

5.21 Inactivated trivalent influenza vaccine (Split Virion) suspension for injection, 180mcg single dose in 0.5mL, Fluzone[®] High-Dose, Sanofi-Aventis Australia Pty Ltd

1 Purpose of Application

- 1.1 The minor submission sought listing on the National Immunisation Program (NIP) for inactivated trivalent influenza vaccine (TIV-HD) (Split Virion).

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 Name and Manufacturer
INACTIVATED TRIVALENT INFLUENZA VACCINE (SPLIT VIRION) Suspension for injection, 180mcg single dose in 0.5mL	1	0	\$█	Fluzone Sanofi-aventis Australia Pty Ltd

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

3 Background

- 3.1 TIV-HD received TGA registration in December 2017 for:
- active immunisation against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine for use in persons 65 years and older.
- 3.2 TIV-HD has not previously been considered by the PBAC. Previous influenza vaccine considerations since 2005 are:

Public Summary Document – March 2018 PBAC Meeting

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

- 3.3 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 Sanofi made the submission on a cost-minimisation basis to the current standard of care quadrivalent influenza vaccine (QIV), in the interests of public health. Sanofi intend to lodge a major submission for this vaccine at a future PBAC meeting seeking a cost effectiveness assessment.

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 TIV-HD 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 enhanced immune response and efficacy produced by TIV-HD for this age group (Submission, P1).
- 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 TIV-HD for the proposed age 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 The TGA Delegate's Overview noted a few implementation points that came from the Risk Management Plan Evaluation Report Round 2:
 - That the sponsor must provide a commitment to conduct an enhanced safety surveillance study in Australia if requested by the TGA. This was not referenced within the minor submission and may be expected to be discussed in any further submission for this medicine, noting that the sponsor proposes that a major submission will be lodged for the July 2018 PBAC meeting seeking a cost effectiveness analysis.
 - Amendment of the product information to amend discrepancies between the draft PI and the Australian Immunisation Handbook regarding persons with egg allergy.
- 4.6 The TGA Delegate's Overview (P12) also noted that viral safety issues were under negotiation with the viral safety unit and the sponsor. No further detail was provided.
- 4.7 ATAGI noted a number of points relevant to the implementation of listing of TIV-HD:
 - Continued availability of QIV as an alternative for use would be important, however stocking both vaccines and preventing confusion amongst providers may be difficult (Pre-Submission Advice).
 - 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 TIV-HD relative to other available vaccine/s used in the NIP for Australians aged 65 and over be evaluated (Pre-Submission PBAC Advice,).

- Monitoring potential adverse events with widespread use of TIV-HD was essential (Pre-Submission PBAC Advice).
- There would be minor increases in cold chain capacity and storage space requirements from the addition of an alternative vaccine (Pre-Submission PBAC Advice).
- 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 (Pre-Submission PBAC Advice).
- Providers would need to be aware the TIV-HD would only be registered for use in adults aged 65 and above, and recording the number of inadvertent administration to other age groups was highly desirable (Pre-Submission PBAC Advice).
- While inadvertent administration to other adult age groups was of concern, the risks were likely to be minor and with appropriate labelling and packaging, it was less likely that inadvertent administration to children would occur (Pre-Submission PBAC Advice).

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

5 Comparator

- 5.1 The minor submission did not clearly nominate a comparator.
- 5.2 The clinical studies presented compared TIV-HD to TIV-SD. The submission acknowledged (P6) the current standard of care to be standard dose QIV, and that QIV was recommended for NIP listing on the basis of non-inferior efficacy and safety to TIV. The sponsor concluded that as TGA and ATAGI acknowledged TIV-HD to have superior efficacy to TIV, it was reasonable to conclude that the therapeutic conclusion also extended to QIV.
- 5.3 ATAGI did not consider that TIV single dose (SD) was an appropriate comparator given that QIV is used exclusively under the NIP and noted there was a level of uncertainty given the absence of head-to-head studies of TIV-HD versus QIV. (Pre-Submission PBAC Advice).
- 5.4 QIV was recommended in March 2015 based on non-inferiority to TIV (Public Summary Document, QIV, March 2015).

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 and welcomed the input from individuals (2) via the Consumer Comments facility on the PBS website. The comments were supportive of the requested listing.

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 the Australian Technical Advisory Group on Immunisation (ATAGI) have considered the clinical evidence for TIV-HD.

6.4 The basis of the minor submission's request was that TIV-HD was non-inferior in efficacy and safety to the comparator.

6.5 The primary evidence available for efficacy, effectiveness and immunogenicity of TIV-HD against laboratory confirmed influenza were provided by one large pivotal clinical trial and three post-market observational studies. ATAGI found that these provided evidence of superior efficacy of TIV-HD compared to TIV-SD and noted uncertainties around the lack of comparative studies of TIV-HD with QIV, and the uncertainties observed year to year with the influenza seasons (Pre-Submission PBAC Advice).

Comparative effectiveness

6.6 Based on evidence from three post-marketing observational studies in the USA, ATAGI considered that the vaccine effectiveness studies for TIV-HD corroborated with the pivotal efficacy clinical trials presented. ATAGI acknowledged superior efficacy of TIV-HD compared with TIV-SD, with the most notable effect being against the A/H3 strain. ATAGI noted that effectiveness varied by a number of factors including age, circulating strains and severity of the season (Pre-Submission PBAC Advice). ATAGI considered an overall relative vaccine efficacy of TIV-HD versus TIV-SD of 24.2% (95%CI: 9.7%-36.5%) to be most appropriate for the base case assessment, as reported in the FIM12 study (Pre-Submission PBAC Advice).

6.7 With regard to immunogenicity, ATAGI found that the immunological findings were largely consistent with findings from efficacy studies; that TIV-HD generated a superior immune response to TIV-SD in geometric mean titre ratios 28 days post vaccination for A/H3 and A/H1 subtypes, and a non-inferior response for B strains, using FDA criteria (Pre-Submission PBAC Advice).

- 6.8 ATAGI noted that the key issue with assessing effectiveness of TIV-HD against QIV was the magnitude of the loss of protection against the alternative B lineage with the use of TIV-HD, which is hard to predict from year to year.
- 6.9 ATAGI found that overall, the potential additional disease burden due to the alternative B lineage not included in TIV-HD was likely to be offset by the potential additional protection provided against the vaccine strains common to TIV-HD and QIV, especially A/H3 in adults aged 65 and above (ATAGI Pre-PBAC Advice). The ATAGI advice (P3-4) 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.

Comparative harms

- 6.10 ATAGI did not identify any studies examining co-administration of TIV-HD with other NIP vaccines that may be used in the proposed age group such as 23-valent pneumococcal polysaccharide vaccine (PPV23) or Zostavax. ATAGI noted this as an uncertainty of the submission, however noted TIV-HD has been used in the USA for several seasons, where PPV23 is used widely in the same population without reports of increased risk of severe adverse events following co-administration. ATAGI concluded there was no major concern regarding concomitant administration with other NIP vaccines used in the relevant age group, however given the lack of data, monitoring of potential adverse events would be essential (Pre-Submission PBAC Advice, P10).
- 6.11 Based on sponsor led studies, ATAGI (Pre-Submission Advice) noted that TIV-HD recipients had significantly more local reactions than TIV-SD recipients (~30% versus 20%), which were mostly mild in severity. Similar rates of systemic reactions, non-serious events and serious adverse events were observed in both groups. ATAGI noted post market passive surveillance data from the USA and post-market telephone surveys which reported varied levels of adverse events, and noted several biases in these data.
- 6.12 Overall, ATAGI found that while there was a higher rate of local reactions associated with TIV-HD, it had no specific concerns regarding the safety of TIV-HD that would preclude its use in the NIP for adults aged 65 and above, subject to TGA approval (Pre-Submission PBAC Advice).

Benefits and harms

- 6.13 ATAGI noted that use of TIV-HD was associated with a higher rate of local reactions than TIV-SD and it did not vaccinate against an additional B lineage, however it was found to be more effective in vaccinating against strains of influenza that more commonly affect those in the proposed population, aged 65 and over.

Clinical claim

- 6.14 The submission claimed superior comparative effectiveness and non-inferior comparative safety of TIV-HD compared with TIV-SD. The submission noted that QIV, the current standard of care, was listed based on non-inferiority to TIV-SD (Submission, P6).
- 6.15 ATAGI considered that TIV-HD was suitable for listing on the NIP designated vaccines list for the prevention of seasonal influenza in adults aged 65 and above, subject to TGA approval for registration (Pre-Submission PBAC Advice).
- 6.16 ATAGI noted that considering the cost-minimisation approach and the trade-off between enhanced protection against strains common between TIV-HD and QIV (particularly A/H3) and the potential for reduced protection against the alternative B lineage, that overall TIV-HD was non-inferior to the current QIV available under the NIP for use in adults aged 65 years and above (Pre-Submission PBAC Advice).
- 6.17 ATAGI considered that the key uncertainty of the submission was the impact of the potential loss of protection against the additional alternative B lineage included in the QIV but not in TIV, relative to the impact of potential additional protection provided by TIV-HD, particularly against A/H3 disease. This is complicated by the unpredictability of circulating strains each season and the extent of cross-protection afforded by TIV against this. These variables mean the magnitude of relative efficacy and effectiveness will likely vary annually.
- 6.18 ATAGI noted that:
- there was sufficient evidence indicating TIV-HD is superior in effectiveness to a TIV-SD against matched influenza strains;
 - that the additional protection was 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
 - TIV-HD had an acceptable safety profile, albeit with a higher frequency of mild to moderate injection-site reactions compared with TIV-SD (Pre-Submission PBAC Advice).
- 6.19 The PBAC accepted the ATAGI advice that TIV-HD is non-inferior overall to QIV for the prevention of seasonal influenza in adults aged ≥ 65 years.
- 6.20 The PBAC agreed with the ATAGI that the evidence supports a claim that TIV-HD has an acceptable safety profile, albeit with a higher frequency of mild to moderate injection-site reactions compared with TIV-SD. The PBAC 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.

Economic analysis

- 6.21 The submission sought a price equal to the nationally negotiated price of the QIV standard of care comparator based on the clinical and safety profile of TIV-HD.
- 6.22 ATAGI considered that although the proportional uptake of TIV-HD was hard to predict, the overall coverage of influenza vaccination in the proposed population would be likely to be similar to existing coverage (approximately 75%) of TIV-HD was introduced as an alternative influenza vaccine under the NIP for this age group (Pre-Submission PBAC Advice, P12).

Drug cost/patient /year: \$ [REDACTED].

- 6.23 The drug cost per patient per year to the NIP was proposed as \$ [REDACTED] for a single dose prior the start of the 2018 influenza season, the same cost as the nationally negotiated price for QIV comparators.

Estimated NIP usage & financial implications

- 6.24 No financial implications to the NIP or changes in NIP usage were anticipated as TIV-HD will substitute for QIV and both vaccines have the same price.

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 (TIV-HD) be a designated vaccine for the purposes of the *National Health Act 1953* for active immunisation against influenza in adults aged ≥ 65 years.
- 7.2 The PBAC considered that the TIV-HD 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 TIV-HD 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 TIV-HD is superior in effectiveness to a standard-dose trivalent inactivated vaccine (TIV-SD) against vaccine-matched influenza strains, particularly against influenza A/H3 disease which accounts for a substantial burden in this age group.
- 7.5 The PBAC agreed with the ATAGI that the additional protection against vaccine-matched strains included in the TIV-HD 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 TIV-HD has an acceptable safety profile, albeit with a higher frequency of mild to moderate

injection-site reactions compared with TIV-SD. The PBAC 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.

- 7.7 The PBAC advised that the equi-effective doses should be considered to be TIV-HD 1 x 180µg dose to QIV 1 x dose.
- 7.8 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.
 - TIV-HD received TGA registration in December 2017.
- 7.9 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

Sanofi welcomes the PBAC's recommendation to list Fluzone High-Dose on the NIP and the diligent work adopted by all parties to make this important vaccine available for older Australians for the 2018 influenza season. We welcome the opportunity for the PBAC to undertake a full evaluation of Fluzone High-Dose at the July meeting as an important step towards ensuring Australians aged 65 and over continue to benefit from access to this more effective influenza vaccine for future seasons.