

An addendum to this minute has been included at the end of the document.

**5.04 INFLUENZA QUADRIVALENT ADJUVANTED VACCINE,
Injection 0.5 mL
Fluad® Quad, and
INFLUENZA TRIVALENT ADJUVANTED VACCINE,
Injection 0.5 mL,
Fluad®,
Seqirus (Australia) Pty Ltd**

1 Purpose of Application

1.1 The submission had two purposes:

- An increased price premium for Fluad (adjuvanted trivalent influenza vaccine; aTIV) for vaccination against influenza in adults aged 65 years and above. The aTIV was listed on the National Immunisation Program (NIP) following a PBAC recommendation in March 2018 on a cost-minimisation basis compared to currently NIP-listed quadrivalent influenza vaccines (QIVs).
- NIP listing of Fluad Quad (adjuvanted quadrivalent influenza vaccine; aQIV) for vaccination against influenza in adults aged 65 years and above. The aQIV is not yet TGA registered and is not expecting a Delegate's Overview until August 2019.

1.2 The basis for increasing the price of aTIV (Fluad) was a claim of superiority of aTIV (Fluad) over QIV, supported by a cost-utility analysis. The basis for listing aQIV (Fluad Quad) on the NIP was a claim of non-inferiority of aQIV (Fluad Quad) over aTIV (Fluad).

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

| Component | Description |
|-----------------|--|
| Population | All persons aged ≥ 65 years of age |
| Intervention | Two interventions 1. Annual, single dose of aTIV (Fluad). Contained within each 0.5mL dose is 15 mcg haemagglutinin for each AH1N1 and A/H3N2 stain, in addition to one B lineage. The adjuvant component is MF59C.1 squalene. 2. Annual, single dose of aQIV (Fluad Quad). Contained within each 0.5mL dose is 15 mcg haemagglutinin for each AH1N1 and A/H3N2 strain, in addition to two B lineages. The adjuvant component is MF59C.1 squalene. |
| Comparator | 1. aTIV (Fluad) was compared to existing non-adjuvanted QIVs (Afluria Quad, FluQuadri and Fluarix Tetra). 2. aQIV (Fluad Quad) was compared to aTIV (Fluad). |
| Outcomes | 1. Hospitalisations for pneumonia and influenza 2. Immunogenicity |
| Clinical claims | 1. <u>aTIV (Fluad) compared to QIV</u> 1.1. aTIV (Fluad) versus TIV "Fluad (aTIV) is superior to non-adjuvanted TIV in effectiveness against clinically relevant outcomes" 1.2. aTIV (Fluad) versus QIVs (Afluria Quad, FluQuadri and Fluarix Tetra) "... the superiority claim [of aTIV over TIV] is proposed to extend to non-adjuvanted QIV where there is a strain match". 2. <u>aQIV (Fluad Quad) compared to aTIV (Fluad)</u> 2.1. aQIV (Fluad Quad) versus aTIV (Fluad) "Fluad Quad (aQIV) is non-inferior to Fluad (aTIV) in immunogenicity measures for A/H1N1, A/H3N2 and the included B/ Victoria and B/Yamagata strains" Additional claim: <u>aQIV (Fluad Quad) compared to QIV</u> "By extension, Fluad Quad (aQIV) is superior to non-adjuvanted QIV in effectiveness against clinically relevant outcomes" |

aTIV: adjuvanted trivalent influenza vaccine; TIV: trivalent influenza vaccine (non-adjuvanted); aQIV: adjuvanted quadrivalent influenza vaccine; QIV: quadrivalent influenza vaccine (non-adjuvanted)

Source: Compiled during the evaluation.

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

2 Requested listing

Essential elements of the requested listing of aTIV (Fluad) on the NIP

| Name, restriction, manner of administration, form | Maximum quantity (units) | No. of repeats | Nationally negotiated price | Proprietary name and manufacturer |
|---|--------------------------|----------------|-----------------------------|---|
| Inactivated influenza vaccine (surface antigen), suspension for injection, adjuvanted | 1 | 0 | \$█████* | Fluad (aTIV), Seqirus (Australia) Pty Ltd |

Source: Compiled during the evaluation, based on Table 1-1 p. 32, of the submission

*The Pre-PBAC Response offered a reduced price of \$█████ per dose for the 2020 season only in the circumstance that aQIV were not able to be listed in time for the 2020 season

Essential elements of the requested listing of aQIV (Fluad Quad) on the NIP

| Name, restriction, manner of administration, form | Maximum quantity (units) | No. of repeats | Nationally negotiated price | Proprietary name and manufacturer |
|---|--------------------------|----------------|-----------------------------|--|
| Inactivated influenza vaccine (surface antigen), suspension for injection, adjuvanted | 1 | 0 | \$ [REDACTED] | Fluad Quad (aQIV), Seqirus (Australia) Pty Ltd |

Source: Compiled during the evaluation, based on Table 1-1 p. 32, of the submission

3 Background

Registration status

- 3.1 The aTIV (Fluad) was TGA registered in October 2002 and updated in 2018 for: Active immunisation against influenza in the elderly (65 years of age and older), especially for those with an increased risk of associated complications (i.e. patients affected by underlying chronic diseases including diabetes, cardiovascular and respiratory diseases).
- 3.2 The submission for aQIV (Fluad Quad) was made under the TGA/PBAC Parallel Process. The Delegate’s Overview was expected in August 2019, with a decision expected in September 2019. At the time of the PBAC meeting, there were no documents available other than the draft Product Information. The proposed indication in the draft PI was: Active immunisation against influenza in persons 65 years of age and older.

Previous PBAC consideration

- 3.3 The PBAC recommended listing aTIV (Fluad) on the NIP in March 2018 on a cost-minimisation basis compared to NIP listed QIVs (Afluria Quad, FluQuadri and Fluarix Tetra).

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

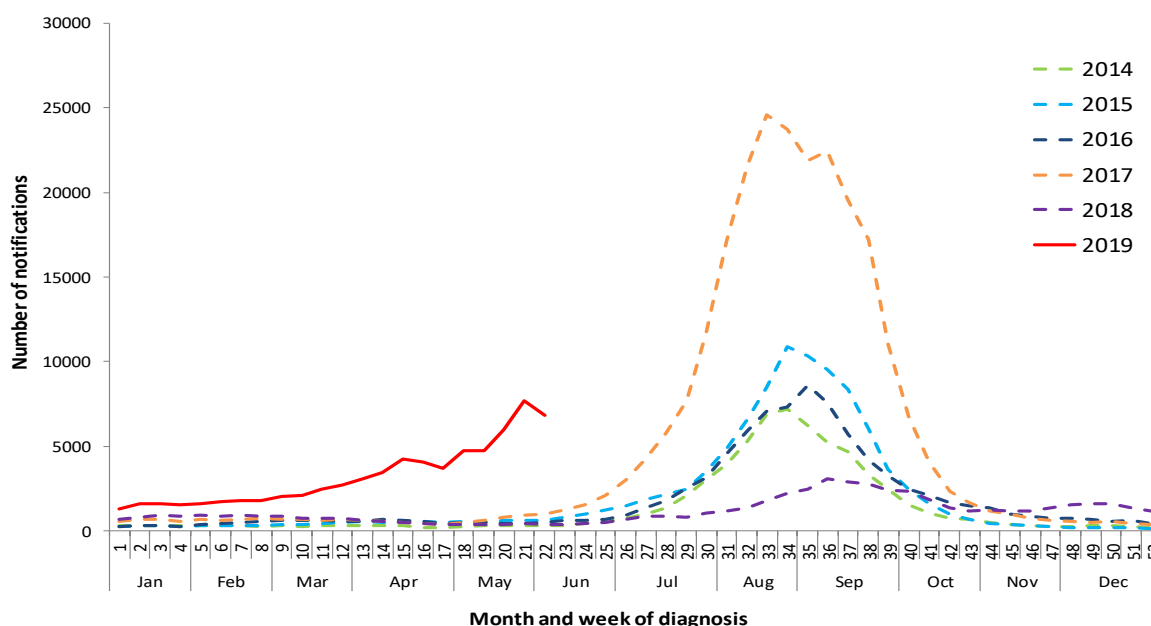
4 Population and disease

- 4.1 Influenza is an acute viral infection of the respiratory tract. Beyond the acute symptoms, influenza is also associated with complications including (but not limited to) acute bronchitis, pneumonia (both primary viral and secondary bacterial pneumonia), and cardiovascular complications including myocarditis and pericarditis. There are four types of influenza viruses: influenza A, B, C, and D but only influenza A and B viruses cause clinically important human disease and seasonal epidemics.
- 4.2 Influenza infection in people aged ≥ 65 years may have severe consequences. In Australia, conservative estimates (coded diagnoses) of hospitalisation and mortality from influenza in this age group are 41 and 2 per 100,000 respectively. However, the actual burden is likely to be higher with estimates of approximately 480 and 20.9 per 100,000 respectively (ATAGI, 2016; Newall, Wood, & MacIntyre, 2008a). This extent

of burden in the ≥ 65 age group, despite vaccination coverage of approximately 70% in Australia, may be partly explained by the suboptimal effectiveness of vaccination in older people due to immunosenescence (Cambier, 2005; Grubeck-Loebenstein, 2010).

- 4.3 Notifications of laboratory-confirmed influenza to the National Notifiable Diseases Surveillance System (NNDSS) were relatively high in 2017. For the year to 27 October 2017, 229,579 notifications of laboratory confirmed influenza were reported to the NNDSS. The ESC noted the trend in 2019 for early and high notifications of laboratory confirmed influenza (see Figure 1). The ESC considered that the higher rates of testing with results being reported faster, particularly point of care testing in emergency departments and residential aged care, and the preliminary advice¹ to immunise later in the year to ensure protection in August/September may have contributed to the 2019 trend.

Figure 1: Notifications of laboratory confirmed influenza, Australia, 1 January 2014 to 2 June 2019, by month

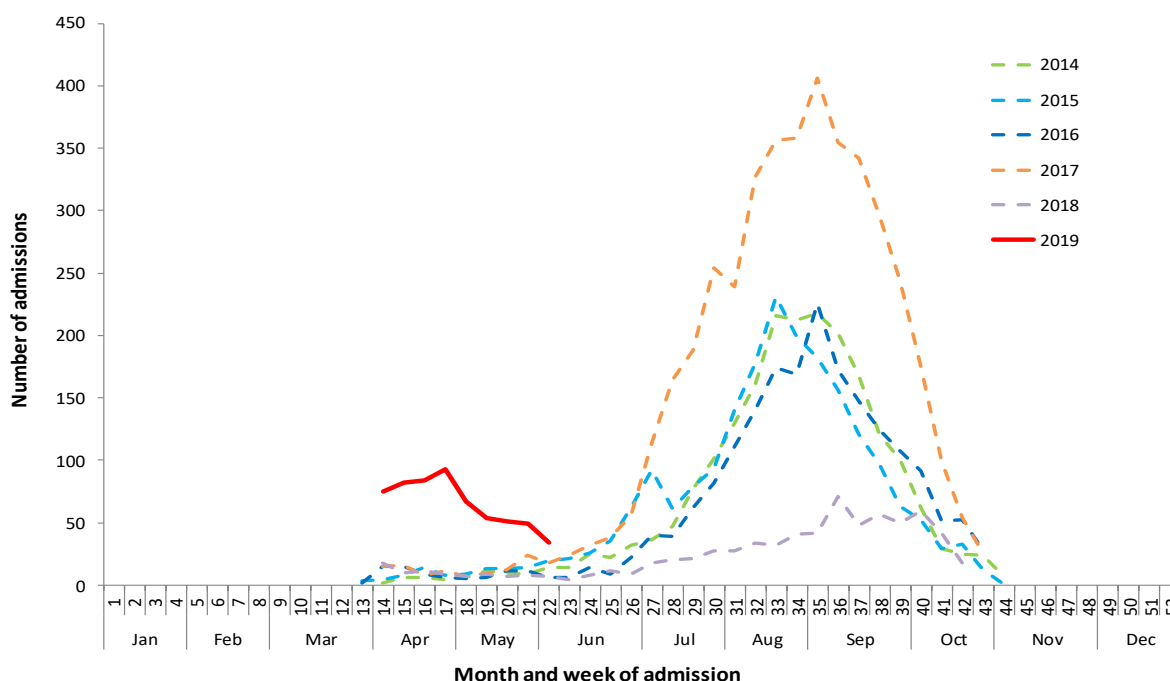


Source: NDSS (2019), Active Influenza Surveillance Report No.3, 2019, Figure 5, p5.
[https://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-ozflu-flucurr.htm/\\$File/flu-03-2019.pdf](https://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-ozflu-flucurr.htm/$File/flu-03-2019.pdf)

- 4.4 The ESC also noted the number of influenza hospitalisations in 2019 has been reducing, possibly as a result of immunisation with aTIV and other NIP vaccines commencing from mid-late April (see Figure 2).

¹ Department of Health (March 2019), 2019 influenza vaccines – Statement from the Chief Medical Officer, <https://beta.health.gov.au/news/2019-influenza-vaccines>

Figure 2: Number of influenza hospitalisations at sentinel hospitals, between March and October, 2014 to 2019 by month and week.



Source: NDSS (2019), Active Influenza Surveillance Report No.3, 2019, Figure 6, p5.
[https://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-ozflu-flucurr.htm/\\$File/flu-03-2019.pdf](https://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-ozflu-flucurr.htm/$File/flu-03-2019.pdf)

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

5 Comparator

aTIV (Fluad) compared to QIV

5.1 The submission nominated three QIVs (Afluria Quad, FluQuadri, Fluarix Tetra) as the main comparators to aTIV (Fluad). The QIVs represent existing standard care available on the NIP.

aQIV (Fluad Quad) compared to aTIV (Fluad)

5.2 The submission nominated aTIV (Fluad) as the main comparator to aQIV (Fluad Quad). The main arguments provided in support of this nomination were that aTIV is the next-best alternative therapy on the NIP to the aQIV for the proposed population.

5.3 The PBAC also considered non-adjuvanted QIV to be a relevant comparator for aQIV.

Both comparisons

5.4 The submission also noted that non-adjuvanted trivalent influenza vaccine, high-dose (TIV-HD, Fluzone) vaccine is a potential near market comparator. While there is no TIV-HD listed on the NIP in 2019, a resubmission of a previously rejected submission for a price increase may be reasonably expected in the near future.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

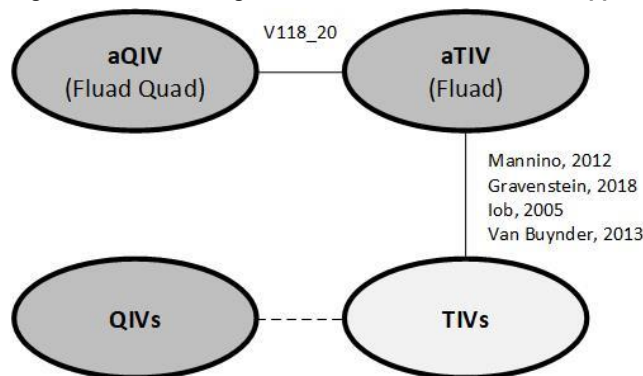
Consumer comments

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

Clinical trials

6.3 The multi-step chain-of-evidence logic and structure of the evidence to support the clinical claims is illustrated in Figure 3.

Figure 3: Network diagram of the studies included to support the clinical claims



aQIV: adjuvanted quadrivalent influenza vaccine; aTIV: adjuvanted trivalent influenza vaccine; QIV: quadrivalent influenza vaccine (non-adjuvanted); TIV: trivalent influenza vaccine (non-adjuvanted)
Source: Compiled during the evaluation

6.4 The sources of evidence that the submission presented as the basis of each clinical claim, is outlined in Table 2.

Table 2: Clinical claims and associated supporting evidence, presented within the submission

| Comparison | Claims | Evidence |
|--|--|---|
| <p>aTIV (Fluad) compared to QIV</p> | <p>Claim 1: aTIV (Fluad) compared to TIV "Fluad (aTIV) is superior to non-adjuvanted TIV in effectiveness against clinically relevant outcomes" (p93 of the submission). "Fluad is superior to TIV in preventing hospitalisations for influenza or pneumonia." (p46 of the submission), and that the submission ... "intends to quantify the magnitude" (p46 of the submission).</p> | <p>The submission draws on the below evidence:</p> <p>PBAC decision on aTIV - "The PBAC agreed with the ATAGI that there is sufficient evidence indicating aTIV is superior in effectiveness to non-adjuvanted trivalent inactivated vaccine (TIV) in some scenarios, particularly in seasons dominated by influenza A/H3 disease which accounts for a substantial burden in this age group" (PBAC, March 2018, Public Summary Document – Fluad, paragraph 7.4)</p> <p>ATAGI advice (p1 of the ATAGI November 2017 pre-submission advice; p1 of the ATAGI February 2019 pre-submission advice).</p> <p>The submission presented 1 observational study comparing aTIV (Fluad) to TIV (n=107,661): LIVE study (Mannino 2012; and Villa 2013).</p> <p>The submission presented 3 supportive observational studies (not used in the economic analysis)</p> <ul style="list-style-type: none"> • Iob et al., 2005, comparing aTIV (Fluad) to TIV (N=3,173) • Van Buynder et al., 2013, comparing aTIV (Fluad) to TIV (N=282) • Gravenstein et al., 2018, comparing aTIV (Fluad) to TIV (N=54,076) |

| Comparison | Claims | Evidence |
|--|--|--|
| | <p>Claim 2: aTIV (Fluad) compared to QIVs (Afluria Quad, FluQuadri and Fluarix Tetra)</p> <p>The submission proposed a range of alternative claims.</p> <p>“The superiority claim [of aTIV over TIV] is proposed to extend to non-adjuvanted QIV where there is a strain match” (Figure 2.1, p46 of the submission).</p> <p>“Fluad (aTIV) is non-inferior to QIV in immunogenicity measures for A/H1N1, A/H3N2 and the <u>included</u> B strain; with the majority of outcomes statistically in favour of Fluad over QIV, including seroconversion against A/H1N1 and A/H3N2” (p93 of the submission)</p> <p>“Fluad (aTIV) is at least as effective as QIV, whereby the additional protection afforded by Fluad against the strains in the vaccine is substantial enough to offset the potential loss of protection against the alternative B strain not in the vaccine” (p93 of the submission).</p> | <p>The submission draws on the below evidence:</p> <p>PBAC decision on aTIV “The PBAC accepted the ATAGI advice that aTIV is non-inferior overall to QIV for the prevention of seasonal influenza in adults aged ≥65 years” (PBAC, March 2018, Public Summary Document – Fluad, paragraph 7.3); and that “The PBAC agreed with the ATAGI that the potential additional protection afforded by aTIV against the strains included in the vaccine is substantial enough to offset, if not outweigh, the potential loss of protection against the alternative B lineage not in the vaccine, in most years, for adults aged ≥65 years” (PBAC, March 2018, Public Summary Document – Fluad, paragraph 7.5).</p> <p>ATAGI advice (p1 of the ATAGI November 2017 pre-submission advice; p1 of the ATAGI February 2019 pre-submission advice).</p> <p>No additional evidence was presented to support this claim.</p> |
| <p>aQIV (Fluad Quad) compared to aTIV (Fluad)</p> | <p>Claim 3: aQIV (Fluad Quad) compared to aTIV (Fluad)</p> <p>“Fluad Quad (aQIV) is non-inferior to Fluad (aTIV) in immunogenicity measures for A/H1N1, A/H3N2 and the included B/ Victoria and B/Yamagata strains” (p93 of the submission)</p> | <p>1 head-to-head immunogenicity RCT comparing aQIV to aTIV (N=1,778): V118_20</p> |
| <p>Additional overarching claim</p> | <p>Claim 4: aQIV (Fluad Quad) compared to QIVs (Afluria Quad, FluQuadri and Fluarix Tetra)</p> <p>“By extension, Fluad Quad (aQIV) is superior to non-adjuvanted QIV in effectiveness against clinically relevant outcomes” (p93 of the submission)</p> | <p>No head-to-head, nor indirect comparisons were presented to support this claim.</p> |

aTIV: adjuvanted trivalent influenza vaccine; TIV: trivalent influenza vaccine (non-adjuvanted); aQIV: adjuvanted quadrivalent influenza vaccine; QIV: quadrivalent influenza vaccine (non-adjuvanted); PBAC: The Pharmaceutical Benefits Advisory Committee; ATAGI: The Australian Technical Advisory Group on Immunisation
 Source: Compiled for the evaluation, based on Table 2-7, p. 53; and Figure 2.1, p46 of the submission

6.5 The clinical evidence that was included in the March 2018 minor submission was not re-presented within this submission. The pivotal evidence, trial V118_20 and

supportive evidence from Gravenstein (2018), were new to the major submission. The submission also presented the results from the LIVE study (Mannino 2012), Iob (2005), Van Buynder (2013), Domnich (2017), Lapi et al. (unpublished), and Izurieta et al. (2018) as additional evidence.

6.6 In March 2018, as a minor submission, no clinical trial evidence was evaluated by the PBAC Secretariat. Both the Therapeutic Goods Administration (TGA) and ATAGI considered the clinical evidence for aTIV (PBAC, March 2018, Public Summary Document – Fluad, paragraph 6.3).

6.7 Details of the trials presented in the submission are provided in Table 3.

Table 3: Trials and associated reports identified through the literature search

| Trial ID | Protocol title/ Publication title | Publication citation |
|--|---|--|
| Studies not previously considered in March 2018 | | |
| Gravenstein, 2018 | Gravenstein et al., A cluster-randomised trial of adjuvanted trivalent influenza vaccine versus non-adjuvanted in US nursing homes. | Unpublished IDWeek Abstract 996, 2018 Interim report dated 2019, (Abstract and conference presentation slides) |
| V118_20 | A Phase 3, Randomized, Double-Blind, Controlled, Multicenter, Clinical Study to Evaluate Safety and Immunogenicity of an MF59-Adjuvanted Quadrivalent Subunit Influenza Vaccine in Comparison With an MF59-Adjuvanted Trivalent Subunit Influenza Vaccine and an MF59-Adjuvanted Trivalent Subunit Influenza Vaccine Containing the Alternate B Strain, in Adults Aged 65 Years and Above | Unpublished Clinical Study Report for V118_20, dated 31 October 2018 |
| Studies previously considered in March 2018 | | |
| LIVE study | Mannino et al., Effectiveness of adjuvanted influenza vaccination in elderly subjects in northern Italy Villa et al., Safety of MF59-Adjuvanted influenza vaccination in the elderly: Results of a comparative study of MF59-Adjuvanted vaccine versus nonadjuvanted influenza vaccine in northern Italy ^ | Am J Epidemiol. 2012; 176(6):527-533 Am J Epidemiol. 2013; 178(7):1139-1145 |
| Iob, 2005 | Iob A. et al., Evidence of increased clinical protection of an MF59-adjuvant influenza vaccine compared to a non-adjuvant vaccine among elderly residents of long-term care facilities in Italy | Epidemiol. Infect. 2005; 133:687-693 |
| Van Buynder, 2013 | Van Buynder et al., The comparative effectiveness of adjuvanted and unadjuvanted trivalent influenza vaccine (TIV) in the elderly | Vaccine 2013; 31:6122-6128 |
| Domnich, 2017 * | Domnich, A. Effectiveness of MF59-adjuvanted seasonal influenza vaccine in the elderly: A systematic review and meta-analysis | Vaccine 2017; 35(4), 513-520. |
| Studies also presented as evidence (not previously considered in March 2018)* | | |
| Lapi, (unpublished) * | (unpublished) | Citation not included in submission |
| Izurieta, 2018 * | Izurieta, H.S. et al., Relative effectiveness of cell-cultured and egg-based influenza vaccines among elderly persons in the United States, 2017-2018 | The Journal of Infectious Diseases 2018; [Epub ahead of print] |

^ While outputs from the LIVE study were previously reported in the minor submission considered in March 2018, the results

within Villa et al. have not been previously referenced.

* The outcomes of these studies could not be validated during evaluation.

Source: Compiled for the evaluation, based on Table 2-4 and 2-6, p49 and p51, and p71-73 of the submission.

6.8 The key features of the included trials are summarised in Table 4.

Table 4: Key features of the included evidence

| Trial | Number of participants | Design/ duration | Risk of bias | Patient population | Outcome(s) | Use in modelled evaluation |
|---|------------------------|------------------|-----------------------|--|--|----------------------------|
| aTIV (Fluad) compared to TIV | | | | | | |
| LIVE study (Mannino 2012; Villa, 2013) | N=107,661 | 3 years | Moderate ¹ | Healthy adults aged ≥65 years | Hospitalisations for influenza or pneumonia | Used |
| Gravenstein | N=54,076 | NA | Not assessed | Nursing home residents | Hospital admissions related to pulmonary and influenza-like illness | Not used |
| Iob | N=3,173 | 4 months | Not assessed | Long-term care residents | Influenza-like illness | Not used |
| Van Buynder | N=282 | 4 months | Not assessed | Adults aged ≥ 65 years, who had been tested for influenza | Laboratory confirmed influenza | Not used |
| Lapi (unpublished) | Could not be verified | | | | | Not used |
| Izurieta et al., | N=13 million | 1 year | Not assessed | Medicare (US) Beneficiaries of influenza vaccines | Influenza-related hospital encounters | Not used |
| Systematic Reviews & Meta Analyses | | | | | | |
| Domnich et al., 2016 | NA | NA | Not assessed | NA | NA | Not used |
| aQIV (Fluad Quad) compared to aTIV (Fluad) | | | | | | |
| V118_20 | N=1,778 | Six months | Low | Adults aged ≥ 65 years who were healthy or had comorbidities and were able to attend all scheduled visits. | Immunogenicity through GMTR, SCR; and vaccine efficacy through CBER criteria | Not used |

aTIV: adjuvanted trivalent influenza vaccine; TIV: trivalent influenza vaccine (non-adjuvanted); aQIV: adjuvanted quadrivalent influenza vaccine; QIV: quadrivalent influenza vaccine (non-adjuvanted); CBER: Centre for Biologics Evaluation and Research; NA: Not available

¹ Assessed during evaluation

Source: Compiled for the evaluation based on Table 2-8, p54; and p66-73 of the submission

aTIV (Fluad) compared to QIV

6.9 The submission did not present any head-to-head RCTs comparing aTIV (Fluad) to QIV. Instead the submission presented a multi-stepped chain-of-evidence based on clinical studies/trials and previous PBAC recommendations.

6.10 The lack of head-to-head RCTs comparing aTIV (Fluad) to QIV, or formal indirect comparison of aTIV to QIV, significantly increased uncertainty in the validity of the presented clinical claims.

6.11 Risk of bias was not assessed within the submission for the observational studies. As such, the Risk of Bias in Non-randomised Studies - of Interventions (ROBINS-I)

assessment tool was employed during the evaluation of the pivotal evidence in the LIVE study (Mannino 2012). The overall risk of bias in the LIVE study (Mannino 2012) was rated as moderate due to non-randomisation of participants and non-blinding of the intervention for either administrators or recipients. Furthermore, adjustments for the presence of baseline confounders using propensity score matching resulted in 4% of observations excluded from the analysis.

aQIV (Fluad Quad) compared to aTIV (Fluad)

6.12 The submission presented one head-to-head RCT comparing aQIV (Fluad Quad) to aTIV (Trial V118_20). The risk of bias was considered to be low.

aQIV (Fluad Quad) compared to QIV

6.13 The submission did not present any head-to-head RCTs comparing aQIV (Fluad Quad) to QIV.

Comparative effectiveness

aTIV (Fluad) compared to QIV

6.14 The results of the LIVE study (Mannino 2012) are presented in Tables 5 and 6, and the time windows defined by influenza incidence/1,000 person-weeks is in Figure 4.

Table 5: Hospitalisations for influenza and pneumonia (cases) and person-seasons at risk by age and vaccine type, within the narrowest time window in the study population in the LIVE study (Mannino 2012), unadjusted for confounders

| Age, years | Fluad (aTIV) | | TIV | |
|------------|----------------|---|----------------|---|
| | Person seasons | Cases, no. [Influenza/Pneumonia Hospitalisations] | Person seasons | Cases, no. [Influenza/Pneumonia Hospitalisations] |
| 65-69 | 14,903 | 10 | 18,230 | 9 |
| 70-74 | 21,071 | 18 | 23,414 | 27 |
| 75-79 | 21,945 | 20 | 18,535 | 22 |
| 80-84 | 16,758 | 35 | 12,319 | 25 |
| > 85 | 9,988 | 31 | 7,091 | 28 |
| Total | 84,665 | 114 | 79,589 | 111 |

aTIV: adjuvanted trivalent inactivated vaccine; CI: confidence interval; TIV: trivalent inactivated vaccine.

Source: Table 2-19, p66 of the submission

Table 6: Vaccine efficacy against hospitalisations for influenza and pneumonia of aTIV versus TIV by time window during the influenza season in the study population, Lombardy, Italy, 2006-2009 in the LIVE study (Mannino 2012), adjusted for confounders^c

| Time Window ^a | Adjusted Odds Ratio ^b | 95% CI |
|--------------------------|----------------------------------|------------|
| Broad | 0.88 | 0.79, 1.02 |
| Intermediate | 0.83 | 0.68, 1.03 |
| Narrow | 0.75 | 0.57, 0.98 |

aTIV: adjuvanted trivalent inactivated vaccine; CI: confidence interval; TIV: trivalent inactivated vaccine.

^a Time Windows were defined on the basis of the intensity of the influenza activity combined for 3 years: broad (the sum of the 3 influenza seasons); intermediate (the period of adjacent weeks having an influenza rate of >0.5 case per 1,000 person-weeks); and narrow (the period of adjacent weeks having an influenza rate of >1 case per 1,000 person-weeks).

^b Mannino 2012 estimate the adjusted vaccine efficacy using a logistic regression model and call these odds ratios within the tables. However, the accompanying text of Mannino 2012 refers to all non-adjusted and adjusted results as risk ratios. Due to low risk of hospitalisation, the odds ratios and risk ratios are similar, however this is a potential source of confusion.

^c Confounders: age, sex, influenza season, community and provider, physical impairment, cumulative length of stay in the hospital and cumulative number of drug prescriptions in the 5 years preceding the vaccination, history of hospitalization for pneumonia, influenza or emphysema, COPD, chronic kidney disease, diabetes, recent infectious disease, and recent transfusion.

Source: Mannino 2012

Figure 4: Time windows in Lombardy, Italy 2006–2009 in the LIVE study (Mannino 2012).

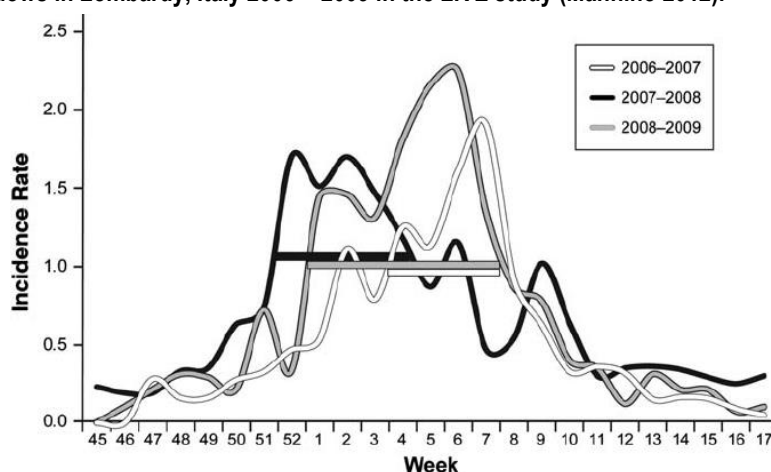


Figure 1. Time windows defined by the influenza incidence/1,000 person-weeks in Lombardy, Italy, 2006–2009. The intermediate time window includes adjacent weeks above the threshold of 0.5 case/1,000 person-weeks each year. Bars represent narrow time windows with a cumulative incidence of influenza rate of 1 case/1,000 person-weeks.

Source: Mannino 2012

6.15 Vaccine effectiveness against hospitalisations in Table 6 was greater after adjusting for cohort differences at baseline and using a narrow time window (adjusted odds ratio (OR), narrowest window: 0.75 (95%CI: 0.57, 0.98). The ESC considered adjusting for cohort differences at baseline using a propensity score as a summary confounder in the logistic regression was appropriate. However, a number of variables used in the derivation of the propensity score also appear to have been used as separate explanatory variables in the multivariate model summarised in Table 3 of Maninno (2012, p531), from which the key aTIV vs TIV adjusted OR of 0.75 was derived; namely age, sex, season, community and provider, length of stay, number of drug prescriptions, historical hospitalisations and COPD. This is double handling (in effect adjusting for the same confounders twice) and may lead to errors, depending upon

the strength of their association with the outcome. As the upper limit of the confidence interval surrounding the OR of 0.75 is very close to the null (i.e. 0.98) then it is possible that a correctly executed model where each of these confounders is managed only once (whether as a component of the propensity score or as a standalone predictor) may result in an estimate of the true OR that overlaps the null and is thus not significant. No model without the double handling is available from the publication.

- 6.16 With regards to the narrow time window, ATAGI considered that the “lower vaccine effectiveness for broader influenza periods may be because of a greater proportion of the outcome (influenza and pneumonia hospitalisations) being due to non-influenza disease” (p5 of the ATAGI February 2019 pre-submission advice). The evaluation noted that while the *a priori* focus on a narrow time window would improve the specificity of the analyses, the study did not test nor discuss the impact of alternative time windows on relevant hospitalisations. This is particularly relevant, given the low number of cases (hospitalisations) involved. The ESC and ATAGI agreed that sensitivity analyses should have applied a wide range of values of relative effectiveness (p3 of the ATAGI February 2019 pre-submission advice). At a minimum, the ESC considered an assessment of the cost-effectiveness using the intermediate time window results of 17% relative effectiveness would be informative. The Pre-PBAC Response (P2-3) accepted the ESC proposal and provided revised ICERs incorporating a lower VE of 17%.
- 6.17 The ESC also noted the reduced applicability of the Maninno (2012) study to the Australian population given the exclusion of patients in residential aged care facilities from the study.
- 6.18 The submission did not present evidence on vaccine effectiveness against mortality.

aQIV compared to aTIV (Fluad)

- 6.19 The immunogenicity results from trial V118_20 are presented in Tables 7 and 8.

Table 7: Trial V118_20 GMTs and vaccine group ratios (GMTR) for each strain Day 22 post-vaccination in adults aged ≥ 65 years, non-inferiority analysis (per protocol set)

| Strain Assessment | GMT Day 22 | | | | GMTR aTIV / aQIV (95%CI) ² |
|-------------------|------------|--------|--------|-------------|--|
| | aQIV | aTIV-1 | aTIV-2 | aTIV pooled | |
| N ¹ | | | | | |
| A/H1N1 | | | | | |
| A/H3N2 | | | | | |
| B/ Yamagata | | | | | |
| B/ Victoria | | | | | |

CI: confidence interval; GMT: geometric mean titre; GMTR: geometric mean titre ratio; aQIV: adjuvanted quadrivalent influenza vaccine; aTIV: adjuvanted trivalent influenza vaccine



Source: Table 2-22, p74 of the submission

Table 8: Trial V118_20 SCRs and vaccine group differences, non-inferiority analysis (per protocol set)

| Strain Assessment | SCR % (95%CI) ¹ | | | SCR difference aTIV - aQIV (95%CI) ² |
|-------------------|----------------------------|---------------------|---------------------|---|
| | aQIV | aTIV-1 ³ | aTIV-2 ³ | |
| N | | | | |
| A/H1N1 | | | | |
| A/H3N2 | | | | |
| B/ Yamagata | | | | |
| B/ Victoria | | | | |

CI: confidence interval; SCR: seroconversion rate; aQIV: adjuvanted quadrivalent influenza vaccine; aTIV: adjuvanted trivalent influenza vaccine



Source: Table 2-23, p75 of the submission

- 6.20 In the comparison of aTIV and aQIV, the pre-specified, non-inferiority criterion for the adjusted geometric mean titre (GMT) ratio was met for all four homologous strains. This was demonstrated as the upper bounds of the two-sided 95% confidence interval (CI) for the adjusted GMT ratios (aTIV/aQIV) did not exceed 1.5 (upper limit of GMTR 95%CI in bold in Table 7).
- 6.21 The pre-specified non-inferiority criterion for the difference in the seroconversion rate (SCR) between aTIV and aQIV was met for all four homologous strains. The upper bounds of the 95% CI of the intergroup difference for SCR (aTIV minus aQIV) did not exceed the non-inferiority margin of 10% for all four strains (upper limit of SCR difference 95%CI in bold in Table 8). The results for the Full Analysis Set were comparable to the Per Protocol Set with the non-inferiority criterion for the difference in SCR between aTIV and aQIV groups met for all four homologous strains.
- 6.22 The submission also compared SCR results to the Centre for Biologics Evaluation and Research (CBER) criteria. While the CBER criteria² were met by aTIV and aQIV for both A strains, this was not the case for either of the B strains. Neither aTIV nor aQIV demonstrated adequate immunogenicity based on the CBER criteria, and SCR and hemagglutination inhibition (HI) titres were similar across the vaccine groups (p74 of the submission).
- 6.23 The submission did not present a comparison of the GMT or SCR for the influenza B strains not in common between aQIV and aTIV. The pre-sub-committee-response (PSCR, p3) provided results for the analyses of aQIV relative to aTIV for the alternate B strain (Full Analysis Set), as presented in the table below.

² Success criteria was met if the lower limit of the two-sided 95% CI for the percentage of subjects achieving SCR for HI antibody met or exceeded $\geq 30\%$ AND the lower limit of the two-sided 95% CI for the percentage of subjects achieving an HI antibody titre $\geq 1:40$ was $\geq 60\%$.

Table 9: Analyses of aQIV relative to aTIV for the alternate B Strain (Full Analysis Set)

| Strain | Comparator aTIV group | GMT ratios aTIV/aQIV (95% CI) | Met pre-defined superiority criteria for GMT ratio? | SCR (%) difference aTIV-aQIV (95% CI) | Met pre-defined superiority criteria for SCR difference? |
|------------|-----------------------|-------------------------------|---|---------------------------------------|--|
| B-Yamagata | | | | | |
| B-Victoria | | | | | |

CI = confidence interval; GMT = geometric mean titre; HI = haemagglutination inhibition; SCR = seroconversion rate.

Source: Table 12, V112_20 Clinical Study Report; PSCR, Table 2, p3.

6.24 The Evaluation noted it is unclear whether the GMT and SCR immunogenicity results translate to non-inferiority in terms of influenza cases, hospitalisations and mortality.

6.25 ATAGI noted in its presubmission advice, that ... “the greatest advantage of QIV over TIV is likely to be in infants and children, who have had less exposure to influenza B, compared to the elderly” (p8 of the ATAGI February 2019 pre-submission advice).

Comparative harms

aTIV (Fluad) compared to QIV

6.26 The safety outcomes from the LIVE study (Villa 2013) comparing aTIV (Fluad) to TIV are presented in Table 10.

Table 10: Numbers of ‘definite’, ‘probable’ and ‘possible’ cases of adverse events of special interest arising during 6-month time window following vaccination (aged > 65 years, secondary analysis)

| Outcome | TIV (n=82,539) | | Fluad (aTIV) (n=88,449) | | Difference Risk (95% CI) ¹ |
|---------------------------------|----------------|----------------------------|-------------------------|----------------------------|---------------------------------------|
| | n | Risk (95% CI) ¹ | n | Risk (95% CI) ¹ | |
| Anaphylaxis | 0 | 0.00 (0.00, 4.47) | 1 | 1.13 (0.00, 6.30) | 1.13 (-1.09, 3.35) |
| Autoimmune hepatitis | 0 | 0.00 (0.00, 4.47) | 0 | 0.00 (0.00, 4.17) | 0.00 (N/A) |
| Bell’s palsy | 1 | 1.21 (0.03, 6.75) | 2 | 2.26 (0.27, 8.17) | 1.05 (-2.88, 4.98) |
| Convulsions | 41 | 49.67 (35.65, 67.39) | 39 | 44.09 (31.36, 60.27) | -5.58 (-26.12, 14.97) |
| Demyelinating disorders | 0 | 0.00 (0.00, 4.47) | 0 | 0.00 (0.00, 4.17) | 0.00 (N/A) |
| Encephalitis | 1 | 1.21 (0.03, 6.75) | 0 | 0.00 (0.00, 4.17) | -1.21 (-3.59, 1.16) |
| Guillain-Barre syndrome | 4 | 4.85 (1.32, 12.41) | 1 | 1.13 (0.03, 6.30) | -3.72 (-8.96, 1.53) |
| Immune thrombocytopenic purpura | 1 | 1.21 (0.03, 6.75) | 3 | 3.39 (0.70, 9.91) | 2.18 (-2.33, 6.69) |
| Vasculitis | 1 | 1.21 (0.03, 6.75) | 5 | 5.65 (1.84, 13.19) | 4.44 (-1.05, 9.94) |

CI: confidence interval; N/A: not available; TIV: trivalent inactivated vaccine

¹ Cumulative incidence (number of cases per 100,000 persons).

Source: Table 2-28, p80 of the submission.

6.27 The submission stated that hospitalisation for any Adverse Events of Special Interest (AESI), except for convulsion, was rare in both groups. Risk of an AESI were similar for

aTIV and TIV. Overall, there was no indication that receipt of aTIV (Fluad) was associated with an increased risk of any AESI.

6.28 ATAGI has previously reported that they “... did not have major concerns regarding the safety of aTIV” (PBAC, March 2018, Public Summary Document – Fluad, paragraph 6.17).

aQIV compared to aTIV (Fluad)

6.29 Table 11, presents an overview of the unsolicited events reported in trial V118_20 comparing aQIV (Fluad Quad) to aTIV (Fluad).

Table 11: Overall summary of unsolicited adverse events (overall safety set)

| | Fluad Quad (aQIV) n (%) | Fluad (aTIV) n (%) | aTIV-2 n (%) |
|---|----------------------------|-----------------------|-----------------|
| Exposed ¹ | | | |
| Subjects with any unsolicited TEAE ² | | | |
| Days 1-22 | | | |
| Days 23-181 | | | |
| Days 1-181 | | | |
| Related unsolicited AEs (Days 1-181) ³ | | | |
| Unsolicited AEs (Days 1-181), by severity | | | |
| Mild | | | |
| Moderate | | | |
| Severe | | | |
| AEs leading to study discontinuation | | | |
| Serious adverse events (SAEs) | | | |
| Related SAEs | | | |
| Deaths | | | |
| Adverse events of special interest (AESI) | | | |
| Related AESIs | | | |
| AEs causing new onset chronic disease | | | |
| Medically-attended AEs ⁴ | | | |

AEs: adverse events; AESI: adverse events of special interest; SAE: serious adverse event; TEAE: treatment-emergent adverse event

[REDACTED]

Source: Table 2-31, p84 of the submission

6.30

[REDACTED] No serious adverse events

were assessed as related to the study vaccines. No imbalance in frequency of serious adverse events was observed between the study groups.

Benefits/harms

aTIV (Fluad) compared to QIV

6.31 The multi-stepped chain-of-evidence presented in the submission did not allow for a quantitative comparison of the benefits and harms of aTIV and QIV. However, a summary of the comparative benefits and harms for aTIV versus TIV is presented in Table 12.

Table 12: Summary of comparative benefits and harms for aTIV (Fluad) and TIV

| Trial | aTIV (Fluad) n/N (unadjusted) | TIV n/N (unadjusted) | OR [^] (95% CI) (adjusted) |
|-----------------------------------|----------------------------------|-------------------------|--|
| Influenza hospitalisations | | | |
| LIVE study (Mannino 2012) | 114/84,665 | 111/79,589 | 0.75 (0.57, 0.98) |

[^] Results were adjusted through the excluding incidences from the analyses for individuals with high propensity scores; and through multivariate models to account for confounding from age, sex, influenza season, community and provider, physical impairment, cumulative length of stay in the hospital and cumulative number of drug prescriptions in the 5 years preceding the vaccination, history of hospitalization for pneumonia, influenza or emphysema, COPD, chronic kidney disease, diabetes, recent infectious disease, and recent transfusion.

* Maximum duration of follow-up: Trial I = 16 weeks, over three years (Yr1: 4 weeks; Yr2: 5 weeks; Yr3: 7 weeks)

OR= odds ratio;

Source: Table 2-19, p66 of the submission and Mannino 2012

6.32 On the basis of direct evidence presented by the submission, for every 10,000 patients vaccinated with aTIV (Fluad) in comparison to TIV:

- Approximately 4 fewer patients would experience an influenza or pneumonia associated hospitalisation.
- No additional patients would experience an adverse event.

6.33 Based on non-inferiority of aQIV to aTIV, the PBAC considered that it was reasonable to assume that the same benefit presented above would apply to aQIV (Fluad Quad) compared to QIV.

6.34 The PBAC noted that the benefits and harms table had been developed using the 25% assumed VE and not the 17% VE used in the Pre-PBAC Response modelling.

Clinical claim

aTIV (Fluad) compared to QIV

6.35 The submission claimed that:

- "Fluad (aTIV) is superior to non-adjuvanted TIV in effectiveness against clinically relevant outcomes" (p93 of the submission).

- “The superiority claim [of aTIV over TIV] is proposed to extend to non-adjuvanted QIV where there is a strain match” (Figure 2.1, p46 of the submission).
- 6.36 The PBAC previously agreed with the ATAGI that “there is sufficient evidence indicating aTIV is superior in effectiveness to non-adjuvanted trivalent inactivated vaccine (TIV) in some scenarios, particularly in seasons dominated by influenza A/H3 disease which accounts for a substantial burden in this age group” (PBAC, March 2018, Public Summary Document – Flud, paragraph 7.4).
- 6.37 The ESC considered that the magnitude of effectiveness of aTIV compared to TIV was uncertain:
- The key clinical evidence presented was a non-randomised, non-blinded observational study comparing aTIV to TIV which was considered to have a moderate risk of bias (LIVE study, Mannino 2012).
 - The primary outcome was hospitalisations for influenza and pneumonia. The presence of influenza was not necessarily laboratory confirmed.
 - Vaccine effectiveness against hospitalisations was adjusted for the presence of baseline confounders using propensity score matching, which resulted in 4% of observations excluded from the analysis.
 - Vaccine effectiveness against hospitalisations was greater after adjusting for cohort differences at baseline and using a narrow time window (adjusted odds ratio, narrowest window: 0.75 (95%CI: 0.57, 0.98)). A number of variables used in the derivation of the propensity scores appeared to have also been used as explanatory variables in the multivariate model, and removal of this double handling may result in an estimate of the true OR that overlaps the null.
- 6.38 There was no data to support estimates of vaccine effectiveness against influenza cases or mortality.
- 6.39 The submission did not provide direct evidence or a formal indirect comparison of aTIV (Flud) to QIV. The submission relied on the previous PBAC recommendation in March 2018 that “the PBAC accepted the ATAGI advice that aTIV is non-inferior overall to QIV for the prevention of seasonal influenza in adults aged ≥ 65 years” and that “the PBAC agreed with the ATAGI that the potential additional protection afforded by aTIV against the strains included in the vaccine is substantial enough to offset, if not outweigh, the potential loss of protection against the alternative B lineage not in the vaccine, in most years, for adults aged ≥ 65 years”.
- 6.40 The magnitude of effectiveness of aTIV (Flud) to QIV is uncertain as no head-to-head RCTs or formal indirect comparison was presented comparing aTIV (Flud) to QIV. Furthermore, the extent to which the benefits of aTIV (Flud) outweighed the

potential loss of protection against the mismatched B strain in QIV in a given year is uncertain given year-to-year variability in influenza.

- 6.41 The Pre-sub-committee response (p5) highlighted that the PBAC raised this issue in the context of an application requesting listing for a trivalent influenza vaccine (TIV-HD) compared to a quadrivalent vaccine (QIV). The sponsor considered that in the context of the current submission's request for a quadrivalent vaccine (aQIV), the issue of the uncertainty of a mismatched B strain is eliminated.
- 6.42 The PBAC considered that the claim of superior comparative effectiveness of aTIV over QIV was highly uncertain and not adequately supported by the data. The PBAC accepted the superiority of aTIV over TIV, however, the magnitude of the benefit was uncertain.

aQIV (Fluad Quad) compared to aTIV (Fluad)

- 6.43 The submission claimed that "Fluad Quad (aQIV) is non-inferior to Fluad (aTIV) in immunogenicity measures for A/H1N1, A/H3N2 and the included B/ Victoria and B/Yamagata strains" (p93 of the submission).
- 6.44 The magnitude of benefit is uncertain as the V118_20 trial reported vaccine effectiveness in terms of immunogenicity outcomes (GMTs and SCRs), rather than influenza cases avoided. As such, the magnitude of aQIV effectiveness in terms of influenza cases or hospitalisations avoided is unknown.
- 6.45 The results presented in V118_20 for the Centre for Biologics Evaluation and Research (CBER) test of immunogenicity indicates that uncertainties remain as to whether the aQIV provide the desired immune response against B lineages. There was no investigation within the presented results of the impact of cross-seroprotection or natural immunity against the B lineages. ATAGI post-submission advice (p2) (received after ESC consideration) noted that use of immunogenicity data to assess non-inferiority in the absence of VE data or a direct comparison was acceptable, in line with standard practice of the US FDA.
- 6.46 ATAGI post-submission advice (p1), advised that ATAGI considered aQIV to be at least non-inferior to aTIV based on immunogenicity data from the single pivotal phase 3 trial undertaken over a single season which demonstrated non-inferiority of aQIV to aTIV and another aTIV containing the alternative B strain in the first aTIV. ATAGI noted this study found aQIV superior to aTIV for the B strain not included in each aTIV.
- 6.47 The PBAC considered aQIV was at least non-inferior to aTIV.

aQIV (Fluad Quad) compared to QIV

- 6.48 The submission also claimed that: "By extension, Fluad Quad (aQIV) is superior to non-adjuvanted QIV in effectiveness against clinically relevant outcomes" (p93 of the submission)

- 6.49 The therapeutic conclusions presented in the submission for aQIV (Fluad Quad) over QIV, were not directly supported by the evidence presented. There were no head-to-head RCTs, nor formal indirect comparisons presented.
- 6.50 The PBAC considered that the evidence of superior benefit for aTIV versus TIV could be extrapolated to similarly apply to aQIV versus QIV.

Economic analysis

aTIV (Fluad) compared to QIV

- 6.51 The submission presented a cost-utility analysis, comparing aTIV (Fluad) to QIVs.
- 6.52 The economic evaluation was presented to support a price premium. A static Markov model was developed to estimate the health benefits for an Australian population cohort aged 65 years, over a 35-year time horizon. Herd immunity was not included.

Table 13: Summary of model structure and rationale

| Component | Summary |
|----------------------------------|--|
| Time horizon | 35 years in the model base case. The evaluation noted that applying a one-year time horizon is a more typical approach as influenza vaccination benefits are likely to be limited to a single season, due to waning antibody levels and antigenic drift. The submission did not assume that vaccine efficacy lasts more than one year. However, the submission applied a modelling approach where the expected utilities over the lifetime of the patient had they not died were estimated per year and then summed over 35 years, rather than estimating the expected total QALYs lost per death (discounted) in the year that the death occurred. The ICER is sensitive to changing the time horizon to 1 year and changing the modelling approach such that the estimating the expected total QALYs lost per death (discounted) in the year that the death occurred is applied. In this case, the ICER is only dominant for patients 75 years or older. |
| Outcomes | Quality-adjusted life years, influenza cases avoided, influenza-attributable mortality |
| Methods used to generate results | Static Markov cohort model |
| Health states | <ul style="list-style-type: none"> • Vaccinated individual remains healthy (i.e., free of influenza) • Vaccinated individual develops influenza at some point during the year, presenting as an outpatient • Vaccinated individual develops influenza at some point during the year, presenting as an inpatient • Vaccinated individual dies from influenza infection • Vaccinated individual dies from other causes. <p>These health states are appropriate. Similar health states are commonly used in modelling of influenza vaccines.</p> <p>Most QALY benefits were gained by reducing inpatient influenza cases and hence reducing the number of days with the disutility associated with inpatient influenza. There were no QALY gains in the originally submitted model from influenza related deaths (the PSCR introduced a mortality benefit claim).</p> |
| Cycle length | One year |
| Transition probabilities | <p><u>Incidence of influenza</u></p> <p>National Notifiable Diseases Surveillance System (NNDSS) data were used to estimate the incidence of influenza in Australia. A five-year average was calculated based on NNDSS data for patients 65 years or older, and the 2017 influenza season increased the average. It is unclear whether 2017 was the peak of the influenza cycle and the incidence would return to lower levels in future years.</p> <p>Population estimates were sourced from the Australian Bureau of Statistics (ABS), and data were stratified by outpatient cases and inpatient cases using estimates from the published literature (Newall et al., 2008).</p> |

| Component | Summary |
|-----------|---|
| | <p><u>Vaccine effectiveness</u></p> <p>The observational LIVE study (Mannino 2012) was used to model the vaccine effectiveness on hospitalisations. This data showed that the risk of hospitalisation for influenza or pneumonia was 25% lower for aTIV (Fluad) relative to TIV (relative risk = 0.75, 95% confidence interval: 0.57-0.98). No difference in effectiveness was applied to mortality or to outpatient cases of influenza. The PSCR (pp3–4) adjusted the model to include a mortality benefit equivalent to the relative benefit of hospitalisations (i.e. a 25% improvement).</p> <p>There are some substantial uncertainties with regards to vaccine efficacy applied in the model. While the model compared aTIV (Fluad) to QIV, the LIVE study (Mannino 2012) compared the effectiveness of aTIV (Fluad) to TIV. ATAGI noted that the LIVE study results were appropriate to be applied to the base case of an economic model comparing the relative effectiveness of aTIV (Fluad) over TIV, in preventing hospitalisation for influenza or pneumonia. The application to the base case of an economic model comparing aTIV to QIV is questionable as it was not demonstrated to what extent influenza cases caused by the additional type B strain would be avoided with QIV. ATAGI also noted that a wide range of other estimates should be applied in sensitivity analyses given the substantial uncertainties associated with this estimate (p7 of the ATAGI February 2019 pre-submission advice).</p> |
| | <p><u>Mortality risk</u></p> <p>Data from Newall et al., (2010) was applied to estimate the influenza-attributable disease burden. The model assumed that influenza-related deaths arise only from inpatient cases. All-cause mortality rates were sourced from Australian Bureau of Statistics (ABS 2018).</p> |
| | <p><u>Utility weights</u></p> <p>The submission sourced the utility weights from a targeted literature review. The submission assumed a baseline utility of 1, for individuals not suffering from an influenza infection. Disutilities for the health states outpatient and inpatient influenza were sourced from Meier et al., 2015, as was the duration spent in these health states.</p> <p>The studies used to estimate utilities associated with influenza were of poor quality limiting the applicability to the Australian setting and this economic evaluation. The studies had small sample sizes, assessed a limited number of strains and had poor methods for eliciting patient preferences.</p> <p>The submission assumed that those over 65 would have a baseline utility of 1, which is equivalent to perfect health. It is more likely that the NIP eligible population would have a baseline utility value of approximately 0.8 (Clemens 2014). This is not appropriate and favours aTIV.</p> |

Source: Table 3.1, p95 of the submission.

6.53 Key drivers of the model are presented in Table 14.

Table 14: Key drivers of the model

| Description | Method/Value | Impact |
|--|--|--------------------|
| Unit cost of inpatient influenza related hospitalisation | The submission applied a unit cost of \$ [REDACTED] based on a list of DRGs covering a range of admissions, including some that are more complex than respiratory-related influenza cases. | High, favours aTIV |
| Vaccine effectiveness against hospitalisations | <p>Vaccine efficacy against hospitalisation (25%): LIVE study (Mannino 2012).</p> <p>The Pre-PBAC response (p1) provided revised ICERs using adjusted model components, including a reduced VE of 17% for aTIV versus QIV for influenza hospitalisations and mortality.</p> <p>The LIVE study compared aTIV to TIV. In comparison, the model evaluated aTIV to QIV however no influenza cases due to the additional B strain covered by QIV were considered.</p> | High, favours aTIV |

Source: Compiled during the evaluation.

6.54 Results of the stepped economic evaluation are presented in Table 15.

Table 15: Results of the stepped economic evaluation

| Step and component | aTIV (Fluad) | QIV | Increment |
|---|---------------|---------------|---|
| Step 1: Incremental cost per inpatient influenza case avoided over a one-year timeframe | | | |
| Expected cost per patient | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| Expected cases of hospitalised influenza per patient | 0.0036 | 0.0043 | -0.0007 |
| Incremental cost per hospitalised influenza case avoided (one year) | | | \$ [REDACTED] |
| Step 2: Incremental cost per inpatient influenza case avoided over a lifetime time horizon | | | |
| Expected cost per patient | \$ [REDACTED] | \$ [REDACTED] | -\$ [REDACTED] |
| Expected cases of hospitalised influenza per patient | 0.1212 | 0.1472 | -0.0260 |
| Incremental cost per hospitalised influenza case avoided (lifetime) | | | aTIV (Fluad) dominates non-adjuvant QIV, offering better outcomes in terms less cases of influenza at a lower expected cost |
| Step 3: Incremental cost per QALY over a lifetime time horizon (base case) | | | |
| Expected cost per patient | \$ [REDACTED] | \$ [REDACTED] | -\$ [REDACTED] |
| Expected QALYs per patient | 12.4313 | 12.4307 | 0.0005 |
| Incremental cost per QALY (lifetime) | | | aTIV (Fluad) dominates non-adjuvant QIV, offering better outcomes in terms of QALYs at a lower expected cost |

aTIV: Adjuvanted trivalent influenza vaccine; QALY: quality-adjusted life year; QIV: quadrivalent influenza vaccine
 Source: Table 3.16, p113 of the submission.

The redacted table shows incremental costs of less than \$15,000 per QALY.

6.55 From the economic evaluation included in the submission it was concluded that aTIV was the dominant strategy compared to QIV resulting in better outcomes at a lower expected cost.

6.56 The population evaluated in the submission model was a cohort of 65 year olds, who were assumed to receive the vaccine every year over their remaining lifetime. Problems with this approach include that the costs and benefits of the vaccine for older cohorts are discounted, and this model structure precludes the appropriate analysis of the cost-effectiveness of the vaccine within different age groups.

6.57 The ESC considered the correct approach is to model cohorts of individuals at different ages separately and then to weight the results for each cohort based on the age distribution of the Australian population. The PSCR accepted the premise of a one-year time horizon and adjusted the model correctly, to run the one-year model for every age between 65 and 99 years and then to weight the results from each model run according to the age distribution of the Australian population (PSCR, Table 1, p5).

6.58 The results should be considered with caution because:

- The relative vaccine efficacy was sourced from the LIVE study (Mannino 2012) which compared aTIV to TIV; whereas the economic model compared aTIV to QIV and hence the additional B strain covered by QIV was not considered.
- The unit cost per inpatient influenza related hospitalisation was overestimated.

- The incidence of inpatient influenza related hospitalisations is uncertain. It is unclear if the incidence of influenza cases in the last five years will reflect the future incidence of influenza cases. The impact of government influenza awareness campaigns on uptake rates is also unknown.
- Utilities were sources from low quality studies.

6.59 Along with the change to a one-year time horizon, the PSCR (pp3-4) revised the unit cost per inpatient episode of influenza-related hospitalisation and proposed a new claim of a relative effect on mortality that is equal to the relative effect on hospitalisation. The ICERs based on the revised model are presented in Table 16.

Table 16: Incremental cost per QALY (one-year time horizon, inpatient episode limited to \$ [redacted] and OR of Flud versus non-adjuvant QIV mortality set to 0.75)

| Parameter | Flud (aTIV) arm | Non-adjuvant QIV arm | Incremental |
|--|-----------------|----------------------|---------------|
| Age = 65 years | | | |
| Expected cost per patient | \$ [redacted] | \$ [redacted] | \$ [redacted] |
| Expected QALYs lost per patient | 0.1399 | 0.1409 | -0.0011 |
| Incremental cost per QALY gained | | | \$ [redacted] |
| Age = 75 years | | | |
| Expected cost per patient | \$ [redacted] | \$ [redacted] | \$ [redacted] |
| Expected QALYs lost per patient | 0.3345 | 0.3377 | 0.0032 |
| Incremental cost per QALY gained | | | \$ [redacted] |
| Weighted for all ages ≥65 years | | | |
| Expected cost per patient | \$ [redacted] | \$ [redacted] | \$ [redacted] |
| Expected QALYs lost per patient | 0.4086 | 0.4128 | -0.0041 |
| Incremental cost per QALY gained | | | \$ [redacted] |
| Weighted for all ages ≥75 years | | | |
| Expected cost per patient | \$ [redacted] | \$ [redacted] | \$ [redacted] |
| Expected QALYs lost per patient | 0.6781 | 0.6860 | -0.0079 |
| Incremental cost per QALY gained | | | \$ [redacted] |

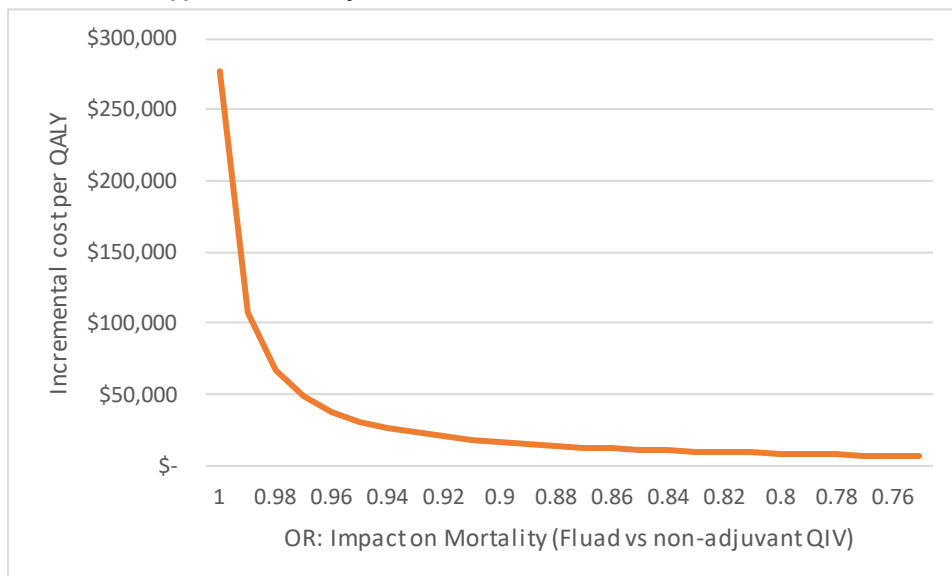
QALY = quality-adjusted life year; QIV = quadrivalent influenza vaccine

Source: Table 1, PSCR, p5.

The redacted table shows incremental costs of less than \$15,000 per QALY gained.

6.60 The ICER falls less than \$15,000 per QALY gained when the mortality OR = 0.91 (see Figure 5 below).

Figure 5: Incremental cost per QALY (one-year time horizon and inpatient episode limited to \$██████) for a range of odds ratios applied to mortality - PSCR



Source: Figure 1, PSCR, p5.

- 6.61 The ESC considered that the estimated QALY effects of non-fatal influenza-related hospitalisations were likely overestimated. It was assumed the effect of influenza remains for 14.3 days and that during those 14.3 days, patients are in a health state almost equivalent to being dead. This resulted in a QALY gain of 0.04 per non-fatal influenza-related hospitalisation avoided.
- 6.62 The ESC considered the source of the utility values was unclear, with the referenced Meier (2015) paper using multiple other sources to derive values. The original source of the utility values was retrieved and it included a sample 21 individuals retrospectively completed the EQ-5D questionnaire after having experienced outpatient influenza.
- 6.63 It is notoriously difficult to get people currently experiencing influenza to complete a utility instrument. On the other hand, most people have experienced influenza. A study by Mauskopf and colleagues (2000)³ drew on this experience to define a health state representing the effects of influenza, in which functional status on a day with influenza symptoms was assumed to be as follows:
- mobility – in house;
 - physical activity – walked with physical limitations;
 - social activity – limited in work, school or housework.
- 6.64 Using the quality of well-being scale, this set of measures gave an index value of 0.56. Assuming a general population utility weight of 0.9, generates a disutility associated

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. 2000;17(6):611-620.

with influenza of 0.34 (0.9 – 0.56). Hospitalised influenza may generate more disutility, but a value of 0.5 (0.9 – 0.4) may be more appropriate than a disutility of approximately 1.

6.65 Also, the duration of an episode requiring hospitalisation was taken as the length of stay for influenza with any complication reported in a UK database study (four references were provided in the Meier (2015) paper). The statement that it was “influenza with any complication” (p752) implies the estimated duration reflects complicated influenza-related hospitalisations.

6.66 On the basis of other economic evaluations for influenza vaccines, the ESC considered it may be more reasonable to assume a duration of 7 to 10 days combined with the estimated utility decrement of 0.5.

6.67 Given the uncertainties in the clinical evidence, the ESC considered it would be informative to use the model as described in the PSCR (as per table 16 above) to run the base case:

- Vaccine effectiveness on hospitalisations and mortality: 0.83 (potentially conservative for hospitalisations, but allowing for a mortality effect)
- QALY gain per non-fatal influenza-related hospitalisation avoided: 0.02
- Unit cost of inpatient episode of influenza: \$ [REDACTED]

The ESC further considered that a separate analysis for individuals aged under 75 years old may be informative.

6.68 The Pre-PBAC Response (p1-2) provided revised ICERs using adjusted model components, as requested by the ESC (above). The revised results demonstrated ICERs remaining less than \$15,000 per QALY gained in all scenarios.

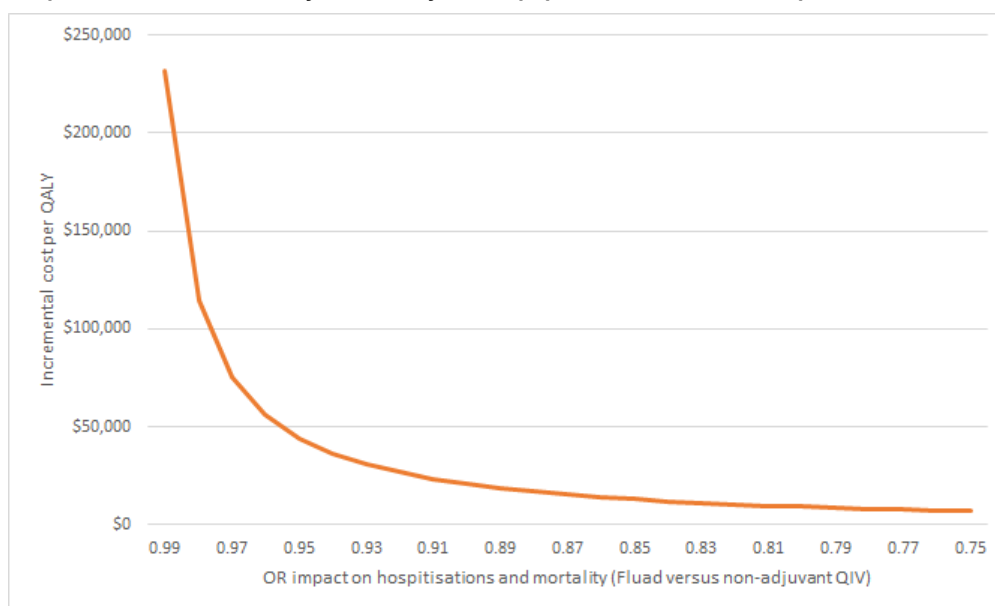
Table 17: Incremental cost per QALY with one-year time horizon, 17% VE of aTIV versus QIV for influenza hospitalisations and mortality, QALY gain per non-fatal influenza hospitalisation avoided set to 0.02 and inpatient episode cost of \$ [REDACTED]

| Parameter | Incremental Cost Effectiveness Ratio |
|------------------------------|--------------------------------------|
| Age = 65 years | \$ [REDACTED] per QALY |
| Age = 75 years | \$ [REDACTED] per QALY |
| Weighted average ICER | |
| Age ≥65 years | \$ [REDACTED] per QALY |
| Ages ≥75 years | \$ [REDACTED] per QALY |
| Age = 65-74 years | \$ [REDACTED] per QALY |

Source: Pre-PBAC Response (P1)

6.69 The Pre-PBAC Response (p2) also provided an updated sensitivity analysis on the incremental effectiveness of aTIV versus QIV against hospitalisations and mortality for 65 year olds showing that the ICER remained below \$45,000 - \$75,000/QALY unless the incremental effectiveness applied was less than 5%. As the incremental effectiveness increases to 11%, the ICER falls below \$15,000 - \$45,000/QALY.

Figure 6: Sensitivity of the economic model to the incremental effectiveness of aTIV versus QIV against hospitalisations and mortality for the 65 year old population – Pre-PBAC response



Source: Pre-PBAC Response, p2

aQIV (Fluad Quad) compared to aTIV (Fluad)

6.70 The submission did not present a cost-minimisation analysis of aQIV (Fluad Quad) to aTIV (Fluad). This was conducted during the evaluation. The equi-effective doses were estimated as aQIV (Fluad Quad) 0.5mL = aTIV (Fluad) 0.5mL.

Vaccine cost/patient/year

6.71 The estimated vaccine cost/patient/year is \$ [redacted] (compared to the current cost of QIV of \$ [redacted]).

6.72 The Pre-PBAC Response proposed a discounted price of \$ [redacted] per dose for aTIV for 2020 only in the event that aQIV could not be supplied in 2020.

Estimated PBS usage & financial implications

6.73 This submission was not considered by DUSC.

aTIV (Fluad) compared to QIV

6.74 Not presented in the submission. The submission proposed a price increase for aTIV (Fluad) but suggested that aQIV (Fluad Quad) is expected to entirely replace aTIV

(Fluad). Consequently, the submission only estimated the financial impact of listing aQIV.

aQIV (Fluad Quad) compared to QIV

- 6.75 The submission used a mixed market share and epidemiological approach based on ABS data and supply forecast provided by the Department of Health (November 2017). The submission did not provide the data from the Department of Health.
- 6.76 A 100% market share was assumed for aQIV. This assumption may overestimate the uptake due to uncertainties around the current clinical evidence. It is unlikely that a complete product substitution will occur with QIV and aQIV because of the limited clinical evidence.
- 6.77 Table 18 reports estimated use and financial implications for listing aQIV on the NIP.

Table 18: Estimated financial implications for the NIP

| | 2020 | 2021 | 2022 | 2023 | 2024 | 2025 |
|--|---------------|---------------|---------------|---------------|---------------|---------------|
| Estimated extent of use | | | | | | |
| Number of aQIV (Fluad Quad) vaccinations | ████████ | ████████ | ████████ | ████████ | ████████ | ████████ |
| Estimated financial implications of aQIV | | | | | | |
| Cost to the NIP | \$ ██████████ | \$ ██████████ | \$ ██████████ | \$ ██████████ | \$ ██████████ | \$ ██████████ |
| Estimated financial implications for alternative vaccinations substituted | | | | | | |
| Cost to the NIP | \$ ██████████ | \$ ██████████ | \$ ██████████ | \$ ██████████ | \$ ██████████ | \$ ██████████ |
| Net financial implications for listing aQIV on the NIP | | | | | | |
| Net cost | \$ ██████████ | \$ ██████████ | \$ ██████████ | \$ ██████████ | \$ ██████████ | \$ ██████████ |

Source: Table 4.6-4.8, p124-125 of the submission.

- 6.78 The submission estimated the net cost to the Government for listing aQIV (Fluad Quad) on the NIP to be over \$100 million over six years.
- 6.79 The net cost of adding aQIV (Fluad Quad) to the NIP was driven by the increased cost of the vaccine compared to other TIV and QIVs. This cost estimate may be overestimated, as it is unlikely that the market share of aQIV (Fluad Quad) will be 100%.

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

7 PBAC Outcome

aTIV (Fluad) compared to QIV

- 7.1 The PBAC did not recommend the requested price increase for adjuvanted trivalent influenza vaccine (aTIV, Fluad) on the *National Health (Immunisation Program – Designated Vaccines) Determination 2014 (No.1)* (the Determination), for vaccination against influenza in adults aged 65 years and above on the basis that the extent of benefit of the adjuvanted trivalent formulation over the non-adjuvanted quadrivalent

vaccine was uncertain given the impact of the loss of the additional B strain differed across influenza seasons.

- 7.2 The PBAC considered that this uncertainty made it difficult to assess the cost-effectiveness of aTIV, and that although a small price premium for aTIV over QIV may be reasonable, the proposed price premium was not justified.
- 7.3 The PBAC considered the clinical need for aTIV was moderate, this was based on the reduced vaccine effectiveness typically observed in older adults with the use of non-adjuvanted vaccines.
- 7.4 The PBAC reaffirmed its March 2018 decision⁴ that the appropriate comparator for aTIV was QIV, which represented existing standard of care available on the NIP. High dose trivalent influenza vaccine (TIV-HD) was considered a near market comparator, but the PBAC noted that no clinical evidence was provided to assess the comparative effectiveness of aTIV with TIV-HD.
- 7.5 The PBAC noted that the submission relied on a complex multi-step chain-of-evidence to support its claims.
- 7.6 The PBAC noted the key clinical evidence compared aTIV to non-adjuvanted TIV in a non-randomised, non-blinded, prospective, population-based cohort study in a community setting covering three influenza seasons (LIVE study, Mannino 2012). The PBAC noted the key outcome of hospitalisations for influenza and pneumonia showed no benefit of aTIV compared to TIV based on the unadjusted data, but propensity score matching and regression analyses resulted in lower hospitalisation rates for aTIV compared to TIV, supporting the claim of superior effectiveness. The PBAC considered using a narrow time window to define events when estimating vaccine effectiveness (VE = 25%) may have been a reasonable approach to increase specificity; however, given the low quality of the evidence, the actual size of the benefit of aTIV over TIV remained uncertain. The PBAC considered it appropriate to use the wider time window (with VE = 17%), to assess the sensitivity of the incremental cost effectiveness to a smaller benefit.
- 7.7 The PBAC noted the safety data from the LIVE study showing no increased risk of Adverse Events of Special Interest (AESI) with aTIV compared to TIV.
- 7.8 The PBAC reaffirmed its March 2018 decision that aTIV is non-inferior overall to QIV for the prevention of seasonal influenza in adults aged 65 years and above⁵. The PBAC considered that the claim of superiority of aTIV over QIV was uncertain and dependent on relative contribution of discordant B strains and additional protection against

⁴ Public Summary Document – Inactivated influenza vaccine (surface antigen), adjuvanted (Fluad®), March 2018 PBAC meeting

⁵ Public Summary Document – Inactivated influenza vaccine (surface antigen), adjuvanted (Fluad®), March 2018 PBAC meeting, p8

shared strains. As such, the PBAC did not consider the likely superiority of aTIV over TIV could be extrapolated to aTIV over QIV.

7.9 The PBAC noted and accepted the revised parameters of the economic model in the pre-PBAC response for determining incremental cost-effectiveness of aTIV over TIV, which included:

- a one-year time horizon,
- 17% VE of aTIV versus TIV for influenza hospitalisations and mortality
- QALY gain per non-fatal influenza hospitalisation avoided set to 0.02
- inpatient episode cost of \$ [REDACTED]
- aTIV cost \$ [REDACTED].

The revised ICER for patients ≥65 years of age was less than \$15,000 per QALY.

7.10 The PBAC noted that hospitalisation cost and vaccine effectiveness against hospitalisations were the key drivers of the economic model.

7.11 Given the comparative benefit of aTIV over QIV was not accepted as being equivalent to the benefit of aTIV over TIV, the PBAC did not consider the economic model could be relied on to determine the cost-effectiveness of aTIV versus QIV. The PBAC considered the incremental cost effectiveness of aTIV over QIV at the revised price in the pre-PBAC response (\$ [REDACTED]) remained too uncertain to accept given the loss of protection against the alternative B lineage. However, the PBAC did consider a smaller price premium may be reasonable given the likely advantages of an adjuvanted formulation for the common strains.

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

Outcome:

Rejected

aQIV (Fluad Quad) compared to QIV

7.13 The PBAC deferred making a recommendation for a new listing for adjuvanted quadrivalent influenza vaccine (aQIV, Fluad Quad®) on the *National Health Immunisation Program – Designated Vaccines Determination 2014 (No.1)* (the Determination), for vaccination against influenza in adults aged 65 years and above. However, the PBAC was of a mind to recommend aQIV on a cost-effectiveness basis to non-adjuvanted quadrivalent (QIV) influenza vaccine pending provision of a positive TGA Delegate’s Overview. The PBAC considered that aQIV would provide additional clinical effectiveness to QIV and the magnitude of the benefit would be similar to that for aTIV over TIV. As such, the economic analysis provided in the submission for aTIV

versus TIV, could be relied on to determine the cost-effectiveness of aQIV versus QIV and aQIV was considered cost-effective at the proposed price.

- 7.14 The PBAC was satisfied that aQIV provides, for adults aged 65 and above, a significant improvement in efficacy over non-adjuvanted QIVs.
- 7.15 The PBAC considered the clinical need for aQIV to be moderate on the basis of the reduced effectiveness of QIV older adults.
- 7.16 The PBAC agreed that aTIV was an appropriate comparator for aQIV, however it considered that QIV was also a relevant comparator.
- 7.17 The PBAC noted the key evidence presented was a single safety and immunogenicity randomised control trial, V118_20, comparing aQIV to aTIV, based on immunogenicity outcomes as surrogate outputs. The PBAC recalled that surrogate outcomes for influenza vaccines have previously been used in PBAC decision-making⁶.
- 7.18 The PBAC noted that trial V118_20 demonstrated non-inferiority of aQIV versus aTIV based on GMT and SCR for the matching strains. The PBAC considered that although CBER criteria were not met for the B strains in either vaccine, the results were comparable for the B strains in both vaccines.
- 7.19 The PBAC noted that there was no imbalance in the frequency of serious adverse events observed between the study groups in trial V118_20.
- 7.20 The PBAC accepted that aQIV would be at least non-inferior to aTIV based on the immunogenicity results from Trial V118_20.
- 7.21 The PBAC noted that there was no comparative outcome data available for aQIV versus QIV, however considered, by extension, that the relative benefit of aQIV over QIV was likely to be similar to that for aTIV over TIV. Further, for the comparison of aQIV versus QIV (as opposed to aTIV vs QIV) the uncertainty of the impact of the missing B strain is removed.
- 7.22 The PBAC considered its views on the revised modelling (paragraph 7.9) would apply to the incremental cost effectiveness of aQIV over QIV and the resulting ICER of less than \$15,000 per QALY is reasonable.
- 7.23 The PBAC noted that the financial impact to the NIP of the listing was high at an estimated more than \$100 million over six years.

Outcome:

Deferred

⁶ Public Summary Document – Influenza Vaccine (quadrivalent) (Fluarix Tetra®), March 2015 PBAC meeting

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

The sponsor had no comment.

August 2019 addendum to the July 2019 PBAC Minutes:

10 Purpose of Application

- 10.1 At its July 2019 meeting, the PBAC deferred making a recommendation regarding the listing of adjuvanted quadrivalent influenza vaccine (aQIV, Flud Quad). The PBAC was of a mind to recommend the listing of aQIV at the proposed price pending provision of a positive TGA Delegate's Overview
- 10.2 The sponsor provided the positive TGA Delegate's Overview on 1 August 2019. The Delegate's Overview included questions which it referred to the Advisory Committee on Vaccines (ACV). The ACV met on 20 August 2019 and was supportive of the benefit of aQIV in the proposed population. TGA approval is anticipated for September 2019.

11 PBAC Outcome

- 11.1 The PBAC recommended the listing of adjuvanted quadrivalent influenza vaccine (aQIV, Flud Quad[®]) on the *National Health (Immunisation Program – Designated Vaccines) Determination 2014 (No.1)* (the Determination), for vaccination against influenza in adults aged 65 years and above. Noting the advice in the TGA Delegate's Overview and the ACV consideration of aQIV, the PBAC was satisfied the remaining outstanding issues relating to the application were satisfactorily resolved.
- 11.2 The PBAC considered that aQIV would provide adults aged ≥ 65 years access to a quadrivalent non-adjuvanted influenza vaccine and that this population typically has reduced vaccine effectiveness with the use of non-adjuvanted vaccines.
- 11.3 The PBAC recalled its July 2019 consideration of aQIV and noted no other factors had changed in the preceding month, such as comparator, evidence base, population and disease or new vaccines.

- 11.4 The PBAC reiterated its July 2019 advice that it was satisfied that aQIV provides, for adults aged 65 and above, a significant improvement in efficacy over non-adjuvanted QIVs and that it considered that aQIV was cost-effective at the proposed price.
- 11.5 The PBAC noted that this submission is not eligible for an Independent Review as it is a positive recommendation and independent review is only relevant to PBS listing.

Outcome:

Recommended

12 Recommended listing

- 12.1 Add new item to the Determination for the population outlined below:

| Name, restriction, manner of administration, form | Maximum quantity (units) | No. of repeats | Proprietary name and manufacturer |
|---|--------------------------|----------------|--|
| Inactivated influenza vaccine (surface antigen), adjuvanted, suspension for injection | 1 | 0 | Fluad Quad (aQIV), Seqirus (Australia) Pty Ltd |

| | |
|-------------------|-----------------------------|
| Category/Program: | NIP |
| Population | All persons aged ≥ 65 years |

13 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.

14 Sponsor’s Comment

The sponsor had no comment.