.

At-risk individuals currently eligible for NIP-funded influenza vaccination

6.42 The submission described QIV (Vaxigrip Tetra) as at least non-inferior in terms of immune response and provides similar safety profile, compared with QIV (FluQuadri).

6.43 The ESC considered that the therapeutic claim of non-inferiority in terms of vaccine efficacy on the basis of an indirect comparison of QIV (Vaxigrip Tetra) and QIV (FluQuadri), with TIVs as the common comparator, was uncertain given:

- There were differences between the baseline and clinical characteristics of participants, trial design, trial duration and trial follow-up, which may cause exchangeability issues.
- The common comparator (TIV) had different SCRs for the same influenza strains in each trial.
- The indirect comparison relied on immunogenicity outcomes (SCRs). As such, the magnitude of QIV (Vaxigrip Tetra) efficacy in terms of influenza cases or hospitalisations avoided is uncertain.
- Many of the estimated odds ratios for SCRs of QIV (Vaxigrip Tetra) and QIV (FluQuadri) had wide confidence intervals, with point estimates that favoured QIV (FluQuadri). The Pre-PBAC Response argued that the data chosen for the comparison was carefully selected; however, there are a range of uncertainties involved in such comparisons such as variation in immune responses. It added that QIV (Vaxigrip Tetra) demonstrated non-inferiority to its TIV form and the alternative TIV in four clinical trials and that on balance, it was reasonable to conclude non-inferiority.

6.44 The ESC considered that the therapeutic claim regarding safety was uncertain, as the submission did not present the safety results from the indirect comparison. The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable. The PBAC noted that the evaluation was based on an indirect comparison to QIV using TIV as the common comparator and that there were uncertainties associated with the indirect comparison. On balance however, the PBAC considered non-inferior comparative effectiveness to be reasonable.

6.45 While the PBAC noted that the submission did not present an indirect comparison of safety results, it considered the safety of QIV (Vaxigrip Tetra) was likely to be comparable to other QIVs.

Economic analysis

Children aged 6 months to <5 years not currently eligible under the NIP

6.46 The submission presented a cost-utility analysis for children aged 6 months to <5 years based on GQM05. Table 9 presents the key components of the economic evaluation.

Table 9: Summary of the economic evaluation for children aged 6 months to <5 years

Component	Summary
Time horizon	1 year, with full life expectancy for deaths avoided.
Outcomes	Influenza cases, hospitalisations, life years and QALYs.
Methods used to generate results	Cohort expected value analysis
Background incidence	Background incident rate of influenza was based on the results from Neuzil (2002) which studied 1,665 healthy children aged <5 years who were enrolled in the Vanderbilt Vaccine Clinic at some point from 1974 to 1999 (incidence of laboratory-confirmed influenza of 13.4%). The ESC considered it was unclear why this data source would be preferred to the GQM05 trial (incidence of 9.8% in the placebo arm of the trial, N=2,591) which was conducted over four influenza seasons (Southern Hemisphere 2014 and 2015 and Northern Hemisphere 2014/2015 and 2015/2016). The Pre-PBAC Response stated that ATAGI had recommended the use of Neuzil (2002) for incidence given that the length of the data set over 25 years was more representative than GQM05 which ran over four seasons and that the submission used the most conservative incidence estimate in Neuzil. The PBAC accepted the use of Neuzil (13.5%) in the base case, in line with advice from ATAGI. The background rate of influenza hospitalisation was based on laboratory-confirmed influenza in 2006-2013 (Li-Kim-Moy (2016)). In line with advice from ATAGI (pre-PBAC submission advice), the submission applied multipliers of 1.8 and 3.9 for children aged <2 years and 2-4 years, respectively, to adjust for under-ascertainment of hospitalisation rates. The ESC noted that the multipliers were based on analyses of principal diagnosis codes using data from the 1990s. The ESC noted that Li-Kim-Moy et al (2017) stated "it is routine practice, but at the physician's discretion, for most hospitalized children with acute respiratory infection to undergo respiratory virological testing for diagnostic purposes and to facilitate infection control". Accordingly, the ESC considered that under-ascertainment is likely to be limited to a small sub-group of hospitalised cases and considered it would be informative to consider the results of the economic evaluation with these multipliers removed. The pre-PBAC response acknowledged that accurate estimation of the true burden of influenza hospitalisations is difficult to determine but noted there is at least a degree of under ascertainment as confirmed by Li-Kim-Moy (2017). Accordingly, the pre-PBAC response considered the ESC analysis should be considered an interesting, yet conservative, sensitivity analysis and not the basis of PBAC decision making. The PBAC noted the advice from ATAGI and considered the results of the model with the under-ascertainment rates removed was a conservative scenario analysis. Background mortality rate due to influenza taken from Li-Kim-Moy (2016) review. This was appropriate, relating to Australian experience.
Vaccine efficacy	A reduction of 52.03% in cases of influenza due to QIV (Vaxigrip Tetra) vs. placebo was taken from trial GQM05. While the ESC noted there is some uncertainty in the treatment effect on influenza cases in clinical practice due to seasonal variations in influenza incidence and strain circulation, the age range of children in trial GQM05 and given there will be a mix of children receiving 1 or 2 doses (based on whether they have been previously vaccinated). Nevertheless, the ESC considered, on balance, that the use of the VE estimate from the trial in the economic evaluation was reasonable. Hospitalisation rate due to influenza QIV (Vaxigrip Tetra) vs. placebo treatment arm assumed equal to rate of reduction of influenza QIV (Vaxigrip Tetra) vs. placebo. In the absence of reliable trial results for this outcome, the ESC considered this assumption may be reasonable. ATAGI advised it was reasonable to assume that VE against influenza-associated hospitalisations is equal to VE against laboratory-confirmed influenza (52.03%) (post-submission advice, June 2019). The PBAC noted the advice from ATAGI and accepted that VE against influenza hospitalisations is likely to be similar to VE against laboratory-confirmed influenza. The treatment effect on mortality was assumed equal to the treatment effect on incidence of influenza. The evaluation considered this was not appropriate. Instead, it would have been preferable to assume no treatment effect on mortality due to influenza, consistent with the experience from trial GQM05. The ESC noted that the results of the economic evaluation were not sensitive to this assumption. ATAGI advised that

Component	Summary
	it was reasonable to assume that VE against mortality was similar to the VE for influenza (52.03%) (Post-submission advice, June 2019). The PBAC noted the advice from ATAGI and accepted that VE against mortality is likely to be similar to VE against laboratory-confirmed influenza.
Utilities	To inform QALY gains associated with the avoidance of death, a long-term utility value of 0.91 was applied (McCaffrey 2016)[2]. It would have been more appropriate to have modelled utility as a decreasing function of age, rather than a constant value for all ages. The ESC considered that the results of the model were unlikely to be sensitive to this assumption. A disutility of 0.44 was applied to the short-term effects of influenza (which was assumed to last 7 days) in the eligible population of under 5 year olds. This was taken from Mauskopf (2000)[3], based on an assumed health state for adults with influenza. The evaluation noted that Mauskopf (2000) presented a scenario analysis in which they assumed a utility for people without influenza as being 0.90, as opposed to 1.00. In this case, disutility of having influenza was 0.34. Consequently, the evaluation considered it was not clear whether it would be preferable to assume a disutility of 0.44 or 0.34. The PSCR argued that it is preferable to assume a utility of 1.0 when estimating the disutility for having influenza, because they claim that the quality of life for healthy children is relevant, which is approximately 1.0 . The ESC considered it was uncertain if the disutility applied in the submission was relevant for the requested population of children aged 6 months to <5 years and may have been overestimated. The ESC noted that the results of the model were sensitive to changes in this value.
Costs	Costs included relate to vaccine acquisition, vaccine administration, hospital treatment, outpatient visits. These were appropriate. An average of 1.25 doses of QIV (Vaxigrip Tetra) per patient per year was assumed, based on four age cohorts eligible for vaccination each year (6-23 months, 24-35 months, 36- 47 months, 48-59 months), one of which will receive two doses in the first year of eligibility for influenza vaccine. By comparison, there was a mean of 2.0 doses of QIV (Vaxigrip Tetra) in trial GQM05 which was conducted in healthy children aged 6-35 months who were naïve to influenza vaccine, which was used to inform the estimated reduction in rate of influenza (of 52%). The ESC noted that from a healthcare system perspective 2 doses would be required for the entire cohort in the first year of listing and 1.25 doses would be required for subsequent years. Over time, the average dose in clinical practice would therefore decrease from 2 in the first year, and 1.63 over the first 2 years etc., to approach 1.25. For example, over 20 years the average dose would be 1.29; this would increase the base case ICER by around less than $15,000/QALY. The ESC noted that the results of the economic evaluation were not sensitive to a small increase in the average dose and therefore accepted the use of an average of 1.25 doses in the base case. The vaccine administration cost was based on a weighted average of MBS items 3 and 82200. The evaluation noted that another appropriate source for the administration cost may have been MBS item 23. The ESC noted that MBS item 82200 related to nurse practitioners, not GP practice nurses, and is rarely used. The ESC considered that it may have been reasonable to assume around 25% of use of MBS item 23, for the first year a child is vaccinated and the remaining 3 years of vaccination being MBS item 3, resulting in a weighted average administration cost of $22.30. The ESC noted that this administration cost may still be underestimated as it did not include the $6 provider information payment for recording a NIP Schedule vaccination for a child under 7 years old on the Australian Immunisation Register. On the other hand, the ESC noted that some vaccinations may be provided through state funded health clinics for which the cost per administration is uncertain. The Pre-PBAC Response argued that as item MBS 3 ($17.20) is specifically for vaccine purposes it was not appropriate to use item 23, and that if item 23 were used for patients it would be because GPs are also investigating other matters, which would mean no additional cost has been imposed on the MBS for administration of the vaccine. The pre-PBAC response also argued that

[2] McCaffrey McCaffrey N, Kaambwa B, Currow D, Ratcliffe J. Health-related quality of life measured using the EQ-5D-5L: South Australian population norms. Health and Quality of Life Outcomes. 2016;14(133):1-12.
[3] Mauskopf J, Cates S, Griffin A, et al. Cost effectiveness of Zanamivir for the treatment of influenza in a high risk population in Australia. Pharmacoeconomics. 2000;17(6):611-620.

Component	Summary
	given the already high interaction between the MBS and this age group, vaccination may be absorbed within current practice and not add a significant additional burden to the MBS. The pre-PBAC response noted that if administration costs can be kept efficient, then vaccination is almost certainly cost-effective. The PBAC noted the average administration cost in clinical practice was unclear but considered the administration cost applied in the submission (of $14.43) was reasonable in the base case. The PBAC also considered an administration cost of $17.20 (i.e. MBS item 3) as a conservative scenario analysis. Hospital costs were based on Independent Hospital Pricing Authority (IHPA, 2018) National Hospital Cost data collection report for the financial year 2015-16, which reports the average cost for admitted acute paediatric separations. The unit cost applied in the economic evaluation was $6,634. The costs per non-hospitalised influenza case was calculated using the average number of healthcare visits, and medication costs per non-hospitalised case of influenza from a prospective cohort study in healthy children aged ≥6 months to <3 years recruited from 90 childcare centres and one paediatric-focused GP clinic in metropolitan Sydney, Australia in the winter of 2010 (Yin 2013) and the costs from the MBS and PBS Schedules and the IHPA.
Herd immunity	Considered in a scenario analysis only. This was appropriate given that ATAGI expects that the proposed vaccination program will have little, if any, measurable population-level herd protection (ATAGI October 2018 Pre-submission advice). The PBAC noted the advice from ATAGI and therefore did not consider the results of this scenario analysis.
Software package	Microsoft Excel 2010.

QALY: quality adjusted life year. QIV: Quadrivalent Influenza Vaccine.
Source: p101-126 of the submission and complied during the evaluation.

6.47 Key drivers of the economic evaluation are given in Table 10.

Table 10: Key drivers of the economic evaluation for children aged 6 months to <5 years

Description	Method/Value	Impact
Treatment effect on rate of hospitalisation	Assumed treatment effect on rate of hospitalization equal to treatment effect on incidence of influenza.	High. Favours QIV (Vaxigrip Tetra).
Utilities	Disutility of having influenza assumed to be 0.44. The evaluation considered this value could reasonably be 0.34 based on the source publication, Mauskopf (2000).	High. Favours QIV (Vaxigrip Tetra).
Vaccine administration cost	Assumed a vaccine administration cost of $14.43. The ESC considered it may have been reasonable to assume $22.30.	High. Favours QIV (Vaxigrip Tetra)
Incidence rate of influenza	Base case value is 13.5%. The incidence rate in the trial GQM05 was 9.8%.	High. Favours QIV (Vaxigrip Tetra).
Multiplier for under-ascertainment of incidence of influenza-related hospitalisations	Assumed multipliers of 1.8 and 3.9 for children aged <2 years and 2-4 years, respectively.	Moderate. Favours QIV (Vaxigrip Tetra)

QIV: Quadrivalent Influenza Vaccine.
Source: Complied during the evaluation.

6.48 The stepped economic evaluation results are given in Table 11.

Table 11: Stepped economic evaluation results in the submission base case for children aged 6 months to <5 years (population size 1,593,927)

Step and component	QIV (Vaxigrip Tetra)	Placebo	Increment
Step 1: Incremental cost per influenza event avoided			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
Influenza cases	82,578	172,144	-89,567
Incremental cost/ influenza case avoided			$ [redacted]
Step 2: Transformed to QALYs			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
QALYs lost	700	1,460	-759
Incremental cost/ QALY gained			$ [redacted]
Step 3: Include non-hospital costs			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
QALYs lost	700	1,460	-759
Incremental cost/ QALY gained			$ [redacted]
Step 4: Include hospital costs			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
QALYs lost	700	1,460	-759
Incremental cost/ QALY gained			$ [redacted]
Step 5: Include mortality benefit costs (base case)			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
QALYs lost	726	1,513	-787
Incremental cost/extra QALY gained			**$** [redacted]

QALY quality-adjusted-life-year; QIV Quadrivalent Influenza Vaccine.
Source: Based on submission Table 3.8.9, p135, with additional data extracted from model

The redacted table shows ICERs in the range of $15,000/QALY -$45,000/QALY.

6.49 The ESC noted that the submission's economic evaluation (which was based on the average population of children aged 6 months to <5 years in 2006-2013) assumed that for each year of listing for the additional population on the NIP:

- 1,593,927 children would be vaccinated (assuming 100% uptake, whereas the financial forecasts assume a maximum uptake of 50% in Year 6 of listing) at a cost of $10 - $20 million for the vaccine and $23.0 million for administration (total cost of $34.0 million);
- 89,567 cases of influenza would be avoided, with a cost saving of around $7.0 million for non-hospitalised cases;
- 1,105 influenza related hospitalisations would be avoided with an associated cost saving of $7.3 million; and
- 1.6 deaths would be avoided.

The resulting ICER for the submission's base case was from $15,000/QALY - $45,000/QALY gained.

6.50 Table 12 presents the results of the key sensitivity analyses conducted in the submission and during the evaluation and ESC consideration.

Table 12: Results of the key sensitivity analyses (population size 1,593,927)

Scenario	Incremental cost	Incremental QALYs	ICER ($/QALY gained)
Base case	**$**	**787**	**$**
Incidence of influenza (base case 13.5%)			
1. 9.8% (GQM05)	$	579	$
Multiplier applied to actual influenza hospitalisations to adjust for under-ascertainment (base case 1.8 for 6-23 months, 3.9 for 2-4 years)			
2. No multiplier applied	$	787	$
Allowance for herd immunity (base case: not included)			
3. Herd immunity included	$	728	$
Vaccine efficacy (cases of influenza) (base case: 52.03%)			
4. 38.88% (95% LCL)	$	588	$
5. 62.56% (95% UCL)	$	947	$
Hospitalisation rate due to influenza QIV (Vaxigrip Tetra) vs. placebo treatment arm (base case 52% reduction)			
6. No difference between QIV (Vaxigrip Tetra) and placebo (from GQM05)	$	787	$
Treatment effect on mortality (base case 52% reduction)			
7. No difference between QIV (Vaxigrip Tetra) and placebo (from GQM05)	$	759	$
Costs			
Mean number of vaccine doses per year (base case 1.25)			
8. 2.0 (from GQM05)	$	787	$
Vaccine administration cost (base case $ per dose, 64% MBS item 3 and 36% MBS item 82200)			
9. $0	-$	787	Dominant
10. $9.60 (100% MBS item 82200)	$	787	$
11. $17.20 (100% MBS item 3)	$	787	$
12. $22.30 (25% MBS item 23, 75% MBS item 3)	$	787	$
13. $37.60 (100% MBS item 23).	$	787	$
Hospital costs (base case $6,634 IHPA 2018)			
14. $3,473 (IHPA 2019)	$	787	$
15. $8,226 (Li-Kim-Moy 2017)	$	787	$
Non-hospital costs (e.g. GP visits, medication) (base case $, Yin 2013)			
16. $66.57 (Lambert 2004)	$	787	$
17. $154.18 (Willis 2018)	$	787	$
Disutility for having influenza (base case 0.44)			
18. 0.34	$	616	$

ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality-Adjusted-Life-Year; MBS: Medicare Benefits Schedule; IHPA: Independent Hospital Pricing Authority. Bolded values represent base case results.
Source: Based on submission Table 3.9.1, p137 and generated during the evaluation and the preparation of the ESC Advice using the submission's Section 3 workbook.

The redacted table shows ICERs in the range of less than $15,000/QALY - $45,000/QALY to $45,000/QALY - $75,000/QALY.

6.51 The ESC considered that a respecified base case, incorporating the following changes to the submission's base case, may be relevant for PBAC decision making:

- use the background influenza incidence rate from the trial of 9.8% (scenario #1 in Table 9); and

- remove the use of multipliers to adjust for under-ascertainment of hospitalised cases (scenario #2 in Table 9).

6.52 In addition, the ESC noted that the results of the economic evaluation were highly dependent on the cost of administering the vaccine, which at the cost applied in the submission of $14.43 was [redacted] the cost of the vaccine itself. As noted in Table 9, the ESC considered that the cost of vaccine administration in clinical practice was uncertain and may have been underestimated in the submission. Accordingly, the ESC advised the PBAC that it may be informative to consider the ICER for the revised ESC base case (as defined above), at the requested price of $[redacted] per dose, across the range of likely administration costs (see Figure 1).

Figure 1: ICER by administration cost for the submission base case and selected sensitivity analyses (see Table 12)

[redacted]

Source: Generated during preparation of the ESC Advice using the submission's Section 3 workbook.
ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality-Adjusted-Life-Year.

6.53 The PBAC considered that the base case ICER in the submission, of $15,000 - $45,000 per QALY gained, was the most informative for decision making (see Figure 1 and Table 9). While the PBAC considered there was a risk that the ICER may be as high as $45,000 - $75,000 per QALY gained, based on the results of a multivariate analysis of scenarios #1, #2 and #11 in Table 12 (see Figure 1), this was considered a conservative and unlikely scenario.

At-risk individuals currently eligible for NIP-funded influenza vaccination

6.54 The submission presented a cost-minimisation analysis based on an indirect comparison for the at-risk population currently eligible for seasonal influenza vaccine through the NIP, including people aged ≥6 months at increased risk of influenza complications, pregnant women, ATSI people aged ≥6 months and adults aged ≥65 years.

6.55 The submission suggested that the dosing schedule is the same for each vaccine; however, the recommended dose volume and number of vaccinations per year differs by age (p139 of the submission). The recommended dose by age for QIVs is:

- ≥6 months to <3 years: 0.25 mL (FluQuadri Junior), 0.5mL (Vaxigrip Tetra and other QIVs), two doses in the first year of vaccination and one dose in subsequent years.
- ≥3 years to <9 years: 0.5 mL, two doses in the first year of vaccination and one dose in subsequent years.
- ≥9 years: 0.5 mL, one dose per year.

6.56 The submission stated that for the purposes of cost-minimisation the price of QIV (Vaxigrip Tetra) (0.50 mL) is set the same as that of QIV (FluQuadri Junior) (0.25 mL).

Vaccine cost/patient/course

6.57 The proposed price for QIV (Vaxigrip Tetra) is $[redacted] per dose. Children aged 6 months to <9 years who have not been previously immunised receive two doses in their first year. The remaining eligible population would receive one dose per year.

Table 13: Vaccine cost per patient for children aged 6 months to <5 years

	Trial dose and duration	Model	Financial estimates
Mean dose	2.0 doses per year	1.25 doses per year	1.25 doses per year
Mean duration	One year	One year	Over six years
Cost/patient/year	$[redacted]	$[redacted]	$[redacted]

Source: Submission p37, 103.

Estimated PBS usage & financial implications

6.58 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the financial implications associated with the proposed expansion of the eligibility for influenza vaccine on the NIP to healthy children aged 6 months to <5 years (see Table 14). The submission assumed that around 8% of all children aged 6 months to <5 years are currently eligible for NIP funded influenza vaccine and that uptake is around 37%, resulting in around 3% of the total cohort currently being vaccinated under the NIP. The submission further assumed that uptake of QIV (Vaxigrip Tetra) in the newly eligible (healthy) children would be 30% in 2020, increasing to 50% in 2025, on the advice of ATAGI (Section 5.2, of the October 2018 ATAGI Pre-submission advice). All estimates of financial impact are uncertain given the uncertainty in the uptake rates of QIV (Vaxigrip Tetra). In this regard, the

ESC noted that data regarding uptake of QIV through the current State/Territory funded programs for children aged 6 months to <5 years would have been informative.

6.59 The submission stated that it did not present estimated use or financial implications of individual QIVs in either the current or proposed expanded NIP populations because the alternative vaccines have the same dosing schedule and the same price, meaning this assumption will have no impact on the net financial of the proposed change to the NIP.

Table 14: Estimated use and financial implications of expanding the eligibility for influenza vaccine on the NIP to children aged 6 months to <5 years

	Year 1 (2020)	Year 2 (2022)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)	Year 6 (2025)
Total children vaccinated						
Current	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proposed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current NIP vaccine cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proposed NIP vaccine cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net impact NIP vaccine cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net vaccine administration costs (MBS)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Hospital costs (State)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Non-hospital costs to MBS (excluding vaccine administration costs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to Australian government (NIP, MBS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Non-hospital costs to PBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net all health care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MBS: Medicare Benefits Schedule; NIP: National Immunisation Program; PBS: Pharmaceutical Benefits Scheme.
Source: Tables 4.2.1, 4.2.2 and 4.2.3, p146-7 of the submission.
[a] Based on a weighted average of MBS items 3 ($17.20) and 82200 ($9.60).

The redacted table shows that at Year 6, the estimated number of children vaccinated ranges from 50,000 -100,000 per year to over 200,000 per year, and the net financial implications to the NIP would be more than $10 million per year.

6.60 The PSCR presented revised utilisation estimates, separating out children receiving the vaccine for the first season versus subsequent seasons, assuming 25% of patient vaccinated in one season will not be vaccinated in the next. The net impact of the revised estimates was of higher costs to the NIP, most significantly in the earlier years (less than $10,000 higher in year 1, over $200,000 per year from years 2 to 5), and $10,000 – 50,000 higher than the original proposed impact by year 6.

6.61 The submission may have underestimated the net costs for the following reasons:

- The submission incorrectly assumed 1.25 doses per child per year, as in the cost-utility analysis. Instead, for the financial impact model, it would have been more appropriate to assume a varying number of doses over the first six years of listing,

to simulate the likely proportions of children who would receive one or two doses, according to whether they have previously been vaccinated. The PSCR agreed that it would have been more appropriate to assume varying mean doses over time, to reflect the likely mix of one and two dose vaccinations in the child population. The revised utilisation estimates in the PSCR that it stated was intended to assume a changing proportion of children receiving one or two doses; have not been independently evaluated.

- As in the cost-utility analysis, the financial implications included an assumed reduction in influenza-associated hospitalisations. The ESC noted that the magnitude of any cost savings resulting from a reduction influenza-related hospitalisations in clinical practice is uncertain given the efficacy against laboratory-confirmed influenza illness associated with hospitalisation could not be assessed in trial GQM05.
- The unit cost per vaccine administration was uncertain. If MBS item 23, professional attendance by a general practitioner lasting less than 20 minutes, was used for a proportion of administrations, then the total MBS and total healthcare costs would increase compared with the submission's estimates. The PBAC noted the average administration cost in clinical practice was unclear but considered the administration cost applied in the submission (of $14.43) was reasonable in the base case.

Quality Use of Medicines

6.62 No quality use of medicines information was provided in the submission. In its October 2018 Pre-PBAC Submission Advice, ATAGI stated that 'should Vaxigrip Tetra be listed under the NIP, safety surveillance and program evaluation, including through AusVaxSafety, are integral activities to ensure the safety and effectiveness of the program. An important component of post marketing surveillance includes gaining evidence on the reactogenicity of concomitant vaccination' (ATAGI October 2018 pre-submission advice).

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of quadrivalent influenza vaccine (QIV, Vaxigrip Tetra) on the *National Health (Immunisation Program – Designated Vaccines) Determination 2014 (No.1)* (the Determination), for the prevention of seasonal influenza in children aged 6 months to <5 years as well as in at-risk individuals who are currently eligible for 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:

- QIV (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 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.

Patients aged 6 months to <5 years not currently eligible under the NIP

7.2 The PBAC noted that the Australian Immunisation Handbook strongly recommends children aged <5 years receive influenza vaccine every year. The PBAC considered that listing a QIV on the NIP for all children aged 6 months to <5 years on the NIP is warranted from a public health perspective as an additional measure to directly target this group which has a relatively high burden of disease[4].

7.3 The PBAC accepted the comparator of placebo for this population as there is no currently NIP funded vaccine for this cohort.

7.4 The PBAC noted that the submission presented one head-to-head RCT (GQM05) comparing QIV (Vaxigrip Tetra) versus placebo in children aged 6-35 months. The PBAC considered that although GQM05 did not cover the full age range of the proposed population, it was reasonable to assume the efficacy to be similar across the study population and proposed population for the listing (6 months to <5 years). The PBAC noted that GQM05 included influenza vaccine naïve children only and ATAGI's advice on vaccine priming in influenza vaccine-naïve children (June 2019 Post-submission advice). The PBAC considered that, on balance, extrapolating outcomes for vaccine naïve children in the trial to children who had been vaccinated in a previous influenza season was reasonable.

7.5 The PBAC considered that the results of GQM05 demonstrated superiority against placebo for the outcome of laboratory-confirmed influenza illness, meeting the pre-defined superiority threshold, with an overall vaccine efficacy (VE) of 52.03%. The PBAC noted that this is similar to the results seen for other influenza vaccines for children in a typical influenza season. The PBAC noted that there were limited events of laboratory-confirmed influenza illness associated with hospitalisation in both trial arms. The trial was not powered to determine the impact on hospitalisations or mortality, and agreed with ATAGI (June 2019 Post-submission advice,) that it was reasonable to assume that VE against hospitalisations and mortality would be similar to the VE for influenza (of 52.03%) for the purposes of the economic evaluation.

[4] Australian Immunisation Handbook, https://immunisationhandbook.health.gov.au/recommendations/children-aged-0.

7.6 The PBAC noted that ATAGI advised (October 2018 Pre-submission advice) it had no specific concerns regarding the safety of Vaxigrip Tetra in children aged 6 months to <5 years, subject to TGA approval. On balance, the PBAC considered that the claim of acceptable safety versus the comparator was reasonable.

7.7 The PBAC considered that the most appropriate scenario for decision-making was the base case presented by the submission that resulted in an ICER of $15,000 - $45,000 per QALY gained. The PBAC considered there was a risk the ICER may be as high as $45,000 - $75,000 per QALY gained, but considered this scenario was based on conservative and unlikely assumptions, such as a lower incidence of influenza and no under-ascertainment of hospitalisations.

7.8 The PBAC noted the estimates of utilisation and financial impact for the newly eligible (healthy) children would be dependent on the uptake rate of QIV (Vaxigrip Tetra). The submission assumed that uptake of QIV (Vaxigrip Tetra) in healthy children would be 30% in Year 1 of listing, increasing to 50% in Year 6, on the advice of ATAGI. In this regard, the PBAC noted the consumer comment from Health Protection NSW (NSW Health) stated that in the first year of the NSW state funded paediatric influenza program, around one quarter of NSW children under 5 were recorded on the Australian Immunisation Register as having received at least one dose of influenza vaccine, with true uptake estimated to be around twice that recorded.

<u>At-risk individuals currently eligible for vaccination under the NIP</u>

7.9 The PBAC accepted the proposed comparators of QIVs, FluQuadri and FluQuadri Junior, as they are QIVs that are currently listed on the NIP for the proposed population. Alternative QIVs, Fluarix Tetra and Afluria Quad, were also appropriate comparators.

7.10 The PBAC noted that there were no head-to-head RCTs comparing QIV (Vaxigrip Tetra) with other QIVs. Rather, the submission presented an indirect comparison of QIV (Vaxigrip Tetra) to the QIV comparators (FluQuadri and FluQuadri Junior) using TIVs as the common comparator.

7.11 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. The PBAC recalled that this is a common limitation with vaccine trials, however it may be reasonable to expect that the VE in sub-populations are unlikely to vary significantly or to vary between the proposed listing and comparator already in use in the vaccinated cohort[5]. The PBAC also noted the seasonal variability in dominant influenza serotypes and that is an uncertainty in all influenza vaccine considerations.

[5] Quadrivalent Influenza Vaccine: 0.5 mL pre-filled syringe; Fluarix Tetra®, Public Summary Document, March 2019 PBAC meeting, p4. Available at: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2019-03/quadrivalent-psd-march-2019

7.12 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[6]. The PBAC noted that 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. However, overall the PBAC considered that the claim of non-inferiority of Vaxigrip Tetra to FluQuadri to be reasonable.

7.13 The PBAC noted that the submission presented a summary of the key adverse events in the QIV trials but did not present an indirect comparison of safety endpoints. The PBAC noted the advice of ATAGI (October 2018 pre-submission advice) that it had no specific concerns regarding safety. On balance, the PBAC considered that the safety of QIV (Vaxigrip Tetra) was likely to be comparable to other QIVs.

7.14 The PBAC accepted the cost-minimisation analysis presented in the submission. The PBAC advised the equi-effective doses should be 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.

7.15 The PBAC noted there was expected to be no net cost to the NIP as a result of listing QIV (Vaxigrip Tetra) for the populations currently eligible for NIP-funded vaccine.

7.16 The PBAC noted that ATAGI (pre-submission advice) stated that safety surveillance and program evaluation, including through AusVaxSafety, would be integral activities to ensure the safety and effectiveness if Vaxigrip Tetra were listed on the NIP for the new and/or currently eligible populations.

7.17 The PBAC noted that this submission is not eligible for independent review as independent review is only relevant to PBS listing.

Outcome:
Recommended

[6] Influenza Vaccine (quadrivalent); 0.5 mL pre-filled syringe; Fluarix tetra® Public Summary Document, March 2015 PBAC meeting. Available at: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2015-03/fluarix-tetra-psd-03-2015

8 Recommended listing

8.1 Add new item to the Determination for the populations outlined below:

Name, Restriction, Manner of administration and form	Proprietary Name and Manufacturer	
Quadrivalent Influenza Vaccine, 0.5mL injection	Vaxigrip Tetra	Sanofi-Aventis (Australia) Pty Ltd

Category/Program:	NIP
Population	Children aged ≥6 months to <5 years. Adults aged ≥65 years; Aboriginal and Torres Strait Islander (ATSI) people aged ≥6 months Persons aged ≥6 months who are at increased risk of influenza complications, specifically: • 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 • a person aged less than 11 years and receiving long-term aspirin therapy. Pregnant women.
Number and timing of doses:	Should be administered in accordance with the national recommendation as per the current Immunisation Handbook: Individuals from 9 years of age: a single 0.5 mL injection. Children from 6 months to <9 years of age: • 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; QIV: quadrivalent influenza vaccine
Source: Table 1.1.3 and Table 1.4.1, p10-11 and p17 of the submission; National Health (Immunisation Program – Designated Vaccines) Determination 2014 (No.1) (compiled 10 January 2019)

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

Sanofi Pasteur welcomes the PBAC's recommendation to list Vaxigrip Tetra to expand the NIP to include all children aged 6 months to less than 5 years.