

5.20 Inactivated influenza vaccine (surface antigen), adjuvanted, suspension for injection, 15mcg in 0.5mL, Fluad[®], Seqirus

1 Purpose of Application

- 1.1 The minor submission sought listing on the National Immunisation Program (NIP) for inactivated trivalent influenza vaccine (surface antigen), adjuvanted (aTIV).

2 Requested listing

- 2.1 The submission sought the following addition to Schedule 1 (Designated vaccines and circumstances in which vaccines may be provided) of National Health (Immunisation Program – Designated Vaccines Determination 2014 (No.1)):

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Nationally Negotiated Price	Proprietary Manufacturer	Name and
INACTIVATED INFLUENZA VACCINE (SURFACE ANTIGEN), ADJUVANTED Suspension for injection, 15mcg in 0.5mL	1	0	\$ [REDACTED]	Fluad	Seqirus

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

3 Background

- 3.1 aTIV is TGA registered for:
- Active immunisation against influenza in the elderly (65 years of age and older), especially those with an increased risk of association complications (i.e. patients affected by underlying chronic diseases including diabetes, cardiovascular and respiratory diseases).
- 3.2 aTIV was TGA Registered in October 2002 but has never been marketed in Australia. It is currently undergoing updates to its registration including:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

• [REDACTED]).

3.3 The TGA is expected to finalise these changes by February 2018. A name change and labelling component revision have been completed.

3.4 aTIV has not previously been considered by the PBAC. Previous influenza vaccine considerations by the PBAC since 2005 are summarised below:

Table 1. PBAC considerations of influenza vaccines

Item considered	Date	Purpose	Outcome	Model
Influenza vaccine (Fluarix, Flubax, Influvac, Vaxigrip)	November 2007	NIP listing for all Australians over 50 years of age	Rejected due to uncertainty of clinical benefits and the results of the modelled economic evaluation and outcomes.	Current influenza vaccination practice in the 50-64 age group
Influenza vaccine (Intanza)	July 2009	NIP listing for patients aged 65 and older via intradermal route	Recommended	CMA to current NIP funded vaccines for this age group eg Vaxigrip
Trivalent influenza vaccine	July 2014	Extend NIP schedule to include vaccination for Indigenous children aged 6 months to 5 years of age	Recommended	Compared to Fluarix trivalent
Quadrivalent influenza vaccine (Fluarix Tetra)	March 2015	People 3 to 9 years and 9 years and older	Recommended (did not recommend expanding beyond existing NIP covered population due to lack of evidence)	CMA to Fluarix trivalent influenza vaccine
Quadrivalent influenza vaccine (Quadri Flu Junior and FluQuadri)	July 2015	NIP listing for children aged 6 months to under 3 years of age, 3 to 9 years and above 9 years	Recommended	CMA to Fluarix Tetra (>36 months of age) and Flu Quadri for 6-<36 months, TIV was appropriate
Quadrivalent influenza vaccination (Afluria Quad)	August 2016	Add a new item to the NIP for adults	Recommended	CMA to Fluarix Tetra

- 3.5 The submission was prepared in response to liaison with the company from the Chief Medical Officer following the outcomes of the 2017 influenza season in Australia. Given the experience of the 2017 influenza season, to contribute to the Government's response to public health concerns around the 2018 influenza season Seqirus made the submission on a cost-minimisation basis to the current standard of care quadrivalent influenza vaccine (QIV), in the interests of public health.

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

4 Current Situation

- 4.1 The submission sought listing on the NIP for subsidised provision of aTIV for those aged ≥ 65 eligible for free influenza vaccines through the NIP due to the high rates of cases of influenza in this age group in 2017 and the broadened immune response produced by aTIV for this age group.
- 4.2 As the submission presented a cost—minimisation analysis (CMA) for a seasonal influenza vaccine, the PBAC consideration will be informed by the advice of the Australian Technical Advisory Group on Immunisation (ATAGI) which considered the vaccine with regards to comparative cost-effectiveness and safety.
- 4.3 ATAGI supported the listing of aTIV for the proposed group based on the claim of non-inferiority. ATAGI's advice is summarised below for the purposes of the PBAC assessment. A full evaluation of the submission has not been undertaken by the PBAC Secretariat.
- 4.4 The proposed price is equal to the nationally negotiated price for the comparator, noting that the tender price for the comparator may be lower.
- 4.5 ATAGI noted a number of points relevant to the implementation of listing of aTIV (Pre-Submission Advice, P9-11):
- Continued availability of QIV as an alternative for use would be important, noting that stocking both vaccines and preventing confusion amongst providers may be difficult.
 - Minor increases in cold chain capacity and storage space requirements would occur due to the addition of an alternative vaccine.
 - Evaluation of the program would be particularly important and that existing surveillance mechanisms were inadequate to estimate the burden of influenza due to under-reporting. ATAGI strongly recommended that the impact of aTIV relative to other available vaccine/s used in the NIP for Australians aged 65 and over be evaluated.
 - Substantial planning and resourcing would be required for communication with and education of general practitioners and other immunisation providers including managing the availability of multiple vaccines types for

the same population group and how to counsel patients on which vaccine to receive, which may be a complicated message.

- Providers would need to be aware aTIV would only be registered for use in adults aged 65 and above and recording the number of inadvertent administration to other age groups would be highly desirable.
- Due to the higher rate of adverse events associated with aTIV and the limited data on the use of aTIV in children; that active surveillance of children vaccinated inadvertently should occur. Implementation should occur in consultation with key stakeholders including states and territories.

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

5 Comparator

- 5.1 The minor submission nominated the comparators as the three NIP listed QIVs for those aged ≥ 65 years of age: QIVs Afluria Quad, FluQuadri and Fluarix Tetra (Submission, P14). ATAGI considered the proposed comparators appropriate (Pre-Submission PBAC Advice, P3).

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 as it was a minor submission.

Consumer comments

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

Clinical trials

- 6.3 As a minor submission, no clinical trial evidence was evaluated by the PBAC Secretariat. Both the Therapeutic Goods Administration (TGA) and ATAGI have considered the clinical evidence for aTIV.
- 6.4 The basis of the minor submission's request was that aTIV was non-inferior in efficacy and safety to the comparator.
- 6.5 The evidence available for aTIV included:
- The pivotal study, a phase III RCT V70_27, comparing aTIV with unadjuvanted TIV
 - Fourteen supplementary RCTs comparing aTIV with unadjuvanted TIV
 - Four RCTs comparing QIV with TIV (one pivotal study and three supplementary studies)

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- Meta-analysis of aTIV versus TIV and QIV versus TIV for immunogenicity and safety outcomes
 - Indirect treatment comparison of aTIV versus QIV via the common comparator TIV using the same study data as the meta-analyses
 - Extended safety assessment of aTIV using the most recent Periodic Safety Update Report (PSUR), a published systematic review of aTIV trials and a published systematic review of trials evaluating MF59-adjuvanted seasonal and pandemic influenza vaccines
 - A review of three published effectiveness studies for aTIV
- 6.6 No direct RCTS of aTIV versus QIV were located however literature on QIV versus TIV was identified. An indirect comparison using TIV as the common comparator was undertaken.
- 6.7 The submission (P14) noted that QIV was originally listed on the NIP based on non-inferior efficacy and toxicity compared to TIV in 2015.

Comparative effectiveness

- 6.8 ATAGI noted that the main evidence for effectiveness of aTIV relative to TIV was from two international observational studies, a small test-negative case-control study and a large post-licensure study (Pre-Submission PBAC Advice, P5-6).
- 6.9 With regard to immunogenicity, ATAGI noted that immunological findings largely supported estimates of enhanced efficacy in observational studies and that the evidence from RCTs demonstrated that aTIV induced non-inferior immunogenicity and sometimes significantly higher antibody responses compared to TIV against both homologous and heterologous strains (Pre-Submission PBAC Advice, P6-7).
- 6.10 ATAGI acknowledged that the key issue with assessing effectiveness of aTIV against QIV is the magnitude of the loss of protection against the alternative B lineage with the use of aTIV, which is hard to predict from year to year.
- 6.11 ATAGI acknowledged the superior effectiveness of aTIV compared to TIV in certain scenarios and in recipients aged 65 and over. ATAGI noted substantial uncertainty about the magnitude of incremental effectiveness of aTIV relative to TIV, which is can vary each influenza season (Pre-Submission PBAC Advice, P1).
- 6.12 ATAGI recognised there was no evidence from RCTs on the efficacy of aTIV against laboratory confirmed influenza and an absence of evidence on strain specific vaccine effectiveness, however ATAGI considered that the studies provided held sufficient evidence of superior relative effectiveness compared to TIV, at least for the A/H3N2 strain. ATAGI also recognised the absence of RCT evidence demonstrating clinical efficacy relative to TIV (Pre-Submission PBAC Advice, P5).
- 6.13 ATAGI noted uncertainty relating to the relative effectiveness of aTIV compared to QIV (Pre-Submission PBAC Advice, P1).

- 6.14 The ATAGI advice (P4) identified that among people with previous influenza exposure, the additional protection against the additional B lineage provided by the inclusion of a second B lineage in a QIV was predicted to not be statistically significant and the greatest advantage of QIV was thus in infants and children.
- 6.15 ATAGI considered aTIV suitable for listing on the NIP designated vaccines list for the prevention of seasonal influenza in adults aged ≥ 65 years, subject to TGA updated registration approval, based on non-inferiority overall against QIVs (Pre-Submission PBAC Advice, P1).

Comparative harms

- 6.16 The submission claimed that that safety data from the available RCTs and the extended assessment found that aTIV was associated with an increased rate of local reactions (mostly mild) in the first few days following vaccination, but with no differences with TIV in safety outcomes after this time (submission, P17).
- 6.17 ATAGI did not have major concerns regarding the safety of aTIV. ATAGI noted that aTIV appeared to be more reactogenic than TIV, however the reactions were generally well tolerated and there was no increase in serious adverse events (Pre-Submission PBAC Advice, P2). ATAGI added that the higher rate of local and systemic reactions would be relevant for communication to immunisation providers and potential recipients (Pre-Submission PBAC Advice, P8). ATAGI noted a lack of studies on coadministration of aTIV with Zostavax (Pre-Submission PBAC Advice, P8).
- 6.18 Based on evidence from studies in younger age groups ATAGI did not have significant concerns regarding possible inadvertent administration to adults under 65 years of age (Pre-Submission PBAC Advice, P2) and considered aTIV to have an acceptable safety profile.

Benefits and harms

- 6.19 ATAGI noted that use of aTIV was associated with a higher rate of local reactions than TIV and it did not vaccinate against an additional B lineage, however that the potential additional protection provided against the strains included in the vaccine was sufficient 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 (Pre-Submission PBAC Advice, P1).

Clinical claim

- 6.20 The submission presented a clinical claim of non-inferiority to QIV for comparative effectiveness in immunogenicity measures and effectiveness, noting a superiority of effectiveness compared to non-adjuvanted TIV (Submission, P154). The submission presented a claim of non-inferior comparative safety overall, noting inferiority for injection site reactions within the first three days (Submission, P154).

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- 6.21 ATAGI considered that aTIV was suitable for listing based on non-inferiority overall against currently used standard dose QIVs (Pre-Submission PBAC Advice, P1).
- 6.22 ATAGI noted that considering the cost-minimisation approach and the trade-off between enhanced protection against strains common between TIV and QIV (particularly A/H3) and the potential for reduced protection against the alternative B lineage, that overall aTIV was non-inferior to the current QIV available under the NIP for use in adults aged 65 years and above (Pre-Submission PBAC Advice, P2).
- 6.23 ATAGI considered that the uncertainties of the submission were the incremental effectiveness of aTIV relative to TIV, which is influenced by characteristics of each influenza season, and the relative effectiveness of aTIV compared to QIV, given the loss of protection against the additional alternative B lineage included in the QIV. This was complicated by the unpredictability of circulating strains each season and the extent of cross-protection afforded by TIV against this. These variables meant the magnitude of relative efficacy and effectiveness would likely vary annually (Pre-Submission PBAC Advice, P2).
- 6.24 ATAGI considered that (Pre-Submission PBAC Advice, P2):
- there was sufficient evidence indicating aTIV was superior in effectiveness to a non-adjuvanted TIV in some scenarios, particularly in seasons dominated by influenza A/H3;
 - that the additional protection afforded by aTIV against the strains in the vaccine were 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 and above; and
 - aTIV had an acceptable safety profile, (Pre-Submission PBAC Advice, P1).
- 6.25 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.
- 6.26 The PBAC agreed with the ATAGI that the evidence supports a claim that aTIV has an acceptable safety profile.

Economic analysis

- 6.27 The submission sought a price ██████ to the nationally negotiated price of the QIV comparator based on the clinical and safety profile of aTIV.

Drug cost/patient/year: \$█████.

- 6.28 The drug cost per patient per year to the NIP was proposed as \$█████ for a single dose ideally administered from April 2018 prior to commencement of the influenza season, the ██████ cost that was recommended by the PBAC for QIV Afluria Quad.

Estimated NIP usage & financial implications

- 6.29 NIP listing is expected to be cost [REDACTED] financial implications to the NIP/changes in NIP usage are anticipated as aTIV will substitute for QIV and both vaccines have the [REDACTED] (Submission, P20).

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

7 PBAC Outcome

- 7.1 The PBAC recommended that inactivated trivalent influenza vaccine (surface antigen), adjuvanted (aTIV) vaccine be a designated vaccine for the purposes of the *National Health Act 1953* for active immunisation against influenza in adults aged ≥65 years of age.
- 7.2 The PBAC considered the aTIV vaccine would be acceptably cost-effective if subsidised on a cost-minimisation basis with the currently NIP listed quadrivalent inactivated vaccines (QIV) for those aged ≥65.
- 7.3 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.
- 7.4 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.
- 7.5 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.
- 7.6 The PBAC agreed with the ATAGI that the evidence supports a claim that aTIV has an acceptable safety profile.
- 7.7 The PBAC also recalled that QIV was originally listed on the NIP after a positive PBAC recommendation in 2015, based on QIV being non-inferior in efficacy and toxicity compared to TIV.
- 7.8 The PBAC advised that the equi-effective doses should be considered to be aTIV 1 x 15 µg dose to QIV 1 dose.
- 7.9 The PBAC further noted that:
- in progressing listing on the NIP, the Office of Health Protection would need to consider a number of issues raised by ATAGI around logistics associated with the introduction of an additional vaccine, program evaluation, education and communication with health care providers and post-market surveillance measures.
 - aTIV was undergoing concurrent changes to its TGA registration, which would need to be finalised prior to it being made available through the NIP.

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

Outcome:

Recommended

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.