

**7.03 HIGH DOSE INACTIVATED TRIVALENT INFLUENZA  
VACCINE (SPLIT VIRION),  
Injection 0.5 mL,  
Fluzone® High-Dose,  
Sanofi–Aventis Australia Pty Ltd.**

**1 Purpose of Application**

- 1.1 Resubmission for the trivalent influenza high dose vaccine (TIV-HD, Fluzone High-Dose) listing on Schedule 1 (Designated vaccines and circumstances in which vaccines may be provided) of the *National Health (Immunisation Program – Designated Vaccines) Determination 2014 (No.1)* (the Determination) from the 2020 influenza season onwards, for people aged ≥65 years at an increased price.
- 1.2 The basis for the price increase was a cost-effectiveness analysis of TIV-HD compared with the nominated main comparator standard dose quadrivalent influenza vaccine (QIV-SD), and near market comparators adjuvanted trivalent influenza vaccine (aTIV) and adjuvanted quadrivalent influenza vaccine (aQIV).

**Table 1: Key components of the clinical issue addressed by the resubmission**

Component	Description
Population	Adults aged ≥ 65 years
Intervention	TIV-HD (Fluzone High-Dose)
Comparator	Main: QIV-SD Near Market: aTIV/aQIV
Outcomes	Clinically diagnosed and laboratory confirmed influenza, cardio-respiratory hospitalisation
Clinical claim	Reduction in cases of clinically diagnosed and laboratory confirmed influenza Reduction in cardio-respiratory hospitalisations Acceptable safety profile

aQIV: adjuvanted quadrivalent influenza vaccine; aTIV: adjuvanted trivalent influenza vaccine; QIV-SD: standard dose quadrivalent influenza vaccine; TIV-HD: high dose trivalent influenza vaccine.

Source: Table 1.1, p18 of the resubmission.

## 2 Requested listing

2.1 The current price for TIV-HD is \$ [REDACTED] per dose. The requested price in the resubmission was \$ [REDACTED] per dose. The requested price in the submission considered at the July 2019 PBAC meeting was \$ [REDACTED] per dose.

2.2 The requested restriction is the same as the current NIP indication.

**Table 2: Essential elements of the requested listing**

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Approved ex-manufacturer price	Proprietary Name and Manufacturer
INACTIVATED TRIVALENT INFLUENZA VACCINE (SPLIT VIRION), 0.5ML, INJECTION, PREFILLED SYRINGE	1	0	\$ [REDACTED]	Fluzone High-Dose Sanofi-Aventis Australia Pty Ltd
Category/Program:	NIP			
NIP indication:	A single injection against influenza disease caused by influenza virus types A and B contained in the vaccine for use in persons ≥ 65 years of age.			

NIP: National Immunisation Program

Source: Table 1.9, p35 of the resubmission.

## 3 Background

### Registration status

3.1 TGA status: TIV-HD was TGA registered on 20 December 2017 for active immunisation against influenza disease caused by influenza virus types A and B contained in the vaccine for use in persons ≥ 65 years of age.

3.2 TIV-HD for intramuscular injection is an inactivated influenza virus vaccine. It contains 180 micrograms (µg) haemagglutinin per 0.5 mL dose in the recommended ratio of 60 µg haemagglutinin of each of three strains. The recommended strains for the 2019 influenza season were:

- A/Michigan/45/2015 (H1N1) pdm09 - like virus (A/Michigan/45/2015 X-275)
- A/Switzerland/8060/2017 (H3N2)-like virus (A/Brisbane/1/2018 X-311)

- B/Phuket/3073/2013 - like virus (B/Phuket/3073/2013; Yamagata lineage).

**Previous PBAC consideration**

- 3.3 TIV-HD was first considered and recommended for listing on the Determination by the PBAC in January 2018. It was subsequently available on the National Immunisation Program (NIP) for the 2018 influenza season. It was recommended on the basis of a minor submission using a cost-minimisation approach in which TIV-HD was recommended at the same price as QIV-SD in response to the severe outcomes of the influenza season in 2017.
- 3.4 TIV-HD was again considered by PBAC in July 2018. The resubmission sought a price increase and provided a cost-effectiveness analysis which compared TIV-HD with QIV-SD. The PBAC did not recommend the requested price increase for TIV-HD based on:
- high financial implications of the proposed increase in price;
  - uncertainty around the loss of protection against the alternative B lineage and the incremental benefit of the strains matched with the comparator vaccine; and
  - associated uncertainty in assessing the incremental cost-effectiveness of the vaccine (para 7.1, p25, TIV-HD Public Summary Document (PSD), July 2018).
- 3.5 The sponsor did not supply TIV-HD on the NIP for the 2019 season.
- 3.6 Table 3 summarises the outstanding matters of concern from the July 2018 PBAC meeting and how they have been addressed in the resubmission.

**Table 3: Summary of outstanding matters of concern**

Component	Matter of concern from previous submission	How the resubmission addresses it
Section 1	The previous submission requested a price of \$█████ per dose. The Committee rejected the submission based on "...the high financial implications of the proposed price increase." (para. 7.1, p25, TIV-HD PSD, July 2018).	The resubmission reduced the requested price to \$█████ per dose. The resubmission suggested a stepped implementation with TIV-HD provided to residents in aged care facilities in 2020.
Section 2	Comparison vs aTIV: Although the previous submission nominated aTIV as a near market comparator, there were no studies identified which could inform a comparison of patient-relevant outcomes.	No RCTs with published results were identified which directly compared TIV-HD to aTIV or aQIV. The resubmission presented an observational study (Izurieta et al. 2018) which reported rVE of TIV-HD and aTIV in reducing influenza-related hospitalisations.
	Comparison vs QIV-SD: PBAC considered the uncertainty around the loss of protection against the alternative B lineage and the incremental benefit of the strains matched with the comparator vaccine (para. 7.1, p25, TIV-HD PSD, July 2018).	Assessed using scenario analyses in the economic evaluation.

Public Summary Document - November 2019 PBAC meeting

Component	Matter of concern from previous submission	How the resubmission addresses it
Section 3	<p>“Given the very large opportunity cost of the proposed price change, the PBAC considered better modelling and scenario analyses around TIV-HD compared with QIV-SD using data from Australian experience over a longer time-frame was required.” (para. 7.1, p25, TIV-HD PSD, July 2018).</p> <p>“The PBAC considered that the extent to which the benefits of TIV-HD outweighed the potential loss of protection against the mismatched B strain in QIV-SD compared to TIV-SD remained uncertain given year to year variability in influenza strains and severity of the season.” (para. 7.6, p26, TIV-HD PSD, July 2018).</p> <p>The ESC considered it inappropriate to model cardiovascular hospitalisation (paragraph 6.43, p23, TIV-HD PSD, July 2018).</p> <p>The ESC preferred use of a narrower definition of influenza-related hospitalisation (paragraph 6.30, p13, TIV-HD PSD, July 2018).</p>	<p>The resubmission included strain distribution data over 15 seasons (2002 to 2016). These were divided into seasons where the prevalence of A strain was high, moderate, or low (approximately five seasons of each), and the matching of the B strain to the TIV vaccine was high, moderate or low (approximately five seasons of each). Taken together, these data allowed for nine possible scenarios over which to assess the value of TIV-HD relative to QIV-SD.</p> <p>Cardiovascular hospitalisation were not included in the Supplementary model, but remained in the Main model.</p> <p>The Supplementary model, but not the main model, used the narrower definition of influenza-related hospitalisation.</p>
Section 4	<p>The proposed listing was projected to cost \$81 mil in Year 1 and \$■ mil in Year 6.</p>	<p>The net cost to the government was projected to be \$■ mil<sup>a</sup> in Year 1 and \$■ mil<sup>a</sup> in Year 6. Based on the economic model, the incremental acquisition costs of the vaccine were claimed to be completely offset by savings accrued to the health system via reductions in hospitalisations and health resource utilisation resulting from influenza infection.</p>

<sup>a</sup> Incorrectly calculated as \$■ million and \$■ million in the resubmission.

aQIV: Adjuvanted quadrivalent Influenza Vaccine; aTIV; Adjuvanted trivalent Influenza Vaccine; ESC: Economics Sub Committee; PBAC: Pharmaceutical Benefits Advisory Committee; PSD: Public Summary Document; QIV-SD: Quadrivalent Influenza Vaccine – Standard Dose; RCT: Randomised Controlled Trial; TIV-HD: Trivalent Influenza Vaccine – High Dose

Source: p10 of the resubmission, and compiled during the Evaluation.

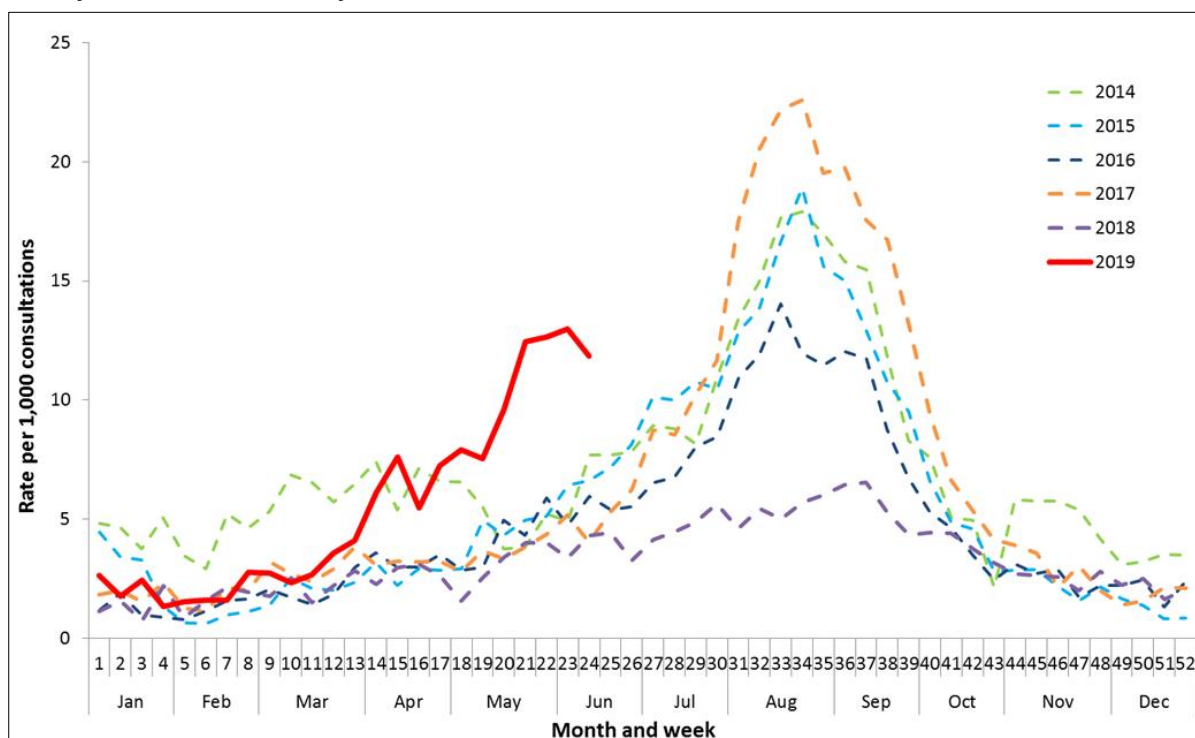
*For more detail on PBAC’s view, see section 7 PBAC outcome.*

## 4 Population and disease

- 4.1 The relevant population is Australians aged ≥ 65 years. This is unchanged from the previous submission.
- 4.2 Influenza is an acute viral infection of the respiratory tract. 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.
- 4.3 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.

- 4.4 Figure 1 shows the unweighted rate of influenza-like illness reported from sentinel GP surveillance systems in Australia (Jan 2014 to Jun 2019). Among the notified laboratory confirmed cases of influenza in all ages, a higher proportion was caused by influenza A/H3N2 in older adults.
- 4.5 The 2019 influenza season has seen most deaths caused by influenza A (98%, n=189), with notifications of influenza A (H3N2) highest in adults aged 80 years and older (71.1 per 100,000). The resubmission claimed, although still early in the season, a more effective vaccine is required for the  $\geq 65$  year cohort.

Figure 1: Unweighted rate of Influenza-like illness reported from sentinel GP surveillance systems, Australia, 1 January 2014 to 16 June 2019, by month and week.

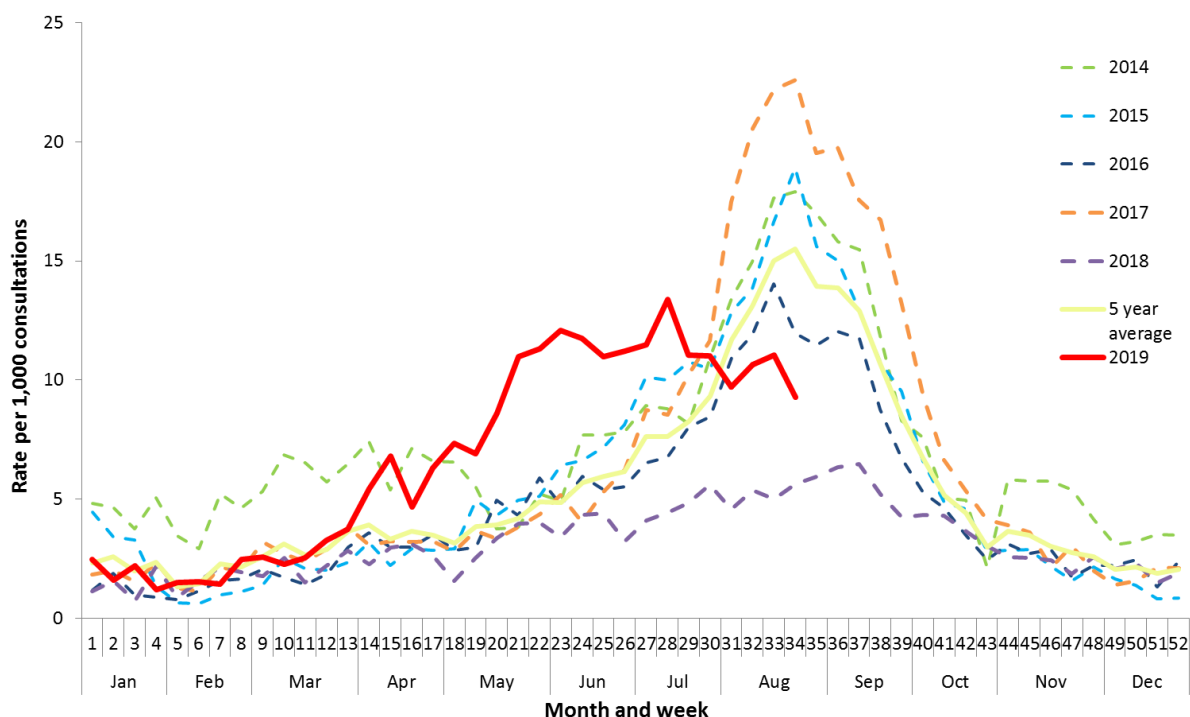


GP: general practitioner

Source: Figure 2, p14 of the resubmission (Australian Influenza Surveillance report June 2019).

- 4.6 After lodgement of the submission, the unweighted rate of influenza-like illness reported from sentinel GP surveillance systems in Australia appeared to plateau (Figure 2).

Figure 2: Unweighted rate of Influenza-like illness reported from sentinel GP surveillance systems, Australia, 1 January 2014 to 25 August 2019, by month and week.



Source: Department of Health, Australian Influenza Surveillance report week ending 26 August 2019, <https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-ozflu-flucurr.htm>

- 4.7 Influenza like illness is not always laboratory confirmed. The higher rates of testing with results being reported faster, particularly point of care testing in emergency departments and residential aged care facilities, and the preliminary advice<sup>1</sup> to immunise later in the year to ensure protection in August/September may have contributed to the 2019 trend.
- 4.8 The resubmission proposed TIV-HD as an alternative to aTIV for the 2020 season. The PBAC did not recommend the requested price increase for aTIV for people aged  $\geq 65$  years at the July 2019 meeting however the PBAC recommended aQIV for listing on the NIP at the August 2019 meeting.
- 4.9 The resubmission suggested that TIV-HD could be the standard of care for influenza immunisation in people aged  $\geq 65$  years in the 2020 influenza season.
- 4.10 The resubmission proposed a stepped approach to adoption where TIV-HD could be provided for an aged care facilities cohort initially (2020) with consideration to broaden access to the full cohort in the future. The NIP does not currently delineate

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

eligibility for people living in aged care facilities in the ≥65 years and older cohort. The resubmission did not analyse this sub-cohort in the economic model or the financial model.

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

## **5 Comparator**

- 5.1 The resubmission proposed QIV-SD as the main comparator. This was unchanged from the previous submission.
- 5.2 The resubmission proposed aTIV and aQIV as near market comparators. The previous submission nominated aTIV as the only near market comparator as it was prior to the introduction of aQIV to Australia. Given the requested price increase for aTIV was not recommended at the July 2019 meeting, the ESC considered that aTIV was not an informative near market comparator. At the August 2019 meeting aQIV was recommended for listing on the NIP, and therefore ESC considered aQIV to be an informative near market comparator.
- 5.3 The ESC considered that QIV-SD and aQIV were appropriate comparators. The PBAC considered aQIV would be the vaccine most commonly replaced by TIV-HD.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from organisations (3) via the Consumer Comments facility on the PBS website:
  - Diabetes Australia, Diabetes NSW & ACT and Diabetes Queensland noted the higher risk of complications associated with influenza for those aged 65 years and over, including hospitalisation and death, and that the risk was further increased for those with diabetes.
  - Diabetes Australia supported the listing of TIV-HD, noted the outcomes of a US study (not referenced) and claimed that reduced respiratory hospitalisations in that study would translate to the Australian setting.
  - Diabetes Queensland noted that there had been high rates of influenza and mortality in those aged 65 years and over in 2019 despite high vaccination rates, and stated its view that there may be a need for a more effective vaccine.
  - Diabetes Queensland outlined its support of measures to vaccinate those aged 65

years and over as well as those who come into contact with this population.

### **Clinical trials**

- 6.3 The resubmission did not re-present details of the relevant trials identified within the previous submission, however key results were re-presented in the Commentary.
- 6.4 The resubmission did not identify any head-to-head randomised controlled trials (RCTs) comparing TIV-HD and QIV-SD. The resubmission relied upon the previous submission's clinical claim that TIV-HD is superior to TIV-SD, and in turn QIV-SD, based on the two following clinical trials comparing TIV-HD to TIV-SD.
- FIM12: A Phase III/IV large scale, multi-centre, randomised, double blind, active-controlled trial comparing the efficacy and safety of TIV-HD to TIV-SD in a population aged  $\geq 65$  years in the US and Canada over two consecutive influenza seasons (N=31,989).
  - Gravenstein 2017: A large cluster trial of 823 nursing home residents aged  $\geq 65$  years conducted over a single influenza season (N=92,269 residents were recruited, N=53,008 met the inclusion criteria), with randomisation at the level of nursing home.
- 6.5 The resubmission used Izurieta to inform the comparison of TIV-HD to aTIV. Izurieta was an observational study comparing cell-cultured QIV and egg-based QIV-SD, TIV-HD, aTIV and TIV-SD in approximately 13 million adults aged  $\geq 65$  years in the US within the 2017-18 influenza season.
- 6.6 An additional relevant study which compares the vaccine effectiveness of aTIV with TIV-SD, Mannino et al. (2012)<sup>2</sup> was identified during the evaluation. This study was not included in the resubmission because it fell outside the inclusion criteria for the literature search, namely a comparison of TIV-HD with aTIV or aQIV. However, the submission used the relative effectiveness of aTIV to TIV-SD from Izurieta, and data for this comparison is also available from Mannino. The ESC noted exclusion of the Mannino trial may not be appropriate and that the results suggested a greater rVE for aTIV vs TIV-SD, and hence a reduced benefit for TIV-HD vs aTIV and aQIV.
- 6.7 Details of the trials presented in the previous submission and in the resubmission are provided in Table 4.

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<sup>2</sup> Mannino, S. M., Villa, M., Apolone, G., Weiss, N. S., Groth, N., Aquino, I., & et al. (2012). Effectiveness of adjuvanted influenza vaccination in elderly subjects in northern Italy. *Am J Epidemiol*, 176(6), 527-533.

Public Summary Document - November 2019 PBAC meeting

Table 4: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
FIM12	DiazGranados CA et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults	N Engl J Med. 2014 Aug 14;371(7):635-45.
	CSR: Efficacy Study of Fluzone High-Dose Vaccine Compared With Fluzone Vaccine In Elderly Adults	21 November 2013
	DiazGranados CA et al. Efficacy and immunogenicity of high-dose influenza vaccine in older adults by age, comorbidities, and frailty	Vaccine. 2015 Aug 26;33(36):4565-71.
	DiazGranados CA et al. Effect of Previous-Year Vaccination on the Efficacy, Immunogenicity, and Safety of High-Dose Inactivated Influenza Vaccine in Older Adults	Clin Infect Dis. 2016 May 1;62(9):1092-1099.
	DiazGranados CA et al. Prevention of serious events in adults 65 years of age or older: A comparison between high-dose and standard-dose inactivated influenza vaccines.	Vaccine. 2015 Sep 11;33(38):4988-93
Gravenstein <sup>a</sup>	Gravenstein et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial	Lancet Respir Med 5 (9): 738-746, (2017).
Izurieta	Izurieta et al. HS, Chillarige Y, Kelman J et al. Relative Effectiveness of Cell-Cultured and Egg-Based Influenza Vaccines Among Elderly Persons in the United States, 2017–2018.  Lu Y. on behalf of the FDA, CMS, and Acumen Team. Relative effectiveness of cell-cultured versus egg-based influenza vaccines, 2017-18.	J Infect Dis. 2018 Dec 18. doi: 10.1093/infdis/jiy716. [Epub ahead of print]  FDA presentation. <a href="https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2018-06/flu-03-Lu-508.pdf">https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2018-06/flu-03-Lu-508.pdf</a> (Accessed 6 June 2019).

CMS: Centers for Medicare and Medicaid Services; CSR: Clinical Study Report; FDA: US Food and Drug Administration; US: United States  
<sup>a</sup> The resubmission also reported identifying Gravenstein (2018), a randomised controlled study comparing the effectiveness of aTIV versus TIV-SD in the care home setting for which “limited information” are currently available in the public domain (p37 of the resubmission). The resubmission reported that while Gravenstein (2017) and Gravenstein (2018) were very similar in design, the two studies differed in such an extent that “neither a quantitative nor qualitative indirect comparison of the reported outcomes would be informative” to the comparison of TIV-HD versus aTIV (p37 of the resubmission). Gravenstein (2018) was not used in the resubmission. A qualitative comparison of the two studies was included in Attachment D-3 of the resubmission.

Source: Table 2.3, p45 of the resubmission and Table 2, para. 6.6 of the TIV-HD PSD, July 2018.

6.8 The key features of trials are summarised in Table 5.

Table 5: Key features of the included evidence

Trial	Number of participants	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>TIV-HD vs TIV-SD</b>						
FIM12	TIV-HD (year 1): 7,254 TIV-SD (year 1): 7,243 TIV-HD (year 2): 8,738 TIV-SD (year 2): 8,748	Two years	Low	Healthy adults aged ≥65 years	Occurrences of culture- or PCR confirmed influenza; Rates of all-cause hospitalisations and selected cardiorespiratory events reported by DiazGranados	Used
Gravenstein	TIV-HD: 26,639 TIV-SD: 26,369	1 year	Moderate	Nursing home residents	Hospital admissions related to pulmonary and influenza-like illness	Not used
<b>TIV-HD vs QIV-SD and aTIV</b>						
Izurieta	~13 million	1 year	Moderate to high risk	Medicare beneficiaries aged ≥65 years in the USA	Influenza-related hospital encounters Influenza-related office visits (pre-specified) Inpatient stays (post hoc)	Used

PCR: Polymerase Chain Reaction; TIV-HD: Trivalent Influenza Vaccine – High Dose; TIV-SD: Trivalent Influenza Vaccine – High Dose. Source: Table 3, p7, of the TIV-HD PSD, July 2018 and Table 2.4, p48 of the resubmission.

- 6.9 The resubmission noted that Izurieta is subject to bias due to confounding factors. Izurieta used inverse probability of treatment weighting (IPTW) to adjust for imbalances between cohorts on all covariates to mitigate the impact of confounders. This approach was appropriate although confounding resulting from unmeasured covariates would remain, and the impact of this on the results is unknown.
- 6.10 Izurieta was conducted during one (2017-18) influenza season in the US and potential egg-adaptation may have affected the efficacy of all egg-based vaccines: QIV-SD, TIV-HD, aTIV and TIV-SD. This potentially impacts on the applicability of the vaccine effectiveness estimates from this study given seasonal variations of influenza strains.
- 6.11 Overall, Izurieta has a moderate to high risk of bias mainly due to non-randomisation of participants. Aged care facility residents were excluded from the study cohort because their medical encounters may not have been reliably captured. People were also excluded if their residence was not located within defined Department of Health and Human Services regions. It was unclear if vaccination timing may have impacted immunity as participants were vaccinated at different points in time.
- 6.12 The Pre-Sub-Committee Response (PSCR) argued that Izurieta was the best available evidence to support comparisons with QIV-SD and aTIV, that the study analysis was robust due to the size of the study and adjustment of confounders using an IPTW, and because the comparison was undertaken during the same season, removing seasonal strain variation across the study season. The PSCR reiterated that the results of Izurieta favoured the use of TIV-HD over TIV-SD, QIV-SD and aTIV.

## Comparative effectiveness

### TIV-HD vs TIV-SD

- 6.13 Table 6 summarises the outcomes from FIM12. Vaccine efficacy of TIV-HD vs TIV-SD against lab-confirmed influenza caused by any viral types/subtypes was 24.24% (95% CI 9.71; 36.50). The lower bound of the 95% CI exceeded 9.1%, the pre-defined superiority threshold for TIV-HD compared to TIV-SD.
- 6.14 The reduction in influenza events for H1N1 was not statistically significant. This was previously noted by ESC, and suggests vaccine efficacy may be impacted by the extent of H1N1 circulating in any one year (para 6.13, p9, TIV-HD, July 2018).

**Table 6: Efficacy of TIV-HD relative to TIV-SD against serious events possibly related to influenza (intent-to-treat analysis, Year 1 and Year 2 combined) in the FIM12 trial**

Serious event category	TIV-HD (N = 15,990), n (rate)	TIV-SD (N = 15,993), n (rate)	Combined, rVE (95%CI) N=31,983
<b>Associated with PD-ILI</b>	<b>228 (1.43)</b>	<b>301 (1.88)</b>	<b>24.24 (9.71; 36.50)</b>
<b>Influenza A</b>	<b>190 (1.19)</b>	<b>250 (1.56)</b>	<b>23.99 (7.84; 37.39)</b>
A/H1N1	8 (0.05)	9 (0.06)	11.09 (-159.6; 70.15)
<b>A/H3N2</b>	<b>171 (1.07)</b>	<b>223 (1.39)</b>	<b>23.30 (5.97; 37.53)</b>
Influenza B	38 (0.24)	51 (0.32)	25.48 (-15.68; 52.36)
Victoria lineage	9 (0.06)	11 (0.07)	18.17 (-117.2; 70.03)
Yamagata lineage	24 (0.15)	36 (0.23)	33.32 (-14.89; 61.94)
<b>All-cause hospitalisation</b>	<b>1530 (95.68)</b>	<b>1643 (102.73)</b>	<b>6.9% (0.5 to 12.8)</b>
<b>Serious cardiorespiratory events</b>	<b>428 (26.77)</b>	<b>520 (32.51)</b>	<b>17.7% (6.6 to 27.4)</b>
<b>Pneumonia events</b>	<b>71 (4.44)</b>	<b>118 (7.38)</b>	<b>39.8% (19.3 to 55.1)</b>
Asthma/COPD/bronchial events	74 (4.63)	75 (4.69)	1.3% (-36.0 to 28.4)
Influenza events	4 (0.25)	6 (0.38)	33.3% (-136.2 to 81.2)
Coronary artery events	121 (7.57)	124 (7.75)	2.4% (-25.3 to 24.0)
Congestive heart failure	57 (3.56)	75 (4.69)	24.0% (-7.2 to 46.1)
Cerebrovascular events	72 (4.50)	77 (4.81)	6.5% (-28.9 to 32.1)
Other respiratory events	31 (1.94)	47 (2.94)	34.0% (-3.8 to 58.1)

Notes: rate = events per 1000 participant-seasons;

Events in bold denotes that the vaccine efficacy in that category was statistically significant.

PD-ILI: Protocol-defined influenza like illness; CI: confidence interval; COPD: chronic obstructive pulmonary disease; TIV-HD: high-dose inactivated influenza vaccine; TIV-SD: standard-dose inactivated influenza vaccine; rVE: relative vaccine efficacy.

Source: Table 2.5.1, p43-44 of the previous submission; Table 2.5.3, p45 of the previous submission.

- 6.15 A 6.9% (95%CI: 0.5%-12.8%) reduction in all-cause hospitalisations, and a 17.7% (95%CI: 6.6%-27.4%) reduction in the composite outcome of serious cardiorespiratory events was observed in FIM12. The reduction in all-cause hospitalisations did not reach the minimally clinically important relative reduction as defined in the Gravenstein trial (15%).
- 6.16 The ESC noted the results from FIM12 and recalled its previous advice that it was reasonable to claim that TIV-HD was superior to TIV-SD in terms of reducing cases of clinically diagnosed and laboratory confirmed influenza. However, the trial did not support the claim that TIV-HD is superior to TIV-SD in terms of reducing

cardiorespiratory hospitalisations given a significant reduction in pneumonia events only and not other cardiorespiratory events (para 6.3, p13, TIV-HD PSD, July 2018).

6.17 Table 7 summarises key outcomes from Gravenstein (2017).

**Table 7: Adjusted regression analysis results of primary outcome accounting for clustering by 817 nursing homes (intent-to-treat analysis) in the Gravenstein study (2017)**

	Adjusted relative risk (95% CI)	p value
FFS group analysis (the primary endpoint)		
Hospital admissions for respiratory illness	0.873 (0.776–0.982)	0.023
FFS group analysis (the secondary outcomes)		
All-cause hospital admissions	0.915 (0.863–0.970)	0.0028
MDS group analysis (the secondary outcomes)		
All-cause mortality	0.985 (0.931–1.038)	0.57
All-cause hospital admissions	0.933 (0.884–0.985)	0.012
Functional decline (change in ADL score of at least four points)	0.996 (0.956–1.038)	0.86

ADL: activities of daily living; FFS: fee-for-service; MDS: minimum dataset

Source: Table 2.5.4, p47 of the previous submission; Table 2.5.5, p47 of the previous submission.

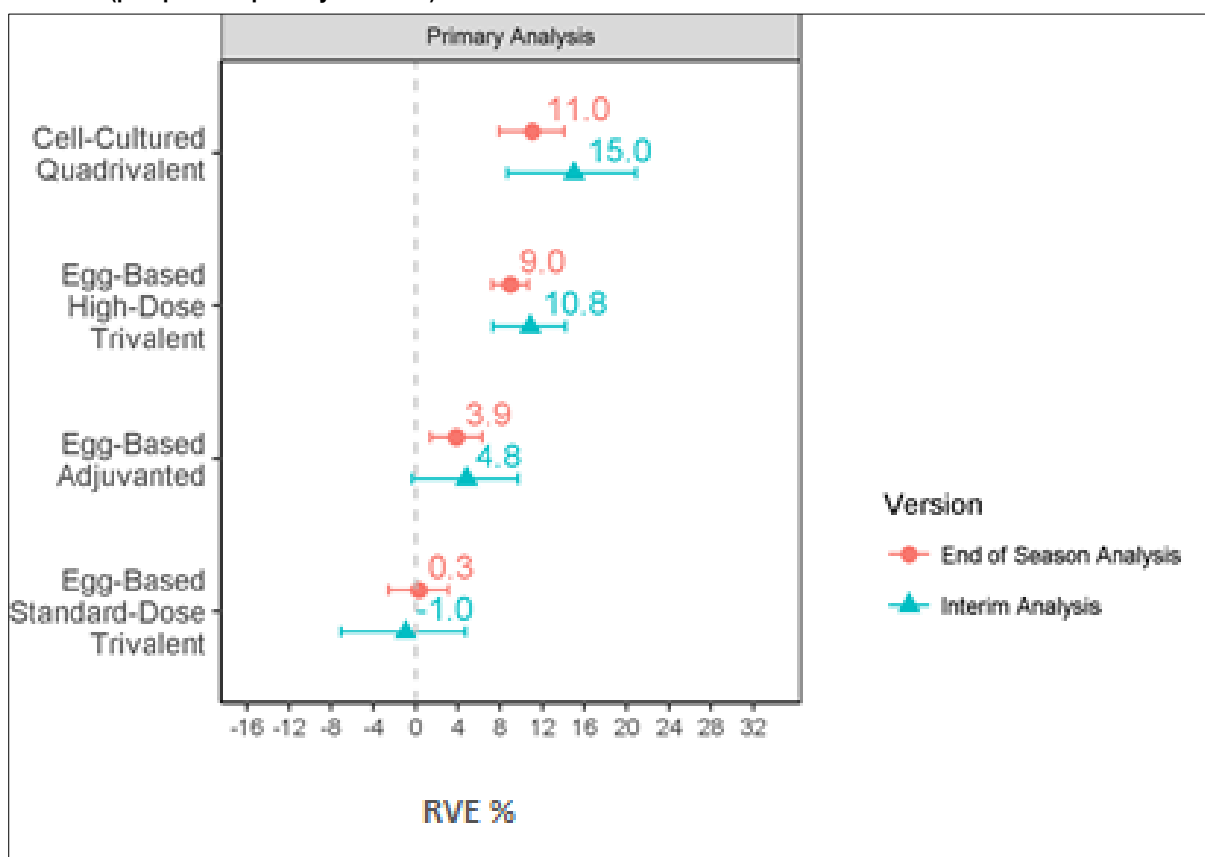
6.18 The risk of hospitalisation related to pulmonary and influenza-like conditions was significantly lower in facilities where residents received TIV-HD than in those that received TIV-SD [0.873 (95%CI: 0.776-0.982)]. The Evaluation and ESC noted that this reduction did not however, reach the minimally clinically important relative reduction (15%).

#### TIV-HD vs QIV-SD and aTIV

6.19 The resubmission presented rVE estimates for influenza hospital encounters as the primary outcome based on Izurieta. The primary comparison for this study was cell cultured vs egg based influenza vaccines. A secondary five way comparison was used to compare the effectiveness of cell cultured QIV-SD and 4 egg-based vaccine types: QIV-SD, TIV-HD, aTIV and TIV-SD.

6.20 Figure 3 presents the rVE estimates for influenza hospital encounters, using egg-based QIV-SD as the reference.

Figure 3: IPTW adjusted rVE estimates for influenza hospital encounters using egg-based QIV-SD cohort as reference (prespecified primary outcome)



IPTW: Inverse Probability of Treatment Weighting; QIV: Quadrivalent Influenza Vaccine; RVE: Relative Vaccine Effectiveness.  
Source: Figure 14, p61 of the resubmission.

- 6.21 The resubmission noted that cell cultured QIV-SD (QIVc) and TIV-HD were both more effective in preventing influenza-related hospital encounters than the egg-based QIV-SD, and both aTIV and TIV-SD. The PSCR stated egg adaption is a rare phenomena and the results from Izurieta with respect to the cell-based vaccine would not be expected to be representative of most seasons.
- 6.22 Izurieta adjusted rVE estimates using IPTW. This increased the rVE of TIV-HD vs QIV-SD from 0.4% (95% CI: -1.8, 2.6) before IPTW to 9.0% (95% CI: 7.2, 10.6) after IPTW.
- 6.23 Table 8 provides the key results from Izurieta as presented in the resubmission.

**Table 8: IPTW-adjusted pairwise rVE estimates for influenza-related outcomes: hospital encounters; office visits and; inpatient stays in the 2017–2018 season**

Vaccine cohort	rVE by Reference Group (95% CI), %	
	Egg-based QIV-SD	Egg-based aTIV
Influenza-related hospital encounters		
Egg-based TIV-HD	<b>9.0 (7.2, 10.6)</b>	<b>5.3 (3.3, 7.3)</b>
Influenza-related Office Visits		
Egg-based TIV-HD	0.7 (-1.5, 2.9)	<b>6.8 (4.6, 8.9)</b>
Influenza-related inpatient stays		
Egg-based TIV-HD	<b>10.0 (7.8–12.3)</b>	<b>7.7 (5.1, 10.2)</b>

aTIV: adjuvanted trivalent Influenza Vaccine standard dose; CI: Confidence Interval; IPTW: Inverse Probability of Treatment Weighting; QIV-SD: Quadrivalent Influenza Vaccine - Standard Dose; rVE: Relative Vaccine Effectiveness; TIV-HD: Trivalent Influenza Vaccine – High Dose.

Data in bold denote results significant at the  $P \leq .05$  level.

Source: Table 2.11, p63 of the resubmission.

- 6.24 Results from Izurieta were not directly applied in the economic model. Instead, rVE of aTIV vs TIV-SD (10%) was calculated as the rVE of aTIV vs TIV-SD from Izurieta (3.6%) multiplied by the ratio of the rVE of TIV-HD vs TIV-SD from FIM12 (24.2%) to the rVE of TIV-HD vs TIV-SD from Izurieta (8.7%). A sensitivity analysis using the direct estimate of 3.6% from Izurieta undertaken during the evaluation resulted in the ICER for TIV-HD vs aTIV using the Supplementary model improving from less than \$15,000 per QALY to TIV-HD dominating aTIV.
- 6.25 The ESC considered that although Izurieta presented real world data, the extent of benefit as reported in this study was uncertain due to:
- The moderate to high risk of bias associated with the study;
  - The IPTW analysis resulted in a large change in the estimated rVE (from 0.4% (95% CI: -1.8, 2.6) before IPTW to 9.0% (95% CI: 7.2, 10.6) after IPTW for TIV-HD vs QIV-SD);
  - There may be additional confounders not accounted for in the analysis;
  - Results for office visit are generally considered to be unreliable;
  - The study only covered one influenza season, and egg-adaption potentially affected the results; and
  - The exclusion of the aged care facility resident population for which the resubmission indicated is the highest need sub-group population.
- 6.26 The Pre-Sub-Committee Response (PSCR) argued that Gravenstein (2017) concluded that TIV-HD reduced hospitalisations for nursing home residents, and that a similar study conducted by Gravenstein (2018) using aTIV did not result in a statistically significant reduction in hospital admissions compared with QIV-SD. The PSCR asserted that given the high use of aTIV during 2019 and the high influenza incidence in aged care facility residents in 2019, aTIV was insufficient in this population whereas TIV-HD

has demonstrated effectiveness for this vulnerable cohort. The PSCR added that the stepped approach with initial access to aged care facility residents was in response to the PBAC concerns of the budgetary impact of TIV-HD and to commence access to the cohort with the highest unmet need first.

- 6.27 The ESC considered there was insufficient clinical evidence presented in the resubmission to support increased efficacy of the vaccine in an aged care facility resident cohort, noting that the two Gravenstein studies were not conducted in the same influenza season. The resubmission stated that it did not present an indirect comparison of the two Gravenstein trials as the two studies differed in such an extent that “neither a quantitative nor qualitative indirect comparison of the reported outcomes would be informative to the comparison of TIV-HD vs aTIV” and as there was only “limited information” available for the 2018 study at the time of submission.

#### TIV-HD vs aQIV

- 6.28 The ESC noted that no studies were identified that compared TIV-HD to aQIV.

#### ***Comparative harms***

- 6.29 The PBAC has previously considered the claim of “acceptable comparative safety” of TIV-HD vs QIV-SD “reasonable” (para. 7.7, p26, TIV-HD PSD, July 2018).
- 6.30 Except for a qualitative comparison of the adverse events reported in the Product Information of TIV-HD (Fluzone High-Dose) and aTIV (Fluad), the resubmission reported no new information regarding the comparative harms of TIV-HD vs TIV-SD or aTIV.
- 6.31 The adverse events presented in the Product Information for TIV-HD (Fluzone High-Dose) were based on those reported in the FIM05 safety trial which compared TIV-HD with TIV-SD. The adverse events presented in the Product Information for aTIV (Fluad) were based on those reported in Phase II/III studies that compared aTIV with a non-adjuvanted comparator vaccine.
- 6.32 Table 9 presents a qualitative comparison of the adverse events of TIV-HD vs aTIV as reported in the resubmission.

**Table 9: Frequency of Solicited Injection-Site Reactions and Systemic Adverse Events (any severity) after vaccination with TIV-HD (Fluzone High-Dose) or aTIV (Fluad), Adults 65 Years of Age and Older<sup>a</sup>**

Data source		Fluzone High Dose PI		Fluad PI	
		FIM05 Safety trial		Phase II/III studies	
Vaccine		TIV-HD (N=2569-2572)	TIV-SD (N=1258-1260)	aTIV (N=1982)	Non-adjuvanted comparator (N=1438)
Injection site reactions	Injection-Site Pain	35.6%	24.3%	40%	13.5%
	Injection-Site Erythema	14.9%	10.8%	18%	13.5%
	Injection-Site Swelling	8.9%	5.8%	-	-
	Induration	-	-	14.9%	9.8%
	Warmth	-	-	18.8%	11.1%
Musculo/Skeletal	Myalgia	21.4%	18.3%	8.7%	2.8%
	Arthralgia	-	-	3.2%	1.9%
Body as a whole	Chills	-	-	3.4%	1.7%
	Malaise	18.0%	14.0%	7.0%	4.5%
	Fever ( $\geq 37.5^{\circ}\text{C}$ )	3.6%	2.3%	0.7%	0.6%
Neurological	Headache	16.8%	14.4%	7.1%	4.9%
Gastrointestinal	Nausea	-	-	2.4%	2.3%
Skin	Rash	-	-	0.5%	0.4%

aTIV: adjuvanted trivalent Influenza Vaccine standard dose; PI: Product Information; TIV-HD: Trivalent Influenza Vaccine – High Dose.

<sup>a</sup> In the FIM05 study, adverse events were those reported within 7 days post-vaccination via diary cards; In the Fluad Phase II/III studies, adverse events were those reported with onset between 0-6 days post vaccination

Source: Reproduced from Table 2.13, p65 of the resubmission. The resubmission compiled the table using the adverse events reported in the Product Information for TIV-HD (Fluzone High-Dose) (January 2018) and the Product Information for aTIV (Fluad) (November 2018).

6.33 The resubmission claimed that the most frequently reported adverse events in the FIM05 study were redness, swelling and pain at the injection site; and systemic reactions including malaise, fever, headache and myalgia, but these were mild and resolved in three days. Missing information in the FIM05 trial for some injection site reactions makes the assessment of comparative harms uncertain.

6.34 Table 10 reports serious adverse events (SAEs) and deaths after vaccination with TIV-HD and TIV-SD based on FIM05 and FIM12, and with aTIV based on a post marketing surveillance study.

Table 10: Frequency of serious adverse events and death after vaccination with TIV-HD or aTIV in Adults ≥65 years of age

	TIV-HD (Fluzone High-Dose) PI				aTIV (Fluad) PI	
	FIM05 safety trial		FIM12 efficacy trial		Large post-marketing study	
	TIV-HD	TIV-SD	TIV-HD	TIV-SD	aTIV	TIV (Non-adjuvanted comparator)
N	2,569 - 2,572	1,258 – 1,260	15,992	15,991	~10,000	~5,000
SAEs 6 to 8 months post-vaccination	6.1%	7.4%	8.3%	9.0%	-	-
SAEs within 30 days post vaccination	-	-	1.3%	1.3%	-	-
AEs requiring physician visit					0.3%	0.3%
Hospitalisations during the season post vaccination	-	-	-	-	5.4%	5.7%
Deaths 28 or 30 days post vaccination	0	0	0.04%	0		
Deaths 1-6 or 1-8 months post vaccination	0.6%	0.6%	0.5%	0.5%		
Deaths during the season post vaccination	-	-	-	-	0.91%	0.83%

aTIV: Adjuvanted trivalent Influenza Vaccine; HD: High Dose; SD: Standard Dose; TIV: Trivalent Influenza Vaccine; TIV-HD: Trivalent Influenza Vaccine – High Dose.

Source: Reproduced from Table 2.14, p66 of the resubmission. The resubmission compiled the table using the adverse events reported in the Product Information for TIV-HD (Fluzone High-Dose) (January 2018) and the Product Information for aTIV (Fluad) (November 2018).

- 6.35 The resubmission claimed that TIV-HD and aTIV appear reasonably comparable in terms of overall safety however, details of the Phase II/III studies were not provided within the resubmission. It is unclear which non-adjuvanted comparator was used to compare comparative harms with aTIV and whether these claims are appropriate. It is also not appropriate to compare the safety from FIM05 and FIM12 trials with that from a large post marketing study given the different study characteristics.
- 6.36 The ESC noted that the events of myalgia and malaise are common, easily managed and not significant vs the comparators. The ESC noted PBAC's previous advice that the claim of acceptable comparable safety was reasonable.

### Benefits/harms

- 6.37 Table 11 shows the benefits and harms data for TIV-HD vs TIV-SD from FIM12 as presented in the evaluation for the July 2018 PBAC consideration. The PBAC has previously noted that the results were derived from FIM12, which relied on data from two influenza seasons in North America with a low prevalence of B strain influenza (para. 6.25, p11, and para. 6.28, p13, TIV-HD PSD, July 2018).

Table 11: Summary of comparative benefits and harms for TIV-HD and TIV-SD

Trial	TIV-HD (n)	TIV-SD (n)	rVE (95% CI)	Event rate/1000 patients*		RD/ 1,000 patients
				TIV-HD	TIV-SD	
<b>Benefits as reported in FIM12</b>						
Protocol-Defined Influenza-Like Illness	228	301	24.24% (9.71% to 36.50%)	14.3	18.8	-4.5
All-cause hospitalisation	1,530	1,643	6.9% (0.5% to 12.8%)	95.68	102.73	-7.05
Pneumonia events	71	118	39.8% (19.3% to 55.1%)	4.44	7.38	-2.94
<b>Harms</b>						
	TIV-HD (n)	TIV-SD (n)	RR (95% CI)	Event rate/100 patients		RD
				TIV-HD	TIV-SD	
<b>FIM12</b>						
SAE	1,323	1,442	N/A	8.27	9.02	-0.75%
Death	83	84	N/A	0.52	0.53	-0.01%
AE of Special Interest	3	6	N/A	0.02	0.04	-0.02%
SAE leading to study discontinuation	99	103	N/A	0.62	0.64	-0.02%
Related SAE	3	0	N/A	0.02	0	-0.02%
<b>FIM05**</b>						
Solicited reaction (D0 to D7)	1,378	556	N/A	53.6	44.1	9.5%
Solicited injection site reaction	1,076	394	N/A	41.8	31.3	10.5%
Solicited systemic reaction	882	370	N/A	34.3	29.4	4.9%

\* Duration of follow-up: FIM12: 2 years

\*\* As FIM12 did not capture immediate reactions or non-serious adverse events, the submission reported data on injection site reactions and low grade systemic reactions such as fever, headache, malaise, and myalgia from the FIM05 trial.

CI: Confidence Intervals; D: Day; N/A: Not Applicable; RD: Risk Difference; RR: Relative Risk; rVE: Relative Vaccine Effectiveness; SAE: Serious Adverse Event; TIV-HD: Trivalent Influenza Vaccine - High dose; TIV-SD: Trivalent Influenza Vaccine - Standard Dose.

Source: Table 8, para. 6.25, p12, of the TIV-HD PSD, July 2018.

6.38 The PBAC has previously considered that, based on the FIM12 randomised controlled trial, for every 1,000 patients vaccinated with TIV-HD vs TIV-SD:

- Approximately 4 fewer patients would have the protocol-defined influenza like illness;
- Approximately 7 fewer patients would have a hospitalisation;
- Approximately 3 fewer patients would have a pneumonia event;
- Approximately 8 fewer serious adverse events;
- Approximately 95 additional solicited reactions;
- Approximately 105 additional solicited injection site reactions; and
- Approximately 49 additional solicited systemic reactions (para. 6.2, p6, TIV-HD PSD, July 2018).

6.39 The comparison of TIV-HD vs aTIV was based on the Izurieta observational study. This did not allow for a quantitative comparison of the benefits and harms of TIV-HD and aTIV. Accordingly, a benefits/harms table was not presented.

### **Clinical claim**

#### TIV-HD vs TIV-SD

6.40 Consistent with the previous submission, this submission claimed that:

- TIV-HD is superior to TIV-SD in terms of a reduction in cases of clinically diagnosed and laboratory confirmed influenza;
- TIV-HD is superior to TIV-SD in terms of reduction in cardiorespiratory hospitalisations. The ESC previously noted a reduction in pneumonia hospitalisations was observed but a reduction in other cardiorespiratory hospitalisations was not observed; and
- TIV-HD is well tolerated with an acceptable safety profile.

6.41 The PBAC reiterated that the claim of superior comparative effectiveness was reasonable and adequately supported by the data.

6.42 The PBAC reiterated that the claim of acceptable comparative safety was reasonable and adequately supported by the data.

#### TIV-HD vs QIV-SD

6.43 The previous submission claimed that the additional disease burden due to the alternative B lineage excluded from TIV-HD will be offset by the additional protection provided against the common vaccine strains, due to the superior protection afforded by the vaccine against the A/H3 strain, relative to TIV-SD. The PBAC previously noted that the extrapolation of benefit of TIV-HD over TIV-SD to QIV-SD was uncertain given the marked variation in B strain prevalence across difference influenza seasons (para 6.32, p14, TIV-HD PSD, July 2018) and that while TIV-HD is likely to be superior to QIV-SD in people aged  $\geq 65$  years on average, the size of any additional benefit of TIV-HD over QIV-SD is uncertain given the loss of the additional B strain (para 7.6, p26, TIV-HD PSD, July 2018).

6.44 The PSCR stated that Izurieta represented the best available evidence to inform comparison of TIV-HD with QIV-SD, noting that the use of IPTW effectively balanced the cohorts of this observational study and that it was unlikely that any unknown confounders would have played a significant role in the observed results. The PSCR also noted that in all seasons from 2002 to 2016 the additional efficacy of TIV-HD over QIV-SD outweighed the loss of the additional B strain because the incremental efficacy was approximately the same for TIV-HD over QIV-SD in matched strains and in QIV-SD over TIV-HD in mismatched strains, and the matched strains were consistently more prevalent than the mismatched strain.

6.45 The ESC considered that the size of any additional benefit of TIV-HD over QIV-SD remained uncertain.

*Public Summary Document - November 2019 PBAC meeting*

- 6.46 The Pre-PBAC Response stated that the claim of superiority for TIV-HD over QIV-SD was primarily based on outcomes from FIM12, which provided a robust basis for determining incremental effectiveness of TIV-HD against TIV-SD with adjustment to account for the lost B strain in TIV-HD against QIV-SD.
- 6.47 The PBAC considered that the claim of superior comparative effectiveness was reasonable and adequately supported by the data.
- 6.48 The PBAC considered that the claim of acceptable comparative safety was reasonable and adequately supported by the data.

TIV-HD vs aTIV

- 6.49 The resubmission claimed that TIV-HD is superior to aTIV in terms of effectiveness and non-inferior in terms of safety based on Izurieta. Izurieta showed that TIV-HD was statistically significantly more effective than aTIV, although this study was observational in design with moderate to high risk of bias and was conducted in the US during a single influenza season (2017/18). It has a high level of bias primarily due to unmeasured confounding and non-randomisation of participants. Further the setting for the study differed to that for the NIP, with likely differences in the strain and severity of influenza seasons.
- 6.50 The ESC considered that the size of any additional benefit of TIV-HD over aTIV was uncertain.
- 6.51 The ESC noted the rVE in the economic model was based on an indirect comparison of TIV-HD and aTIV using FIM12 (TIV-HD vs TIV-SD) and Izurieta (TIV-SD vs aTIV). The ESC noted Mannino rather than Izurieta could be used to inform the comparison of TIV-SD and aTIV. With the use of Izurieta the rVE for TIV-HD vs aTIV is 15.8% (68.4% for TIV-HD and 62.5% for aTIV). With the use of Mannino the rVE for TIV-HD vs aTIV is -1.1% (68.4% for TIV-HD and 68.8% for aTIV).
- 6.52 The Pre-PBAC Response stated that the results observed in Izurieta are consistent with other studies which have shown limited difference in efficacy for aTIV over QIV-SD, in contrast with the evidence base for TIV-HD which indicates that TIV-HD has superior efficacy over standard dose vaccines.
- 6.53 The PBAC considered that the claim of superior comparative effectiveness was uncertain.
- 6.54 The PBAC considered that the claim of acceptable comparative safety was reasonable.

TIV-HD vs aQIV

- 6.55 The resubmission did not make a clinical claim for the comparison of TIV-HD vs aQIV due to absence of data. Instead the resubmission used a scenario analysis in the

economic model, where TIV-HD is claimed to be superior in effectiveness to aQIV, and implicitly, non-inferior to aQIV in terms of safety. This conclusion is highly uncertain.

- 6.56 The ESC considered there was insufficient evidence to accurately quantify the incremental benefit, if any, of TIV-HD vs aQIV. The ESC noted the concerns for the comparison of TIV-HD vs aTIV, together with the additional assumption for aQIV of the efficacy against the mismatched B strain being the same as for the matched B strain.
- 6.57 Overall, the ESC considered the claim of superior efficacy for TIV-HD over aQIV to be inadequately supported.
- 6.58 The Pre-PBAC Response acknowledged there is a lack of evidence comparing TIV-HD over aQIV and argued that this is due to a lack of quality evidence for aQIV against any vaccine. The Pre-PBAC Response stated that based on non-RCT evidence available that aQIV had been recommended on a cost-effectiveness basis to QIV-SD. It added that use of data from Izurieta provided the most robust means of estimating a comparative effect between TIV-HD and aQIV and that use of an indirect comparison informed by Mannino to estimate rVE would render any estimate highly uncertain.
- 6.59 The PBAC considered that a claim of superior comparative effectiveness could not be adequately supported by the data.
- 6.60 The PBAC considered that a claim of acceptable comparative safety would be reasonable.

### ***Economic analysis***

- 6.61 The ESC considered, given the claim of superiority for TIV-HD over aQIV was not adequately supported, that a cost-minimisation analysis vs aQIV would have been more appropriate than a cost-utility analysis.
- 6.62 The resubmission presented two cost-utility models for Australians aged  $\geq 65$  years:
- The economic model that compared TIV-HD to QIV-SD used within the previous submission (the Main model), but with a revised TIV-HD price (previously \$ [REDACTED], now \$ [REDACTED]). The resubmission claimed the modelling approach and data inputs used within the Main model remained valid and were the most appropriate approach to assess the full benefit of influenza vaccination.
  - A new economic model presented as a supplementary analysis (the Supplementary model) that compared TIV-HD to QIV-SD, aTIV and aQIV. The Supplementary model was developed in response to the PBAC's previous consideration "...scenario analyses around TIV-HD compared with QIV-SD using data from Australian experience over a longer time-frame was required" (para. 7.1, p25, TIV-HD PSD, July 2018). The resubmission claimed the Supplementary model was "fit for purpose" allowing uncertainty around vaccine effectiveness to be specifically addressed through scenario-based multivariate sensitivity analysis.

*Public Summary Document - November 2019 PBAC meeting*

- 6.63 The ESC noted the Main model did not include a comparison with aQIV, which was considered relevant given the PBAC's recommendation at the August 2019 meeting for this vaccine to be available on the NIP. The ESC also noted the Supplementary model utilised a simpler structure and revised some of the model inputs based on PBAC's advice from the July 2018 meeting, and importantly enabled the impact of the mismatched B strain on the cost-effectiveness of TIV-HD to be explored. The ESC therefore focused its discussion on the Supplementary model. Information regarding the Main model is included in the Commentary and the submission.
- 6.64 Table 12 presents a summary of the Supplementary model structure and rationale.

**Table 12: Summary of the Supplementary model structure and rationale**

Component	Description	Justification/comments
Type of analysis	Cost-utility analysis.	This is appropriate.
Outcomes	Confirmed influenza cases, hospitalisations, fatal influenza events prevented, years of life and QALYs.	This is appropriate.
Time horizon	Time horizon of 1 year. The loss of future years of life due to premature mortality were discounted to the 1-year horizon of the model.	This is reasonable.
Methods used to generate results	Cohort expected value.	This is reasonable.
Health states	<ul style="list-style-type: none"> <li>• Well</li> <li>• Confirmed influenza cases (resulting in GP visits, ED visits or neither)</li> <li>• Hospitalisations</li> <li>• Influenza related mortality</li> <li>• Background mortality</li> </ul>	The estimated hospitalisations, death from influenza, GPs visits and ED visits were all contingent on the occurrence of influenza.
Background incidence	Influenza incidence with no vaccine: 4.51% (FIM12 incidence with TIV-SD and VE for TIV-SD i.e. 1.88(1-0.5836)).	Consistent with previous ATAGI advice (p1 of the ATAGI February 2018 pre-submission advice & para. 6.34, p15, TIV-HD PSD, July 2018). FIM12 was conducted over low and high incidence influenza seasons.
	<p>Influenza A subtypes strain prevalence: National Notifiable Diseases Surveillance System (NNDSS) time series 2002-2016 data.</p> <p>Influenza B lineage prevalence: WHO-CC time series data 2002-2015.</p> <p>Average over 2002-2016</p> <p>Matched A: 83.2%</p> <p>Matched B: 10.0%</p> <p>Mismatched B: 6.8%</p>	<p>ATAGI noted data on the proportion of influenza A disease attributable to A subtypes is generally not reliable in Australia (p24 of the ATAGI February 2018 pre-submission advice). ATAGI also did not consider it appropriate to use a simple average estimate of the proportion of influenza due to different subtypes over a longitudinal period (p24 of the ATAGI February 2018 pre-submission advice).</p> <p>The proportion of influenza cases attributable to A and B strains varies with season, which impacts the weighted rVE calculations. This has been addressed within scenario analyses in the Supplementary model.</p>
Vaccine efficacy	<p>TIV-SD: 58.36% (Clements et al., 2014<sup>3</sup> and average distribution of strains over 2002-2016)</p> <p>QIV-SD: 59.85% (Clements et al., 2014 and average distribution of A/B strains over 2002-2016)</p> <p>TIV-HD vs TIV-SD: 24.2% (FIM12) (absolute VE of 68.44%)</p> <p>aTIV vs TIV-SD: 10.0% (Izurieta et al.2018 and FIM12) (absolute VE of 62.53%)</p> <p>aQIV: 63.87% (Izurieta et al.2018 and FIM12 for aTIV with assumption of same efficacy for both B strains)</p>	As for the July 2018 submission, Clements et al. (2014) was the source of the rVE against Type A (58%), B matched (69%) and B mismatched (47%). The ESC noted the estimates based on Clements 2014 to be uncertain.

<sup>3</sup> Clements, K. M., Meier, G., McGarry, L. J., Pruttivarasin, N. & Misurski, D. A. 2014. Cost-effectiveness analysis of universal influenza vaccination with quadrivalent inactivated vaccine in the United States. *Hum Vaccin Immunother*, 10, 1171-1180.

Public Summary Document - November 2019 PBAC meeting

Component	Description	Justification/comments
Influenza-related hospitalisation	Probability of hospitalisation given a person has influenza: 44.68% (FIM12). Sensitivity analysis: 19.3% (Newall 2008).	Based on a narrower definition of influenza-related hospitalisation in FIM12. ESC has previously noted that using a broader category of all-cause hospitalisations was inappropriate (para 6.43, p23, TIV-HD PSD, July 2018). The ESC considered use of the rate from Newall 2008 to be more appropriate for the base case.
Influenza-related mortality	Probability of influenza-related mortality given a person has influenza: 4.7% (Newall 2008 <sup>4</sup> ).	The Supplementary model used a higher rate of influenza-related mortality compared to the Main model (3.48%). The evaluation considered the lower mortality rate to be appropriate. The ESC considered the mortality rate from Newall et al.(2008) reasonable to use in the Supplementary model together with the hospitalisation rate from Newall et al.(2008).
Costs	Vaccine cost per administration: TIV-HD: \$ [REDACTED] QIV-SD: \$ [REDACTED] aTIV: \$ [REDACTED] aQIV: \$ [REDACTED]	Proposed price for TIV-HD. Current price for QIV-SD. The costs for aTIV and aQIV were unknown to the Sponsor and were set as proxies.
	Direct medical costs, including vaccine administration costs, GP and ED treatment of confirmed cases, along with averaged AR-DRG costs for cardiovascular and respiratory-related influenza hospital admissions.	Unchanged from the previous submission.
Utilities	Published studies including Turner et al., 2003, McPhail and Haines, 2010 and Hawthorne et al., 2013	Unchanged from the previous submission.
Discount rate	5% per annum.	As per PBAC guidelines.

aQIV: adjuvanted Quadrivalent Influenza Vaccine standard dose standard dose; AR-DRG: Australian Refined Diagnosis Related Group; ATAGI: Australian Technical Advisory Group on Immunisation; aTIV: adjuvanted trivalent Influenza Vaccine standard dose; ED: Emergency Department; ESC: Economics Sub Committee; GP: general practitioner; NNDSS: National Notifiable Diseases Surveillance System; PBAC: Pharmaceutical Benefits Advisory Committee; PSD: PBAC Public Summary Document; QALY: Quality-Adjusted Life Year; rVE: Relative Vaccine Efficacy; TIV-HD: Trivalent Influenza Vaccine – High Dose; TIV-SD: Trivalent Influenza Vaccine – Standard Dose; QIV-SD: Quadrivalent Influenza Vaccine – Standard Dose; WHO-CC: World Health Organisation – Collaboration Centre.

Source: Table 3.1.1 p57 of the previous submission and compiled during the evaluation.

6.65 Key drivers of cost-effectiveness are given in Table 13.

Table 13: Key drivers of the economic model

Description	Method/value	Impact
Background influenza attack rates in Australia	Rates were taken from FIM12 in North America, where high and low influenza activity was evident. The results of the economic model are affected by the cyclical nature of low-moderate-high influenza seasons.	Very high. Favours TIV-HD if Australian attack rates increase.
Assumed split of influenza cases between strains A and B	Average split over 2002-2016, and in scenario analyses high, medium and low rates of A strain.	High. Favours cost-effectiveness of TIV-HD vs QIV-SD if proportion of A strain is high.

<sup>4</sup> Newall AT, Wood JG, MacIntyre CR (2008) Influenza-related hospitalisation and death in Australians aged 50 years and older. Vaccine 26, 2135-2141.

Public Summary Document - November 2019 PBAC meeting

Description	Method/value	Impact
Proportion of matched B strains	Average split over 2002-2016, and in scenario analyses high, medium and low rates of B matching assumed.	Moderate. Favours cost-effectiveness of TIV-HD vs QIV-SD if proportion of B matching is high.
Assumed treatment effect of TIV-HD vs aTIV and aQIV	Sourced from the observational study of Izurieta et al. (2018), and other modelling assumptions. The ESC noted this could also be informed by Mannino et al (2012).	High. Favours TIV-HD if assumed effect of adjuvanted vs non-adjuvanted is low.
Rates of hospitalisation due to influenza	Sourced from FIM12 based on a narrow definition of hospitalisation.	High. High hospitalisation rates favour TIV-HD.
Rates of mortality due to influenza	Sourced from Newall et al (2008).	High. High mortality rates favour TIV-HD.
VE against mismatched B strain	Sourced from Clements 2014. The ESC noted Clements was a cost-effectiveness analysis which referenced a meta-analysis by Tricco 2013 <sup>5</sup> . The VE estimates were not precise with wide 95% CI (adults: VE=0.52, 95% CI 0.19, 0.72; all: VE=0.46 95% CI 0.27, 0.60).	High. High VE for the mismatched strain favours TIV-HD.

aQIV: adjuvanted quadrivalent Influenza Vaccine standard dose; aTIV: adjuvanted trivalent Influenza Vaccine standard dose; QIV-SD: Quadrivalent Influenza Vaccine - Standard Dose; TIV-HD: Trivalent Influenza Vaccine - High Dose; TIV-SD: Trivalent Influenza Vaccine - Standard dose.

Source: compiled during the current evaluation.

#### TIV-HD vs QIV-SD

6.66 In the Main model, as for the previous submission, TIV-HD was dominant, resulting in cost savings and additional QALYs vs QIV-SD. With the revised assumptions and inputs in the Supplementary model, the estimated ICER was less than \$15,000 per QALY (Table 14). The reduction in incremental costs and increase in incremental QALYs in the Supplementary model was largely due to the differences in modelling assumptions regarding:

- reduced rate of non-cardiovascular hospitalisation; and
- excluded cardiovascular hospitalisation.

The above factors were partly offset by the application of a higher rate of influenza-related mortality. Approximately 96% of the QALY gains in the Supplementary model were due to avoidance of influenza-related mortality, with the remaining due to influenza-related morbidity.

Table 14: TIV-HD vs QIV-SD (Supplementary model)

Component	TIV-HD	QIV-SD	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	7.5175	7.5161	0.00139
<b>Incremental cost / extra QALY gained</b>			<b>\$ [REDACTED]</b>

QALYs: Quality-Adjusted Life Years; QIV-SD: Quadrivalent Influenza Vaccine – Standard Dose; TIV-HD: Trivalent Influenza Vaccine – High Dose.

<sup>5</sup>Tricco A. C., Chit, A., Soobiah, C., Hallett, D., Meirer, G., Chen, M.H., Tashkandi, M., Bauch, C. T., Loeb, M. (2013), Comparing influenza vaccine efficacy against mismatched and matched strains: a systematic review and meta-analysis. *BMC Medicine*, 11(153)

*Public Summary Document - November 2019 PBAC meeting*

All values are per Australian aged ≥ 65 years.  
Source: Compiled during the evaluation.

- 6.67 The ICER was sensitive to influenza incidence. For example, the base case ICER for TIV-HD vs QIV-SD of less than \$15,000 per QALY, assumed a rate of influenza of 1.88%, taken from FIM12. The ICER increased to \$15,000 - \$45,000 per QALY assuming a plausible lower rate of influenza of 0.58% (year 1 of FIM12), and decreased to less than \$15,000/QALY assuming a higher rate of influenza of 2.96% (year 2 of FIM12). Influenza incidence is uncertain given it will vary each year.
- 6.68 The PSCR and Pre-PBAC Response argued that it was appropriate that the Supplementary model would be sensitive to influenza incidence as it was developed in response to areas of uncertainty around incidence and strain variation. It argued that given the sensitivity to incidence rate, an adequate assessment of cost-effectiveness of TIV-HD was to model against a representative season or against a number of seasons, as had been done in the scenario analyses. The PSCR reiterated that under most conditions, TIV-HD was cost-effective in this analysis.
- 6.69 The ICER was sensitive to the rate of hospitalisation. In the base case of the Supplementary model, the assumed rate of influenza-related hospitalisation given a person has influenza was 44.68%. The ICER for TIV-HD vs QIV-SD increased from less than \$15,000 to \$15,000 - \$45,000 per QALY with the hospitalisation rates based on Newall 2008 (19.3%). The ESC considered the hospitalisation rates from Newall 2008, an Australian study, to be more applicable than those from the US FIM12 trial. Given the preference for using hospitalisation rates from Newall 2008, it was considered reasonable to use the higher mortality rates reported in Newell 2008 (4.7% vs. 3.2%).
- 6.70 The ESC noted that the VE against the mismatched B strain was stated in the submission to be sourced from Clements 2014, although this was a secondary source. The primary source was a meta-analysis by Tricco 2013. The VE estimates for the mismatched B strain were not precise with wide 95% CI (adults: VE=0.52, 95% CI 0.19, 0.72; all: VE=0.46 95% CI 0.27, 0.60). The ESC noted using the lower 95% CI for the VE in adults (0.19) increased the ICER from less than \$15,000 to \$15,000 - \$45,000 per QALY.

TIV-HD vs aTIV and aQIV

- 6.71 Table 15 presents the results of the Supplementary model for TIV-HD vs aTIV and aQIV. A 'proxy' value of \$ [redacted] was assumed for the price of aTIV and aQIV.

**Table 15: Results of the economic evaluation from the resubmission Supplementary model**

Component	TIV-HD	aTIV	aQIV	TIV-HD - aTIV	TIV-HD - aQIV
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
QALYs	7.5175	7.5165	7.5167	0.0010	0.0007
<b>Incremental cost / extra QALY gained</b>				\$ [redacted]	\$ [redacted]

aQIV: adjuvanted quadrivalent Influenza Vaccine standard dose; aTIV: adjuvanted trivalent Influenza Vaccine standard dose; QALYs: Quality-Adjusted Life Years; TIV-HD: Trivalent Influenza Vaccine – High Dose.  
All values are per Australian aged ≥ 65 years.

Source: Adapted from Table 3.5, p75 of the resubmission.

- 6.72 The evaluation considered there was substantial additional uncertainty relating to the comparative cost-effectiveness of TIV-HD with adjuvanted vaccines given the uncertain rVE as outlined in paragraphs 6.25 and 6.49-6.51, and for the comparison with aQIV the additional assumption that the VE for the unmatched B strain is equal to that for the matched B strain.
- 6.73 With use of the rVE for aTIV vs TIV-SD of 3.6% directly from Izurieta the vaccine effectiveness of aTIV and aQIV is reduced (aTIV from 62.53% to 59.86%; aQIV from 63.87% to 61.29%) which had the following impact on the estimated ICERs:
- from less than \$15,000 per QALY for TIV-HD vs aTIV to TIV-HD dominates aTIV.
  - from less than \$15,000 - \$45,000 to less than \$15,000 per QALY for TIV-HD vs aQIV.
- 6.74 With use the rVE for aTIV vs TIV-SD of 25% from Mannino the vaccine effectiveness of aTIV (68.6%) and aQIV (69.9%) is greater than that for TIV-HD (68.4%) and hence TIV-HD is dominated by aTIV and aQIV.
- 6.75 The ESC noted the uncertain estimates for rVE (10% for aTIV vs TIV-SD in the base case model using FIM12 and Izurieta, 3.6% from Izurieta and 25% from Mannino) which impacted on the conclusion of the cost-effectiveness analyses.
- 6.76 With use of the lower 95% CI for the estimated VE in adults (0.19) against mismatched B strains, the ICER for TIV-HD vs aQIV increased from less than \$15,000 to less than \$15,000 per QALY.
- 6.77 The ICER was sensitive to influenza incidence. For example, the base case ICER for TIV-HD vs aQIV of less than \$15,000 per QALY, assumed a rate of influenza of 1.88%, taken from FIM12. The ICER increased to \$15,000 - \$45,000 per QALY assuming a plausible lower rate of influenza of 0.58% (year 1 of FIM12), and decreased to less than \$15,000 per QALY assuming a higher rate of influenza of 2.96% (year 2 of FIM12).
- 6.78 With use of the hospitalisation rate from the Newall 2008:
- the ICER/QALY for TIV-HD vs aTIV increased from less than \$15,000 to less than \$15,000 ; and
  - the ICER/QALY for TIV-HD vs aQIV increased from less than \$15,000 to less than \$15,000.

#### TIV-SD vs QIV-SD and aQIV – scenario analyses

- 6.79 The resubmission presented results from scenario analyses undertaken using the Supplementary model in response to the PBAC's previous comments regarding the extent to which the benefits of TIV-HD outweighed the potential loss of protection against the mismatched B strain in QIV-SD compared to TIV-SD remained uncertain

given year to year variability in influenza strains and severity of the season (para 7.6, p26, TIV-HD PSD, July 2018).

- 6.80 The PBAC also noted data presented in the ATAGI pre-submission advice showing the proportion of B strain influenza, distribution of B lineage and vaccine matching success from 2002 to 2016 (para 6.23, p10, TIV-HD PSD, July 2018). The resubmission applied this data to the Supplementary model to develop the scenario analyses by categorising fifteen influenza seasons (2002 to 2016) into nine scenarios that included a different combination of A strain prevalence with B strain match to the TIV-HD (see Table 16). The scenario analysis applied within the Supplementary model used a range of influenza activity (incidence) rates (low being based on year 1 of FIM12, high being based on year 2 of FIM12 and moderate being based on years 1 and 2 of FIM12).

**Table 16: Strain distribution scenarios applied to the resubmission Supplementary economic model**

Scenario	Seasons	A prevalence	B match
A prevalence High; B match High	2003; 2010	90.7%	100.0%
A prevalence High; B match Mod	2014	90.1%	93.0%
A prevalence High; B match Low	2009; 2016	95.2%	34.5%
A prevalence Mod; B match High	None	N/A	N/A
A prevalence Mod; B match Mod	2005; 2012	86.2%	62.0%
A prevalence Mod; B match Low	2002; 2007	87.1%	0.0%
A prevalence Low; B match High	2006; 2011; 2013	78.7%	96.0%
A prevalence Low; B match Mod	2015	60.4%	63.0%
A prevalence Low; B match Low	2004; 2008	71.9%	29.0%
2002 to 2016 (average)	2002 to 2016	83.2%	59.7%

Each season was assigned an A strain prevalence and a B matching of high, moderate, or low (approximately 5 of each). Due to ties, there were 6 low seasons of each, 4 moderate seasons and 5 high seasons. The values for A prevalence and B match are a simple average of the values from the respective seasons.

Source: Table 7, p11, of the July 2018 PSD and Table 3.3, p72 of the resubmission.

- 6.81 The cost-effectiveness results from the scenario analyses for TIV-HD vs QIV-SD are presented in Table 17. The Supplementary model base case ICER was less than \$15,000/QALY. The ICER for TIV-HD vs QIV-SD was lowest when:

- the prevalence of strain A was high, and the match of strain B was high;
- hospitalisation rates from FIM12 were used rather than from Newall et al.(2008); and
- the incidence of influenza was high.

Table 17: TIV-HD vs QIV-SD results of the Supplementary economic model by influenza activity, strain distribution and hospitalisation rate

Model result	IC/QALY (trial-based hospital rates)			IC/QALY (Newall 2008 hospital rates)		
	Mod	Low	High	Mod	Low	High
<b>Flu activity<sup>a</sup></b>						
<b>Strain distribution scenarios</b>						
A prev High; B match High	\$████	\$████	██████	\$████	\$████	\$████
A prev High; B match Mod	\$████	\$████	██████	\$████	\$████	\$████
A prev High; B match Low	\$████	\$████	██████	\$████	\$████	\$████
A prev Mod; B match High	N/A	N/A	N/A	N/A	N/A	N/A
A prev Mod; B match Mod	\$████	\$████	██████	\$████	\$████	\$████
A prev Mod; B match Low	\$████	\$████	\$████	\$████	\$████	\$████
A prev Low; B match High	\$████	\$████	██████	\$████	\$████	\$████
A prev Low; B match Mod	\$████	\$████	\$████	\$████	\$████	\$████
A prev Low; B match Low	\$████	\$████	\$████	\$████	\$████	\$████
2002 to 2016 (average <sup>b</sup> )	\$████	\$████	\$████	\$████	\$████	\$████

<sup>a</sup> Flu seasons of moderate, low and high activity were estimated from FIM12 data which include two flu seasons with variable flu incidence (0.58% and 2.96% in SD-TIV vaccinated cohorts for the two seasons). The low and high seasons of FIM12 were used as proxies for low and high activity seasons in the model. The moderate activity season is the overall FIM12 result (1.88%).

<sup>b</sup> based on average strain distribution and average extent of matching of B strain

IC: Incremental Cost; Mod: Moderate; N/A: Not Applicable; QALY: Quality-Adjusted Life Year.

IC/QALY values exceeding \$████ as shown in bold font.

The base case ICER is shown in large, bold, underlined font.

Source: Table 3.4, p74 of the resubmission.

The redacted table shows ICERs in the range of dominant - \$75,000/QALY.

- 6.82 The ICERs increased substantially (40-56%) for the scenarios where the incidence of the A strains was low and the match with the B strains was either low or moderate. This was the case in 2004, 2008 and 2015.
- 6.83 During the evaluation it was considered appropriate to use the mortality rate from the Main model. The PSCR stated that the mortality estimate of 0.028 used in the Main model, based on AIHW NHMD and rates of hospitalisation from FIM12 is subject to poor ascertainment and underreporting. It argued that use of the conservative morality assumption, although increasing the ICER, did not fundamentally change the conclusion (Table 18, these results have not been independently evaluated).

Table 18: Results of scenario-based sensitivity analysis for TIV-HD vs QIV-SD – using mortality rate of 2.8% from the Main model

Model result	IC/QALY (trial-based hospital rates) 44.68% of influenza requiring hospitalisation			IC/QALY (Newall 2008 hospital rates) 19.3% of influenza requiring hospitalisation		
	Mod	Low	High	Mod	Low	High
<b>Flu activity<sup>a</sup></b>						
<b>Strain distribution scenarios</b>						
A prev High; B match High	\$████	\$████	██████	\$████	\$████	\$████
A prev High; B match Mod	\$████	\$████	██████	\$████	\$████	\$████
A prev High; B match Low	\$████	\$████	██████	\$████	\$████	\$████
A prev Mod; B match High	–	–	–	–	–	–
A prev Mod; B match Mod	\$████	\$████	██████ 	\$████	\$████	\$████
A prev Mod; B match Low	\$████	\$████	\$████	\$████	\$████	\$████
A prev Low; B match High	\$████	\$████	██████ 	\$████	\$████	\$████
A prev Low; B match Mod	\$████	\$████	\$████	\$████	\$████	\$████
A prev Low; B match Low	\$████	\$████	\$████	\$████	\$████	\$████
2002 to 2016 (average <sup>b</sup> )	\$████	\$████	\$████	\$████	\$████	\$████

<sup>a</sup> Flu seasons of moderate, low and high activity were estimated from FIM12 data which include two flu seasons with variable flu incidence (0.58% and 2.96% in SD-TIV vaccinated cohorts for the two seasons). The low and high seasons of FIM12 were used as proxies for low and high activity seasons in the model. The moderate activity season is the overall FIM12 result (1.88%).

<sup>b</sup> based on average strain distribution and average extent of matching of B strain

IC: Incremental Cost; Mod: Moderate; QALY: Quality-Adjusted Life Year.

IC/QALY values exceeding \$████ as shown in bold font.

Source: Table 2, p4 of the PSCR.

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

6.84 The results of the scenario analyses for TIV-HD vs aQIV using the estimate of rVE as calculated in the resubmission are presented in Table 19 (using the mortality rates from Newall) and Table 20 (using the mortality rate from the Main model).

Public Summary Document - November 2019 PBAC meeting

Table 19: TIV-HD vs aQIV results of the Supplementary economic model by influenza activity, strain distribution and hospitalisation rate with mortality rates from Newall

Model result	IC/QALY (trial-based hospital rates)			IC/QALY (Newall 2008 hospital rates)		
Flu activity <sup>a</sup>	Mod	Low	High	Mod	Low	High
Strain distribution scenarios						
A prev High; B match High	\$████	\$████	██████	\$████	\$████	\$████
A prev High; B match Mod	\$████	\$████	██████	\$████	\$████	\$████
A prev High; B match Low	\$████	\$████	██████	\$████	\$████	\$████
A prev Mod; B match High	N/A	N/A	N/A	N/A	N/A	N/A
A prev Mod; B match Mod	\$████	\$████	\$████	\$████	\$████	\$████
A prev Mod; B match Low	\$████	\$████	\$████	\$████	\$████	\$████
A prev Low; B match High	\$████	\$████	██████	\$████	\$████	\$████
A prev Low; B match Mod	\$████	\$████	\$████	\$████	\$████	\$████
A prev Low; B match Low	\$████	\$████	\$████	\$████	\$████	\$████
2002 to 2016 (average <sup>b</sup> )	\$████	\$████	\$████	\$████	\$████	\$████

<sup>a</sup> Flu seasons of moderate, low and high activity were estimated from FIM12 data which include two flu seasons with variable flu incidence (0.58% and 2.96% in SD-TIV vaccinated cohorts for the two seasons). The low and high seasons of FIM12 were used as proxies for low and high activity seasons in the mode. The moderate activity season is the overall FIM12 result (1.88%).

<sup>b</sup> based on average strain distribution and average extent of matching of B strain

IC: Incremental Cost; Mod: Moderate; N/A: Not Applicable; QALY: Quality-Adjusted Life Year.

IC/QALY values exceeding \$████ as shown in bold font.

Source: Compiled by Evaluation post ESC meeting, pre PBAC meeting.

The redacted table shows ICERs in the range of dominant - \$200,000/QALY.

Table 20: TIV-HD vs aQIV results of the Supplementary economic model by influenza activity, strain distribution and hospitalisation rate with mortality rates from the Main model

Model result	IC/QALY (trial-based hospital rates)			IC/QALY (Newall 2008 hospital rates)		
Flu activity <sup>a</sup>	Mod	Low	High	Mod	Low	High
Strain distribution scenarios						
A prev High; B match High	\$████	\$████	██████	\$████	\$████	\$████
A prev High; B match Mod	\$████	\$████	██████	\$████	\$████	\$████
A prev High; B match Low	\$████	\$████	██████	\$████	\$████	\$████
A prev Mod; B match High	N/A	N/A	N/A	N/A	N/A	N/A
A prev Mod; B match Mod	\$████	\$████	\$████	\$████	\$████	\$████
A prev Mod; B match Low	\$████	\$████	\$████	\$████	\$████	\$████
A prev Low; B match High	\$████	\$████	██████	\$████	\$████	\$████
A prev Low; B match Mod	\$████	\$████	\$████	\$████	\$████	\$████
A prev Low; B match Low	\$████	\$████	\$████	\$████	\$████	\$████
2002 to 2016 (average <sup>b</sup> )	\$████	\$████	\$████	\$████	\$████	\$████

<sup>a</sup> Flu seasons of moderate, low and high activity were estimated from FIM12 data which include two flu seasons with variable flu incidence (0.58% and 2.96% in SD-TIV vaccinated cohorts for the two seasons). The low and high seasons of FIM12 were used as proxies for low and high activity seasons in the mode. The moderate activity season is the overall FIM12 result (1.88%).

<sup>b</sup> based on average strain distribution and average extent of matching of B strain  
 IC: Incremental Cost; Mod: Moderate; N/A: Not Applicable; QALY: Quality-Adjusted Life Year.  
 IC/QALY values exceeding \$ [REDACTED] as shown in bold font.  
 The Evaluator base case ICER is shown in large, bold, underlined font.  
 Source: Compiled during the evaluation.

The redacted table shows ICERs in the range of dominant - \$200,000/QALY.

6.85 Using the Newall 2008 hospitalisation rate and the moderate influenza incidence, the ICER for TIV-HD vs aQIV increased by approximately 33-35% for the scenario with a moderate A prevalence and a low B match (\$15,000/QALY - \$45,000/QALY using the mortality rate from Newall 2008; \$15,000/QALY - \$45,000/QALY using mortality rate from the Main model). This scenario was observed in 2002 and 2007. The ICER increased by 73-77% for the scenario with a low A prevalence and a moderate B match to \$15,000/QALY-\$45,000/QALY. This scenario was observed in 2015. The ICER increased by 139-144% for the scenario with a low A prevalence and a low B match to \$15,000-\$75,000/QALY. This scenario was observed in 2004 and 2008.

### ***Vaccine cost/patient/year***

6.86 The proposed price was \$ [REDACTED] per dose. Table 21 gives the costs for all vaccines relevant to the resubmission. These costs were used both in the economic and financial models.

**Table 21: Vaccine costs included in the Main and Supplementary economic models**

Vaccine	Unit of measurement	Unit cost (AUD)	Source of unit cost	Vaccine Usage in models	Use in model
TIV-HD	Per dose	\$ [REDACTED]	Proposed	1 dose per person	Main and Supplementary models
QIV-SD	Per dose	\$ [REDACTED]	Nationally Negotiated Price	1 dose per person	Main and Supplementary models
aTIV	Per dose	\$ [REDACTED]	"Proxy"	1 dose per person	Supplementary model only
aQIV	Per dose	\$ [REDACTED]	"Proxy"	1 dose per person	Supplementary model only

aQIV adjuvanted quadrivalent Influenza Vaccine standard dose; aTIV: adjuvanted trivalent Influenza Vaccine standard dose; QIV-SD: Quadrivalent Influenza Vaccine – Standard Dose; TIV-HD: Trivalent Influenza Vaccine – High Dose.  
 Source: compiled during this evaluation using information from Sections 3.3 and 4 in the submission.

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

6.87 This submission was not considered by DUSC. The submission employed an epidemiological approach to estimate the financial implications from the substitution of aTIV for TIV-HD for Australians aged ≥65 years. The key drivers were costs of the vaccines, eligible population size and uptake rates.

6.88 The previous submission assumed an uptake rate of 74.6%. The resubmission assumed an increased rate of 94.4%. The evaluation considered this inappropriate as it assumed

*Public Summary Document - November 2019 PBAC meeting*

a 100% substitution rate between TIV-HD and aTIV, which is unlikely given there are several potential comparator vaccines, including QIV-SD, aTIV and aQIV.

6.89 The PSR and Pre-PBAC Response argued that given the 2019 influenza outcomes to date, there was an unmet need in those aged  $\geq 65$  years and requested the PBAC to consider subsidising TIV-HD for the whole cohort.

6.90 The net costs to the NIP and the Australian Government are presented in Table 22.

**Table 22: Estimated use and financial implication for Australian Government**

	2020	2021	2022	2023	2024	2025
<b>Costs of TIV-HD</b>						
Eligible subjects						
Uptake	94.4%	94.4%	94.4%	94.4%	94.4%	94.4%
Subjects vaccinated						
Doses per subject	1	1	1	1	1	1
Doses administered						
Cost per dose	\$	\$	\$	\$	\$	\$
Total cost NIP	\$	\$	\$	\$	\$	\$
<b>Estimated net cost to NIP/MBS</b>						
Net cost to the NIP	\$	\$	\$	\$	\$	\$
Net cost to the MBS*	\$	\$	\$	\$	\$	\$
<b>Net cost to government health budget</b>	\$	\$	\$	\$	\$	\$
<b>Net cost to government health budget*</b>	\$	\$	\$	\$	\$	\$

\* Corrected values calculated in this evaluation. The resubmission included an error in the calculation of a reduction in GP visits and used an out of date MBS Item 23 schedule fee.

MBS: Medicare Benefits Schedule; NIP: National Immunisation Program; TIV-HD: Trivalent Influenza Vaccine – High Dose  
Source: Based on Tables 4.1, 4.2 and 4.5, p78-9 of the resubmission.

The redacted table shows that at Year 6, the estimated number of subjects vaccinated was over 200,000.

6.91 The estimated uptake rate of 94.4%, was uncertain. However, the upper bound for the uptake rate is 100%, which is only slightly higher than the value assumed. Hence, the overall net costs to the NIP and Australian Government are unlikely to substantially exceed the values presented in Table 22.

6.92 The cost to the NIP from TIV-HD as proposed in the resubmission was likely to exceed \$100million per year in year 6, with a net cost to Government in year 6 of \$60 - \$100 million.

6.93 A comparison of net costs to the NIP and the Australian Government between the previous submission and resubmission are given in Table 23.

**Table 23: Comparison of net costs to the NIP and Australian Government between the previous submission and resubmission**

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Net cost to NIP						
Previous submission <sup>a</sup>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Resubmission	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to Australian Government						
Previous submission <sup>b</sup>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Resubmission <sup>c</sup>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

<sup>a</sup> data extracted from July 2018 financial impact model in this resubmission.

<sup>b</sup> data extracted from July 2018 financial impact model in this resubmission and corrected during this evaluation.

<sup>c</sup> Corrected values calculated in this evaluation.

NIP: National Immunisation Program.

Source: Compiled during this evaluation from Section 4 of the previous submission and Table 4.5, p79 of the resubmission.

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

## 7 PBAC Outcome

- 7.1 The PBAC recommended an increase in the price of inactivated trivalent influenza vaccine (Fluzone High-Dose, TIV-HD), on the *National Health (Immunisation Program – Designated Vaccines) Determination 2014 (No.1)* (the Determination), for active immunisation against influenza in adults aged ≥65 years. The PBAC recommendation was on the basis that, on balance, TIV-HD was at least as effective as adjuvanted quadrivalent influenza vaccine (Fluad Quad, aQIV). The PBAC considered a claim of superiority vs aQIV could not be adequately supported by the clinical evidence presented and therefore a cost-minimisation approach in which TIV-HD was the same price as aQIV [REDACTED] would be appropriate.
- 7.2 The PBAC reaffirmed its July 2018 advice<sup>6</sup> that the proposed clinical place for TIV-HD was appropriate, noting the high incidence of influenza, high mortality and hospitalisation rates associated with influenza in the proposed population, as well as the typically lower vaccine effectiveness observed in this population.
- 7.3 The PBAC considered that the proposed comparator, quadrivalent influenza vaccine (QIV-SD), was a less appropriate main comparator given that aQIV was recommended for listing on the NIP in August 2019 and the high utilisation of aTIV in 2019 was expected to transfer to aQIV from 2020. Accordingly, the PBAC considered aQIV would be the vaccine most commonly replaced by TIV-HD and thus the main comparator.

<sup>6</sup> Public Summary Document – Trivalent Influenza Vaccine (high dose) (Fluzone® High-Dose), July 2018 PBAC meeting, paragraph 7.2

- 7.4 The PBAC noted that no studies were identified that compared TIV-HD to aQIV. The PBAC noted it had previously considered the two large randomised controlled trials relied on for this resubmission (FIM12 and Gravenstein) which compared hospitalisations for TIV-HD to TIV-SD. The resubmission also presented an observational study (Izurietta) comparing cell-cultured QIV and egg-based QIV-SD, TIV-HD, aTIV and TIV-SD over one US season to inform the comparison of TIV-HD to aTIV. The PBAC noted that the evaluation identified an additional study (Mannino) relevant to consideration which compared aTIV to TIV-SD, in a prospective population-based cohort study.
- 7.5 The PBAC recalled its previous conclusions that<sup>7</sup>:
- TIV-HD had demonstrated benefits over TIV-SD; and
  - TIV-HD was likely to be superior to QIV-SD in the target population on average, however the Committee was not confident of the size of any additional benefit of TIV-HD given the loss of the additional B strain.
- 7.6 The PBAC considered that the rVE based on Izurietta was imprecise, however the results from FIM12 with the scenario analyses in the economic model in the resubmission adequately supported the claim of superiority of TIV-HD over QIV-SD as uncertainty around the impact of the lost B strain had been sufficiently resolved.
- 7.7 The PBAC accepted that the data for TIV-HD vs TIV-SD is of better quality than the data for aTIV vs TIV-SD, but that the comparative effectiveness of TIV-HD and aTIV was nonetheless uncertain, noting the benefit of aTIV over TIV-SD for influenza hospitalisations in Mannino was comparable (17-25%)<sup>8</sup> to that of TIV-HD over TIV-SD in FIM12 (24.2%).
- 7.8 The PBAC considered that superiority of TIV-HD over aQIV could not be adequately supported, however on balance TIV-HD was likely to be at least as effective as aQIV. Based on a cost-minimisation approach, the PBAC considered the relevant equi-effective doses to be one dose of TIV-HD 0.5 mL and one dose of aQIV 0.5 mL.
- 7.9 The PBAC also reaffirmed its July 2018 advice<sup>9</sup> that the claim of acceptable comparative safety of TIV-HD vs QIV-SD was reasonable. The PBAC considered that the rates of adverse events presented in the qualitative comparison of adverse events were reasonable for an influenza vaccine in the proposed population. On this basis the PBAC considered that TIV-HD was likely to be non-inferior in safety to aQIV, noting that although there was an increased frequency of injection site reactions, these were mild to moderate in nature and well managed.
- 7.10 The PBAC agreed with the ESC that the supplementary economic model was the most

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<sup>7</sup> Public Summary Document – Trivalent Influenza Vaccine (high dose) (Fluzone® High-Dose), July 2018 PBAC meeting, paragraph 7.5,

<sup>8</sup> Public Summary Document, Inactivated influenza vaccine (surface antigen), adjuvanted (Fluad®), July 2019

<sup>9</sup> Public Summary Document – Trivalent Influenza Vaccine (high dose) (Fluzone® High-Dose), July 2018 PBAC meeting, paragraph 7.7

appropriate for consideration as it included comparison against aTIV and aQIV and appropriately incorporated PBAC's July 2018 concerns. However, given a superior benefit over aQIV could not be adequately supported, the cost-utility analysis could not be used to inform a price for TIV-HD higher than aQIV.

- 7.11 The PBAC noted that the submission proposed a stepped implementation, starting with residents of aged care facilities to reduce expenditure in the first year of implementation. The PBAC considered that insufficient evidence of an improved benefit in this group had been presented, that it would not be feasible to implement this approach under the NIP and accordingly PBAC did not support this approach to implementation.
- 7.12 The PBAC considered the substitution rate estimate of 100% between TIV-HD and aTIV in the financial estimates may be overestimated as it ignored the potential availability of aQIV. The PBAC noted the request for TIV-HD to be subsidised for the whole NIP cohort, however noted that its role was to provide advice to the Minister on the comparative cost-effectiveness of TIV-HD and that determination of market share arrangements for NIP vaccines was outside of its remit.
- 7.13 The PBAC noted that this submission is not eligible for independent review as independent review is only relevant to PBS listing and because it was a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

- 8.1 Amend price in existing listing:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
INACTIVATED TRIVALENT INFLUENZA VACCINE (SPLIT VIRION), 0.5ML, INJECTION, PREFILLED SYRINGE	1	0	Fluzone High-Dose Sanofi-Aventis Australia Pty Ltd
Category/Program:	NIP		
NIP indication:	A single injection against influenza disease caused by influenza virus types A and B contained in the vaccine for use in persons ≥ 65 years of age.		

NIP: National Immunisation Program

## 9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not

necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **10 Sponsor's Comment**

Sanofi acknowledges the positive recommendation from the Pharmaceutical Benefits Advisory Committee (PBAC) for Fluzone High-Dose. We will continue to work with all relevant stakeholders so they recognise the burden of influenza in older Australians and the value of Fluzone High-Dose for this part of our community.